should be offered after serious deliberation. Moreover, if limited to patients who had been clinically diagnosed as T4 before the definitive CRT, the rate of non-curative surgery increased to 64% (7/11). Considering this high rate, salvage surgery should be avoided for patients with T4 before the definitive CRT. Instead, palliative therapy such as intraluminal stent placement or bypass surgery might become a choice of treatment. Patients who show mucosal recurrence can be treated by endoscopic mucosal resection or photodynamic therapy.

On the other hand, if the 8 patients with non-curative surgery were excluded from the analysis, the survival rate of the remaining 16 patients with curative surgery is nearly 50% at 5 years. Therefore, if it is possible to select curatively respectable patients, salvage surgery would give a great clinical benefit to patients. In the future, in addition to establishing new criteria for the T factor in irradiated patients, new tools with higher accuracy for T factor assessment such as PET-CT or other techniques should help determine the treatment strategy for patients after definitive CRT.

CONCLUSIONS

Salvage esophagectomy is a highly invasive and morbid operation, which is performed on immunocompromized hosts. Therefore, it is important to accurately assess the preoperative T factor, and surgeons must exercise care when deciding on the indication for salvage surgery.

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Imaging, Diagnosis, Prognosis

Computer-Assisted Analysis of Biopsy Specimen Microvessels Predicts the Outcome of Esophageal Cancers Treated with Chemoradiotherapy

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Abstract

Purpose: A computer-assisted microvessel analysis system was developed to evaluate correlations between the architecture of biopsy specimen microvessels and the outcome for patients with esophageal cancer treated with chemoradiotherapy.

Experimental Design: Biopsy specimens from 51 patients with esophageal cancer (T_{2-3}, any N, M_0) treated with chemoradiotherapy were immunostained with an anti-CD31 antibody and quantified using computerized image analysis. We evaluated the association of several microvessel factors with overall survival, including the ratio of total microvessel perimeter to total tumor area (TP/TA), the tumor hypoxic ratio, and the ratio of total microvessel number to total tumor area (TN/TA). Results from traditional manual microvessel density (MVD) hotspot count and computerized hotspot count were compared and the relation between hotspot MVD count and survival rate was evaluated.

Results: The median follow-up time was 32 months. Both univariate and multivariate analyses revealed that computer-counted hotspot MVD and TN/TA and TP/TA ratios correlated significantly with the outcome of chemoradiotherapy. Kaplan-Meier survival curves showed that patients with high computer-counted hotspot MVDs and high TN/TA and TP/TA ratios had better overall survival rate than patients with low MVDs or ratios ($P = 0.025$, 0.008, and 0.031, respectively). Combining computer-counted MVD or TN/TA ratio with TP/TA ratio proved more predictive than any single factor. Two researcher-counted hotspot MVDs had no significant relation with outcome.

Conclusion: Computer-assisted tumor microvessel analysis is a powerful tool in predicting the outcome for patients with esophageal cancer treated with chemoradiotherapy because intraobserver and interobserver variability is minimized.

Esophageal cancer is a common malignancy that causes ~ 10,000 deaths each year in Japan (1) and >300,000 deaths annually worldwide (2). Surgery with or without preoperative chemoradiotherapy is generally done for resectable cases and chemoradiotherapy is used for unresectable cases or resectable cases where patients do not wish to have surgery. In recent years, chemoradiotherapy is increasingly being reported as a curative treatment modality for clinically resectable cases, which does not compromise disease control. In the Radiation Therapy Oncology Group 85-01 randomized trial, definitive chemoradiotherapy using 5-fluororuracil, cis-diammine-dichloroplatinum (cisplatin), and concurrent radiation (50 Gy) has achieved a 26% 5-year survival (3), similar to surgery alone (4, 5). Stahl et al. (6) reported a randomized trial comparing chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma. Chemoradiotherapy resulted in equivalent survival compared with chemoradiotherapy followed by surgery.

Because chemoradiotherapy can achieve similar survival rates to surgery or surgery combined with chemoradiotherapy, patient characteristics and tumor histologic features that favor chemoradiotherapy should be carefully assessed before choosing treatment. However, the factors that can predict the response to treatment of esophageal cancer remain uncertain. In our studies, we reported that hotspot microvessel density (MVD) in biopsy specimen is of strong prognostic significance for patients with laryngeal squamous cell cancers and with hypopharyngeal cancers treated with radiation (7, 8). The ratio of total microvessel perimeter (TP) to total tumor area (TA) of biopsy specimens, the ratio of total microvessel number (TN) to TA, and the tumor hypoxic ratio calculated from microvessel distributions in biopsy specimens have been further proved to

be good prognostic factors for patients with early stages of laryngeal carcinoma treated with radiation (9). In the present study, microvessel factors, including hotspot MVD and TP/TA, TN/TA, and hypoxic ratios, in biopsy specimens from 51 patients with esophageal cancer treated with chemoradiotherapy were analyzed, and the relations between these factors and overall survival were assessed. All factors including tumor hotspot MVD counts were analyzed using a computer-assisted image analysis system, with the aim of minimizing intra-observer and interobserver variation in microvessel counting and analysis.

Materials and Methods

Patients. A total of 348 patients with esophageal cancers were diagnosed and treated at the National Cancer Center Hospital East between 1992 and 1999. Surgery was done as the main treatment for 139 patients, and 209 received definitive chemoradiotherapy. Among the 209 patients, 51 met the following criteria to be included in this study: (*a*) the tumor was histologically diagnosed as squamous cell carcinoma; (*b*) patient age was ≤75 years; (*c*) sufficient biopsy specimens (tumor area >0.6 mm^2, which is about thrice of ×400 magnification field) were available before treatment; (*d*) performance status on the Eastern Cooperative Oncology Group scale ≤2; and (*e*) stage T$_{2-3}$, any N, M$_0$ on the International Union against Cancer tumor-node-metastasis classification. The patients' characteristics are listed in Table 1.

Treatment protocol. Chemotherapy consisted of continuous infusion of 5-fluorouracil (400 mg/m^2/d, on days 1-5 and 8-12) and a weekly infusion of cisplatin (40 mg/m^2, days 1 and 8). Concurrent radiotherapy was given at 2 Gy/d for 5 d/wk with a 2-week break after a dose of 30 Gy, and restarted on day 36 along with the same schedule of chemotherapy as before. The total radiation dose was 60 Gy. After concurrent chemoradiotherapy, two additional courses of chemotherapy (5-fluorouracil, 800 mg/m^2/d, on days 1-5 and 29-33; cisplatin, 80 mg/m^2, on days 1 and 29) were basically administered if patients responded to treatment without serious side effect. Further additional courses were optional although they were limited to a total of four courses.

Definition of tumor response. The first evaluation was done ~1 month after treatment. Patients then received computed tomography scanning and esophagoscopy every 2 or 3 months during the first year and every 6 months thereafter. Tumor recurrences were all proved histologically by biopsy.

Response at the primary site was evaluated by endoscopic examination. The criteria for evaluation were as follows: complete remission was defined as disappearance of tumor lesion and ulceration for ≥4 weeks with negative biopsy results; partial remission was determined when primary tumor was observed on esophagography as being reduced in area by ≥50%. Responses of metastatic lymph nodes were assessed by computed tomography scanning according to the WHO criteria for measurable disease.

Immunohistochemical staining of blood microvessels and computer-assisted image analysis. All biopsy specimens were taken at the time of diagnosis. Immunohistochemical staining of blood microvessels was done with the standard avidin-biotin complex technique using diaminobenzidine as a chromogen and hematoxylin as counterstain. Antigen was retrieved by treating with 0.05% pepsin in 0.01 N HCl for 5 minutes at room temperature. A mouse antibody for CD31 was used as primary antibody (4°C, overnight, 1:50 dilution; DAKO, Glostrup, Denmark). After washing, sections were incubated with an avidin-biotin complex reagent (DAKO). Color reactions were developed for 5 minutes in diaminobenzidine-Tris buffer (pH 7.6) containing 0.3% hydrogen peroxide.

Table 1. Patient characteristics

Characteristic	No. patients
Total number	51
Gender	
Male	43
Female	8
Age	
Mean	61.7
Range	38-75
Performance state	
0	38
1	13
Tumor location	
Upper and middle	36
Lower	15
Histology type	
W/D	1
M/D	36
P/D	14
T stage	
T$_2$	10
T$_3$	41
N stage	
N$_0$	20
N$_1$	31
Stage	
IIA	20
IIB	6
III	25

Digitized images of immunohistochemically stained sections of whole specimen at ×100 magnification (10× objective and 10× ocular) were obtained using a KS 300 image analysis system (capture resolution 768 × 580, Karl Zeiss Vision K.K., Jena, Germany). Vessels with lumens located around or inside tumor nest were traced by one of the authors (H.S.). The process of image analysis has been described elsewhere (9). Briefly, traced microvessels and the outline of the total specimen were converted to binary images and TN, TP, and TA were calculated. Data were recorded as TN/TA, TP/TA, and TP/TA ratios. As the oxygen diffusion distance from blood vessels is ~150 μm (10), the hypoxic ratio was calculated as the ratio of tumor area >150 μm from blood vessels to the TA (Fig. 1A).

Two of the authors (Z.S. and H.S.) counted hotspot microvessel numbers independently without knowledge of patient outcomes. The immunohistochemically stained specimens were first scanned at low magnification (×10-×100); three high-magnification (×400) fields with plentiful vascular tumor areas were then selected and counted as hotspots. The mean number of vessels from three fields was recorded as the hotspot MVD.

As an alternative for manual counting, a computer-assisted method was used to identify hotspot and count vessels in specimens. The previously traced vessels were converted to binary images and were scanned consecutively. The scanning circle was 500 μm in diameter and 0.196 mm^2 in area, which was the same as a ×400 magnification field. Microvessels within each circle were counted by computer. The overlay of adjacent circles in both the X and Y axes was set arbitrarily at 375 μm (three fourths of the diameter). The mean number of MVDs in the three circles containing the highest MVD count was recorded as the hotspot MVD of the corresponding specimen (Fig. 1B).
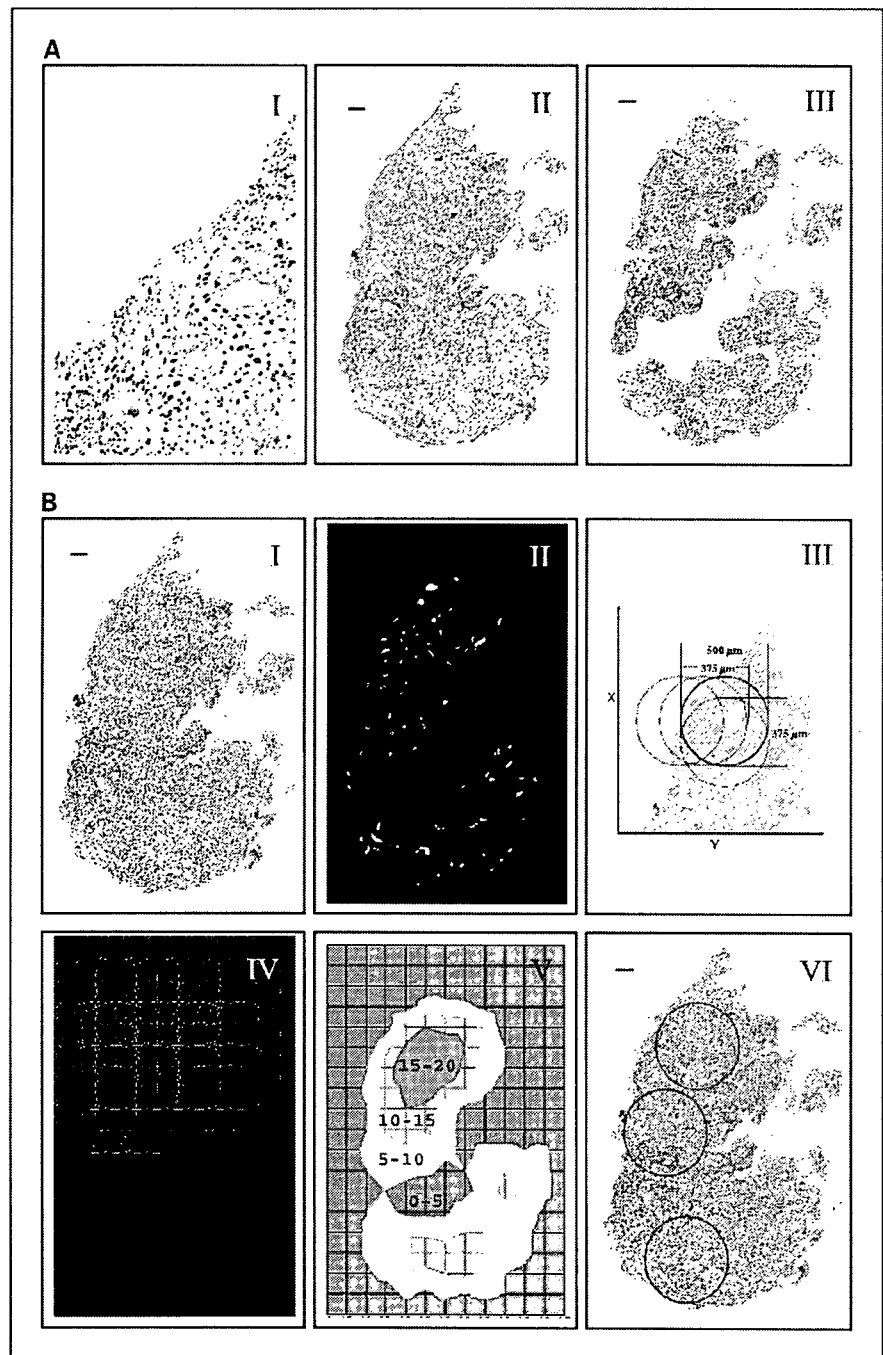
Fig. 1. *A*, image analysis of microvessels. *I*, the lumen of each microvessel was traced by an observer and counted by the computer. The TP was then calculated using the computer. *II*, the tumor region was outlined by the observer and the tumor area was calculated using the computer. *III*, the area of the tumor located >150 µm from the nearest vessel was calculated by the computer (*yellow area*) and then hypoxia ratio was calculated.

B, microvessel hotspot counted by computer. *I*, microvessels were labeled by an observer. Bar, 100 µm. *II*, labeled vessels were converted to binary images. *III*, the scanning circle is 500 µm in diameter and 0.196 mm² in area, which equals the area of a ·400 power field. The overlay of two neighboring circles is 375 µm. *IV*, the binary image was scanned. *V*, a schematic image of microvessel distribution derived from computer analysis.*VI*, areas with the highest microvessel number were identified as microvessel hotspots.

Statistical analysis. Correlations between different factors were assessed using Pearson's correlation coefficient. A Cox proportional hazard analysis was used to evaluate clinicopathologic and microvessel factors in the prediction of treatment outcome. Survival curves were generated using the Kaplan-Meier method and statistical differences between curves were calculated using the log-rank test. For evaluation of continuous variables in survival analysis, patients were divided into two groups based on an optimal cutoff derived from receiver operating characteristic analysis. GraphPad Prism software (GraphPad Software, San Diego, CA) was used for receiver operating characteristic analysis and Statistica (StatSoft, Tulsa, OK) was used for all other analysis.

Results

Treatment outcome. All 51 patients completed the concurrent chemoradiotherapy with a total radiation dose of 60 Gy. Seven patients (14%) received one additional course of chemotherapy, and 25 patients (49%), 2 patients (4%), and 2 patients (4%) received an additional two, three, and four courses, respectively. The median patient follow-up time was 32 months (range, 5.9-121.5 months). Thirty-nine patients (76%) achieved clinical complete remission and 12 patients (24%) achieved partial remission at primary site. Among the

Table 2. Correlation between different MVDs

	r	P
Observer 1 vs observer 2	0.514	0.0001
Observer 1 vs computer	0.579	<0.0001
Observer 2 vs computer	0.472	0.0005

39 with clinical complete remission at primary site, 12 patients developed recurrence in the primary area, 3 in a distant area (a different site in esophagus), and 4 had distant metastases during follow-up (3 in the liver and 1 in the lung). Up to January 1, 2005, 23 patients had died of esophageal cancer, 8 patients died of other disease or accidents, and the other 20 cases were alive at the last follow-up time point.

Image analysis of microvessels in biopsy specimens. Areas of inflammation, sclerotic tumor, and adjacent benign tissue were identified and excluded by observer when calculating the TA, which ranged from 0.99 to 3.37 mm^2, with a median of 1.92 mm^2. The TN varied from 3 to 204, with a median of 100. The TP ranged from 0.35 to 41.26 mm, with a median of 11.81 mm. Tumor hypoxic ratio ranged from 0.11% to 78.63%, with a median of 8.34%.

Comparison of manual MVD counting and computer-assisted MVD counting. The results of two manual MVD counts and the computer-assisted counts are shown in Table 2.

Although hotspot MVD counts for a given patient varied between different observers and the computer, analysis showed that they were correlated linearly (Table 2).

Receiver operating characteristic analysis. To evaluate the ability for the prediction of survival, we evaluated the accuracy of prediction of death of esophageal cancer at 2 years for each microvessel factor. This interval of 2 years was selected because most of the complete cases happened in this interval (19 in 23 cases) and only three patients (all of whom died of other diseases and were excluded from the receiver operating characteristic analysis) censored before the end of 2 years. The predictive power was estimated by calculating the area under receiver operating characteristic curves (11, 12). All factors, including TN/TA, TP/TA, and hypoxic ratios and observer-counted and computer-derived hotspot MVDs, were found to be predictors of 2-year survival (Table 3); the observer-counted MVD showed the weakest power in predicting death 2 years after treatment.

Univariate analysis of survival. Univariate Cox proportional hazard analysis was done to evaluate the relation between clinicopathologic factors and overall survival. The result is presented in Table 4. No clinicopathologic factor correlated with overall survival.

From the receiver operating characteristic curves, the optimal cutoffs for varied microvessel factors were determined to stratify patients into two groups, and univariate Cox proportional analysis revealed that patients with low TN/TA ($P = 0.023$) or low TP/TA ($P = 0.037$) had a higher risk of dying of esophageal cancer after chemoradiotherapy (Table 5). Patients with a low ratio of tumor hypoxic area tended to survive longer after treatment but this was not statistically significant ($P = 0.329$). The hotspot MVDs counted by the two observers had no relation with overall survival ($P = 0.203$ and 0.119, respectively) whereas hotspot MVDs counted by the computer showed a significant association with survival ($P = 0.036$).

Multivariate analysis for survival. In the multivariate Cox proportional hazard analysis, computer-derived hotspot MVD counts and the TN/TA and TP/TA ratios were analyzed combined with T and N stage, which showed the highest significance among clinicopathologic factors by univariate analysis. All three microvessel factors proved to be independent predictors for overall survival ($P = 0.019$ for hotspot MVD, $P = 0.018$ for TN/TA, and $P = 0.044$ for TP/TA; Table 6).

Kaplan-Meier survival analysis. Figure 2 shows the survival curves generated using the Kaplan-Meier method. Patients with high MVD and high TN/TA and TP/TA ratios had 5-year survival rates of 73%, 79%, and 73%, respectively, whereas the group of patients with low such factors had 5-year survival rates of 46%, 45%, and 41%, respectively. Log-rank test showed that these differences were statistically significant ($P = 0.025$ for hotspot MVD, $P = 0.008$ for TN/TA, $P = 0.031$ for TP/TA).

Because hotspot MVD count and the TN/TA and TP/TA ratios all proved to be predictive factors for the outcome of patients treated with chemoradiotherapy, we investigated whether combinations of these factors would provide more powerful and more precise predictors. Hotspot MVD showed a strongly positive correlation with TN/TA (Pearson test, $r = 0.843$, $P < 0.000001$) whereas TP/TA was independent of hotspot MVD ($r = 0.023$) and was relatively weakly correlated with TN/TA ($r = 0.318$, $P = 0.022$). We therefore selected the combinations of MVD and TP/TA, TN/TA and TP/TA ratios as new factors and investigated if they could

Table 3. Receiver operating characteristic curve analysis

Variable	Area under the curve	95% confidence interval	Best cutoff
Hotspot			
Computer	0.593	0.441-0.732	29
Observer 1	0.529	0.381-0.668	51
Observer 2	0.564	0.418-0.710	15
TN/TA	0.649	0.502-0.779	73.74
TP/TA	0.647	0.504-0.782	9.944
Hypoxic ratio	0.623	0.467-0.748	30.421%

Table 4. Univariate Cox proportional hazard analysis of relations between clinical and pathologic characteristics and overall survival

Variables	No. patients	Risk ratio (95% confidence interval)	P
Age (y)			
≦62	27		
>62	24	1.104 (0.491-2.511)	0.809
Performance state			
0	38		
1	13	1.038 (0.381-2.837)	0.946
Tumor location			
Upper and middle	36		
Lower	15	1.011 (0.423-2.455)	0.982
T stage			
T_2	10		
T_3	41	1.443 (0.589-3.514)	0.423
N stage			
N_0	20		
N_1	31	1.664 (0.682-4.077)	0.262
Histology type			
W/D and M/D	37		
P/D	14	1.273 (0.538-3.023)	0.584
Stage			
II	26		
III	25	1.233 (0.542-2.878)	0.625

predict survival of patients. The high hotspot MVD plus high TP/TA group included eight patients and the high TN/TA plus high TP/TA included 11 patients (including all the eight in the high MVD plus high TP/TA group). Surprisingly, none of the patients with both high MVD and high

TP/TA ratio died of esophageal cancer during follow-up and only one patient died of esophageal cancer in the high TN/TA plus high TP/TA group. The Kaplan-Meier survival curve of the high TN/TA plus high TP/TA group was presented in Fig. 3.

Table 5. Univariate Cox proportional hazard analysis of relations between microvessel characteristic and overall survival

Variables	No. patients	Risk ratio (95% confidence interval)	P
Hotspot MVD			
Computer			
<29	31		
≥29	20	2.892 (1.066-7.80)	0.036
Observer 1			
<51	38		
≥51	13	2.033 (0.679-6.002)	0.203
Observer 2			
<15	15		
≥15	36	2.024 (0.833-4.909)	0.119
TN/TA			
<73.741/mm²	35		
≥73.741/mm²	16	4.208 (1.252-14.208)	0.023
TP/TA			
<9.944 mm/mm²	28		
≥9.944 mm/mm²	23	2.617 (1.058-6.477)	0.037
Hypoxic ratio			
<30.421%	39		
≥30.421%	12	1.597 (0.623-4.093)	0.329

Table 6. Multivariate Cox proportional hazard analysis of relations between microvessel characteristic and overall survival

Variables	Risk ratio (95% confidence interval)	*P*
Model 1		
T stage	1.023 (0.402-2.552)	0.966
N stage	1.988 (0.813-4.903)	0.133
Hotspot MVD	3.233 (1.139-9.113)	0.019
Model 2		
T stage	1.074 (0.428-2.646)	0.877
N stage	1.784 (0.733-4.335)	0.214
TN/TA	4.263 (1.235-14.646)	0.018
Model 3		
T stage	1.214 (0.488-2.987)	0.674
N stage	1.653 (0.676-4.045)	0.271
TP/TA	3.591 (1.046-12.239)	0.044

Discussion

We previously reported that hotspot MVD and the TN/TA, TP/TA, and hypoxic ratios in biopsy specimen are prognostic factors for laryngeal cancer patients treated by radiotherapy (9). Here we found that, for patients with T_{2-3} esophageal cancers, hotspot MVD, TN/TA, and TP/TA were favorable predictors for overall survival. The combinations of hotspot MVD with TP/TA, or TN/TA with TP/TA, may provide more powerful predictors for predicting the outcome of such patients scheduled to undergo chemoradiotherapy.

It is likely that a low density of microvessels will lead to a decrease in oxygen transport and drug delivery into local tumor environments. Bhattacharya et al. (13) investigated avascular regions of human head and neck cancer xenografts and found that cells in these areas were hypoxic and chemotherapy resistant. Hypoxia-related factors, such as hypoxia-induced factor 1α and carbonic anhydrase IX, and hypoxic area imaging by pimonidazole or misonidazole binding have been discussed as prognostic factors for radiotherapy of cancers (14-17). Although there are substantial data implying that poorly vascularized tumors are resistant to chemotherapy and/or radiotherapy, no definitive conclusion has been drawn at present on the clinical usefulness of MVD as a marker for prognosis. There are some studies that did not show a relationship between MVD and survival (18, 19) and a reverse relationship between MVD and survival has been reported by some groups (20, 21).

These contradictory conclusions might be explained by the difficulty in evaluating MVD accurately. Manual hotspot MVD counting has been the predominant method for analysis. The observer first scans a section at low magnification (×10-×100). High angiogenesis areas can be recognized as hotspots and a higher magnification (×200-×400) is then selected to count the number of microvessels in these areas (22). All procedures, including screening hotspot area and counting vessels, are done subjectively and intraobserver or interobserver variability is almost inevitable. Our study presents one resolution of this

problem. Because pathologic section is converted into digitized image, the observer only needs to trace the outlines of the microvessels and the following work is all accomplished by the computer with minimum variability and perfect reproducibility. When two observers counted the microvessels of the same patients in our study using the manual hotspot counting method, the results differed and both failed to predict the survival of patients.

Using a computerized system to evaluate tumor microvessels has been reported by some groups (23-26). The present method has two novel features. The first is observer intervention in microvessel tracing. Although completely automated analysis will undoubtedly be developed, the nonspecific
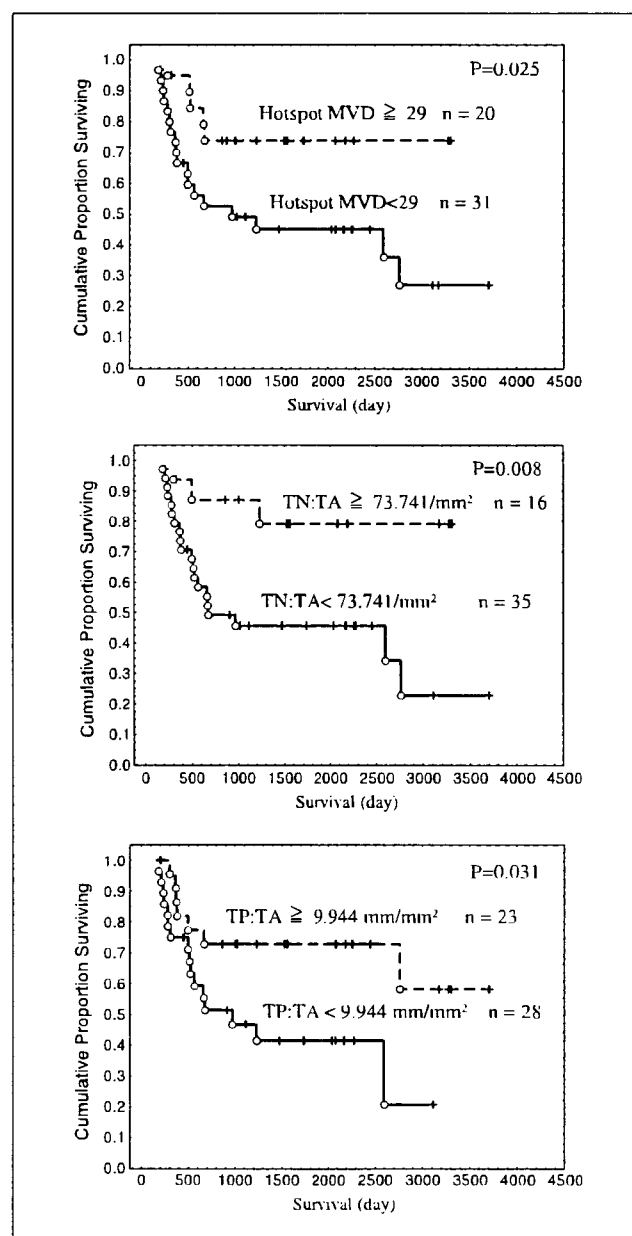
Fig. 2. Kaplan-Meier overall survival curves for patients with T_{2-3} M_0 esophageal cancer treated with chemoradiotherapy.
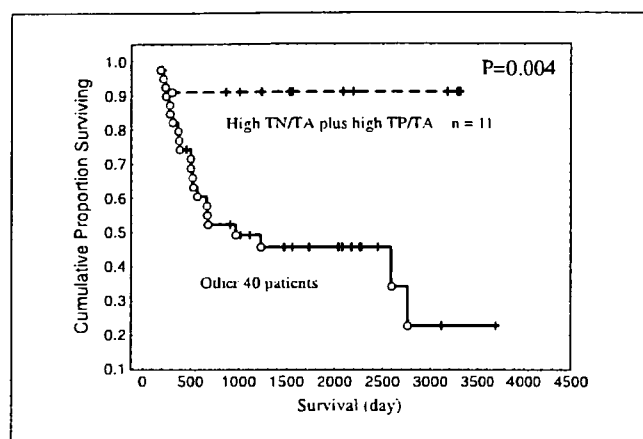
Fig. 3. Kaplan-Meier overall survival curves for patients with high TN/TA and high TP/TA.

staining and the varying threshold for positive endothelial staining are likely to comprise this. Manual tracing ensures the accuracy of microvessel recognition and therefore maintains a high specificity of this analysis. The second feature is the use of full section scanning to determine microvessel hotspots, which provides the most objective information on microvessel distribution within any biopsy sample.

The tumor hypoxic ratio counted by computer has been shown as a predictor for radiosensitivity (9). In the present study, there was a tendency for a low hypoxic ratio to show good patient prognosis, but this was not statistically significant. The predictive power of the hypoxic ratio for the outcome of chemoradiotherapy thus needs further investigation.

A surprising finding in our study is that in the group of patients with both high hotspot MVD and high TP/TA ratios, none died of esophageal cancer, and in the group with high TN/TA and TP/TA ratios, only one patient died of esophageal cancer during follow-up. Six of eight patients (75%) in the high hotspot MVD plus high TP/TA ratio group and 8 of 11 patients (73%) in the high TN/TA plus high TP/TA ratio

group survived longer than 3 years, compared with the average level of 45% (23 of 51) for all patients. These data suggested that well-vascularized tumor may be more sensitive to chemoradiotherapy.

The subjects of this study were patients who received definitive chemoradiotherapy. Because induction chemoradiotherapy before surgery is one of the most adopted multimodal treatments for esophageal cancer, whether the computer-assisted microvessel analysis is useful in predicting the outcome in these patients remains to be determined. After induction chemoradiotherapy, only 15% to 56% of patients achieved pathologic complete remission (27, 28). This method may be extremely helpful for treatment selection in residual disease after induction chemoradiotherapy. Similarly, the usefulness of this method in assessing treatment advantage of postoperative chemoradiotherapy is also an interesting topic needing further investigation.

Esophageal adenocarcinomas were not included in this study because most esophageal cancers in Japan (>90%) histologically are squamous cell carcinoma (29). However, in western countries, adenocarcinomas account for >60% of all esophageal cancers (5, 30). An independent study is needed to investigate whether microvessel analysis is suitable for adenocarcinoma when this method is expected to be used in these countries.

High MVD was reported to correlate with distant metastasis and short survival in solid tumors (31, 32). It should be noted that surgery was the main treatment modality in most of these prognosis analysis studies. For esophageal cancer, if it is proved that patients with a high MVD have short survival after surgery, chemoradiotherapy should then be more strongly recommended for these patients.

In conclusion, using a computer-assisted image analysis system for biopsy specimens, we found that hotspot MVD and the TN/TA and TP/TA ratios were powerful predictors for the outcome of patients with esophageal cancer treated with chemoradiotherapy. Compared with manual microvessel counting, this computer-assisted method produced lower variability and higher reproducibility for the evaluation of tumor vasculature.

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Release of band cells from the bone marrow is impaired by preoperative chemoradiation in patients with esophageal carcinoma: increased risk of postoperative pneumonia

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Abstract

Purpose To examine the difference in hematological data and postsurgical course after esophagectomy between patients receiving preoperative chemoradiation and patients without preoperative treatment.

Methods Twenty-two patients with squamous cell carcinoma of the esophagus who underwent esophagectomy during the past 2 years were retrospectively analyzed in the study. Six patients had preoperative chemoradiation (CRT group) and 16 patients had no preoperative treatment (non-CRT group). The hematological data, postoperative course, and surgical complications were compared between the two groups.

Results Patients in the CRT group were given cisplatin and 5-FU (143 and 6,000 mg on average, respectively) plus an average of 35 Gy of radiation. Although the neutrophil count did not show a significant difference between the two groups, the band cell count was lower in the CRT group compared with the non-CRT group on postoperative day 1 ($P<0.05$). Postoperative pneumonia was detected in three patients (50%) from the CRT group versus none of the non-CRT group.

Conclusion Preoperative CRT may be a risk factor for postoperative pneumonia in patients with esophageal carcinoma who undergo esophagectomy. The normal bone marrow response of releasing band cells from the post-

mitotic marrow pool after surgery could be disturbed by CRT, which might contribute to an increase in later pulmonary complications.

Introduction

Esophagectomy as a standard treatment in patients with local-regional esophageal carcinomas still remains [1]. In some surgical series, 5-year survival after esophagectomy exceeds 20% [2–5]. Ando et al. [2] showed the 5-year survival rate for all patients to be 40.0%, and the survival of patients undergoing surgery for advanced carcinoma (p stages IIa to IV) of the thoracic esophagus has improved during the past 15 years. The improvement of survival can be attributed to advances in surgical technique and perioperative management [2]. The others have added advances in preoperative staging and patient selection as the reason for the improvement in 5-year survival after esophagectomy [1, 6, 7]. In recent years, neoadjuvant chemoradiation (CRT) for esophageal carcinoma has become common to treat locally advanced cases. Slater et al. [8] reported that neoadjuvant CRT downstages esophageal carcinoma for T and N status and confers a significant survival advantage. Liao et al. [9] reported that local-regional control was better in clinical stage II or III esophageal cancer patients treated with concurrent CRT plus esophagectomy. Urschel and Vasan [1] reported that neoadjuvant CRT and surgery improved 3-year survival and reduced local-regional cancer recurrence compared with surgery alone. Moreover, Noguchi et al. [10] reported that CRT can create tumor regression and allows resection

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surgery in T4 esophageal carcinoma; this confers a survival advantage in T4 esophageal carcinoma. Long-term survival can be achieved in patients with esophageal carcinoma who undergo CRT and esophagectomy, and Lew et al. [11] asserted that recurrence is unlikely in patients who survive for 3 years or longer after undergoing this multimodality treatment.

On the other hand, operative risk is reportedly increased in patients receiving neoadjuvant CRT prior to esophagectomy [1, 8, 12–15]. Others also reported that preoperative CRT is an associated risk for pulmonary complications after esophagectomy, but the reasons for this risk are unclear [16–20]. We hypothesized that preoperative CRT might impair the normal bone marrow stimulation, which is an important immunological response, against major surgery such as esophagectomy, and this could lead to postoperative complications. In this study, we compared the postoperative course and hematological data between patients receiving preoperative CRT and patients without preoperative treatment focusing on neutrophil differentiation as a marker for bone marrow stimulation [21–23].

Methods

Subjects

We have retrospectively analyzed all 22 patients with squamous cell carcinoma of the middle or lower thoracic esophagus who underwent esophagectomy with two-field (mediastinal and abdominal) lymph nodes dissection and intrathoracic esophagogastric anastomosis during the past 2 years in Mito Red Cross Hospital (Ibaraki, Japan). The patients were examined by CT, upper gastrointestinal endoscopy, and barium swallowing study before treatment. All the patients with local advanced esophageal carcinomas, having possible invasion to near organs (T4 suspected), were recommended preoperative CRT during the study period. If the lesion did not downstage to T3, we did not perform esophagectomy. We analyzed all the data during the study period in the study (6 patients in CRT group vs 16 patients in non-CRT group).

Protocol for CRT

Our protocol for preoperative CRT was as follows. On the first course of CRT, patients were given cisplatin (20 mg/m2) and 5-FU (700 mg/m2) for 5 days and concurrent radiation of 30 Gy (2 Gy/day × 15 days) in the "long-T field" including the cervical and mediastinal lymph nodes. The radiation field is shown in Fig. 1. The patients were examined by CT, upper gastrointestinal endoscopy, and barium swallowing study after the first course of CRT. If patients obtained enough

reduction of tumor and downstaging of carcinoma from T4 to T3 after the first course of CRT, esophagectomy was recommended without a second course of CRT. If the response after the first course was partial and not enough, the second course of CRT was recommended. If there was no response or progressive disease after the first course, the second course of CRT was not recommended. After 20 Gy in the second course, lesion was evaluated. If patients could not obtain downstaging to T3, 10 Gy was added (total 60 Gy). If the lesion did not downstage to T3 even after 60 Gy, esophagectomy was not performed.

Postoperative evaluation

Esophagectomy was planned to be performed approximately 6 weeks after the completion of CRT after clinical restaging. The white blood cell (WBC) count, neutrophil differentiation, and biochemical data were compared between the two groups before and after surgery. The postoperative course and surgical complications were also compared between the two groups.

Fig. 1 A planning radiograph demonstrating the radiation filed for one of the patients in the CRT group

Statistical analysis

All values are expressed as mean±standard error of mean (SEM). Analysis of variance (ANOVA) for repeated measures were used for continuous data. Results in operating time and intraoperative blood loss were analyzed using paired or two-sample t test. Statistical significance was defined as a P value of less than 0.05.

Results

Patients

Table 1 shows the study population of the CRT group and the non-CRT group. In the 16 patients of the non-CRT group, 7 patients were at stage III, 3 patients at stage II, 5 patients at stage I, and 1 patient at stage 0. On the other hand, in the 6 patients of CRT group, 1 patient was histologically diagnosed at stage III, 2 patients at stage II, 1 patient at stage I, and 2 patients at stage 0 after CRT, which had statistically no difference with the non-CRT group. One patient in the non-CRT group had pulmonary emphysema. Four patients in the non-CRT group and two patients in the CRT group had hypertension. There was no difference in the tumor location between the CRT group and the non-CRT group, and all the patients were treated with the same surgical procedure with a similar operative technique by the same operator (Table 1).

Chemoradiation

The CRT group (mean age, 64.8 years) and the non-CRT group (mean age, 65.0 years) did not show any differences with respect to age, sex ratio, smoking history, and preoperative respiratory function. Patients in the CRT group were given cisplatin and 5-FU (143 and 6,000 mg on average, respectively) plus an average of 35 Gy of radiation ("long-T field" including the cervical and mediastinal lymph nodes shown in Fig. 1). The mean interval between the last day of radiotherapy and the operation was 40.8 days. Table 2 shows the detailed information of the patients in the CRT group.

Operating time and intraoperative blood loss

The operating time was 512.7±46.9 min in the CRT group and 431.6±33.4 min in the CRT group (Table 1). The intraoperative blood loss was 595.0±123.9 g in the CRT group and 376.3±51.4 g in the CRT group (Table 1). The CRT group and the non-CRT group did not show significant differences in operating time (P=0.12) and intraoperative blood loss (P=0.08).

Hematological data

The preoperative WBC counts did not show a significant difference between the two groups ($6.3 \pm 0.4 \times 10^9$/L in the CRT group vs $5.1 \pm 0.5 \times 10^9$/L in the non-CRT group). After surgery, the WBC counts also did not show any difference between the groups until postoperative day (POD) 7. Figure 2 shows C-reactive protein (CRP) value in the two groups. There was a trend that CRP was higher in the CRT group than in the non-CRT group (P=0.06 on POD1 and P=0.08 on POD5; Fig. 2). Figure 3 shows the neutrophil counts in the two groups. Contrary to CRP, the neutrophil ounts tended to be lower in the CRT group than in the non-CRT group before surgery (2.9×10^9/L in the CRT group vs 4.3×10^9/L in the non-CRT group, P=0.15; Fig. 3) but did not change after surgery (Fig. 3). Lymphocyte counts did not show a difference between the two groups during the study period (data not shown). Regarding neutrophil differentiation, Fig. 4 shows band cell counts in the two groups. The band cell counts were significantly lower in the CRT group compared with the non-CRT group on POD1 ($4.2 \pm 1.7 \times 10^8$/L in the CRT group vs $13.8 \pm 3.3 \times 10^8$/L in the non-CRT group, P<0.05; Fig. 4). The band cell counts on POD2 tended to be lower in the CRT group than in the non-CRT group ($3.5 \pm 0.9 \times 10^8$/L in the CRT group vs $10.3 \pm 2.5 \times 10^8$/L in the non-CRT group, P=0.07; Fig. 4).

Postsurgical course

Adhesion between the lung and pleura was found in 50% (8 cases in 16 cases) of the non-CRT group and 100% (6 cases in 6 cases) of the CRT group. Postoperative pneumonia was detected in 3 patients (3 cases in 6 cases, 50%) from the CRT group versus none of the non-CRT group (none in 16

Table 1 The study population of the CRT group and the non-CRT group

Group	Number	Age (years)	Location		Tumor size (cm)	T factor			Stage				Operation time (min)	Blood loss (g)
			Mt	Lt		T3	T2	T1	III	II	I	0		
CRT	6	64.8±2.1	5	1	6.1±0.7	2	1	3	1	2	1	2	512±47	595±123
Non-CRT	16	65.0±1.8	12	4	5.4±0.3	8	2	6	7	3	5	1	432±33	376±51

Mt middle thoracic, *Lt* lower thoracic

Table 2 The patients in the CRT group

Age	Sex	CRT course	Radiation (Gy)	Extubation (POD)	Postoperative pneumonia	Interval[a] (days)	Stage	
							Before	After
66	f	1	30	11	+	45	III	I
63	m	1	30	10	+	41	III	III
57	m	1	30	6	–	38	III	0
65	m	2	60	4	–	44	III	0
73	m	1	30	11	+	37	III	II
65	m	1	30	15	–	40	III	II

[a] The interval between the end of radiation and the operation

cases, 0%, $P<0.01$ compared to the CRT group), which was diagnosed by chest x-rays film and bacteriological examination of expectoration. By the bacteriological examinations of pneumonia patients, *Staphyrococcus aureus* were found in two patients and *Pseudomonas aeruginosa* was found in one patient. The chest radiographs showed air bronchograms and infiltrating shadow in lung fields with these three patients. We treated the patients using bronchoscopy to aspirate sputum and by antibiotics; all three patients eventually recovered in 3 weeks. All the patients after esophagectomy were treated in ICU until the next day of the extubation. The time until the extubation and the artificial respiration period was significantly longer in the CRT group than in the non-CRT group ($P<0.01$). No anastomotic leakage or other major complication occurred in either group.

Discussion

The preoperative CRT is a risk factor for pulmonary complications after esophagectomy, but this reason is still unclear [16–20]. Our hypothesis was that preoperative CRT might impair the normal bone marrow stimulation, which is an important immunological response. We have focused on the increase in circulating band cells as a marker for bone marrow stimulation [21–23]. Our results show that the band

cell count was significantly lower in the CRT group compared with the non-CRT group on POD1 ($P<0.05$; Fig. 4). This means that the normal bone marrow response of releasing band cells from the postmitotic marrow pool after surgery might be disturbed by CRT or the postmitotic marrow pool itself might be reduced by CRT. Figure 5 shows the band cell counts on POD1 and the number of days until extubation, which may represent pulmonary complication. The correlation between these two parameters was not significant, possibly due to the low case numbers. In three patients with pneumonia, the band cell counts on POD1 tended to be lower than that in patients without pneumonia ($P=0.057$; Fig. 5).

The interval between the last day of radiotherapy and the operation was 40.8 days in the study. This may be an important factor in the recovery of the bone marrow function after CRT, and 40.8 days was equivalent to that in Kelly et al. [24], Lee et al. [18], or Noguchi et al. [10] (4–6 weeks) and close to that in Liao et al. (6–8 weeks) [9]. Surgery was performed 2–4 weeks after neoadjuvant chemotherapy for esophageal carcinoma, but at least 4 weeks is needed after CRT [8]. Our data suggest that normal marrow response to esophagectomy is impaired even after 40 days from the completion of CRT. This marrow response could not be predicted until surgery was performed because preoperative WBC counts and neutro-
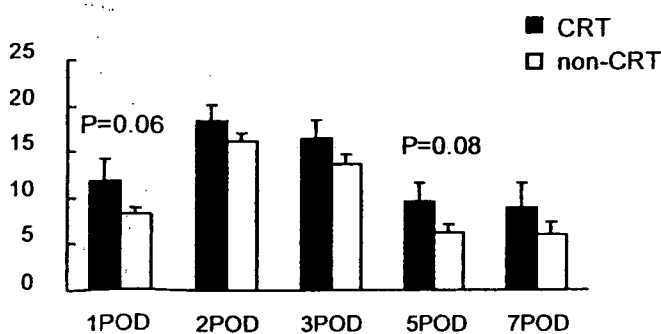

Fig. 2 The CRP value in the CRT group and in the non-CRT group. There was a trend that CRP was higher in the CRT group than in the non-CRT group ($P=0.06$ on POD1 and $P=0.08$ on POD5)
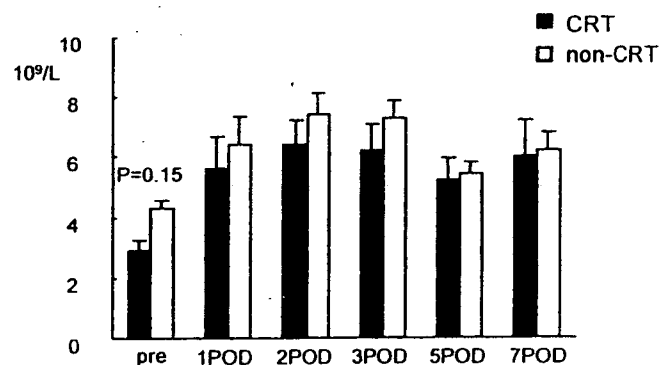

Fig. 3 The neutrophil counts in the CRT group and in the non-CRT group. The neutrophil counts tended to be less in the CRT group than in the non-CRT group ($P=0.15$ on POD1)
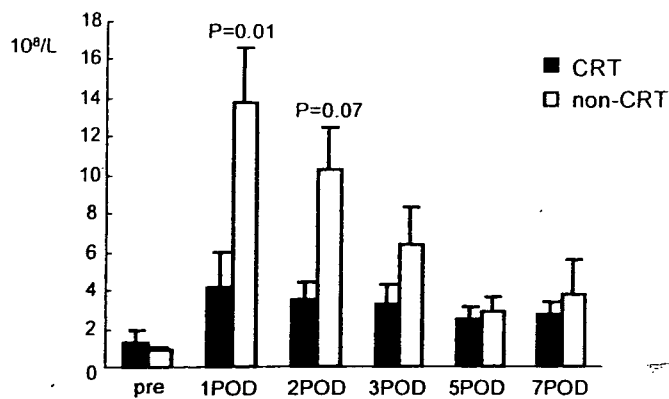
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Fig. 4 The band cell counts in the CRT group and in the non-CRT group. The band cell counts were significantly lower in the CRT group compared with the non-CRT group on POD1 ($P<0.05$). The band cell counts on POD2 tended to be lower in the CRT group than in the non-CRT group ($P=0.07$)
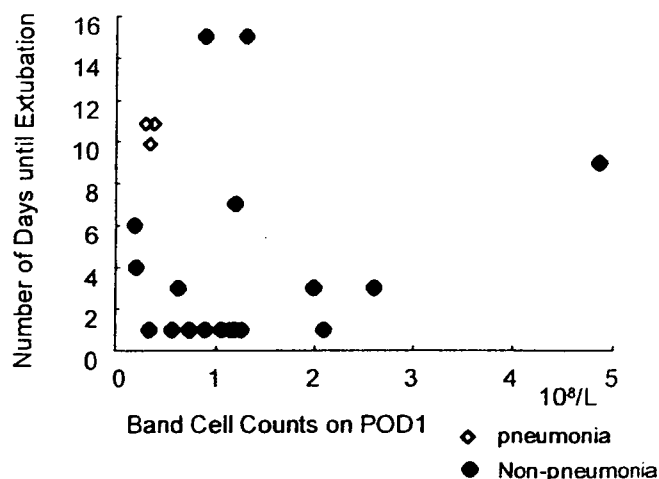

Fig. 5 The band cell counts on POD1 and the number of days until extubation. In three patients with pneumonia, band cell counts on POD1 tended to be lower

phil counts (Fig. 3) did not show a significant difference between CRT and non-CRT groups.

The radiation field in the study was "long-T," including the cervical and mediastinal lymph nodes, which is a broader range of the study compared to Kelly et al. [24], Lee et al. [18], or Liao et al. [9], and even to Noguchi et al. [10]. The release of band cells from the bone marrow may be impaired, and there was a higher rate of postoperative pneumonia (3 cases in 6 cases, 50%) compared to the CRT group (0 case in 16 cases, 0%). Lee et al. have [18] reported that pulmonary complications were noted more often (35% vs 8%) when the pulmonary percentage receiving at least 10 Gy was ≥40% versus <40% of total lung volume. They also found that none of the other factors analyzed (surgical procedure, tumor location, use of induction chemotherapy, or smoking history) was associated with the occurrence of pulmonary complications after CRT [18]. The field might differ between neoadjuvant CRT and definitive CRT plus salvage surgery. A definitive CRT needs to include regional lymph nodes according to lymph nodes metastasis as for the radiation field, but neoadjuvant CRT can reduce it as long as it includes the site needed that is downstaging before surgery. In the study, the radiation field was "long-T," which is common in Japan for the middle portion of the thoracic esophageal carcinoma (Fig. 1), but it might be a reason for the high incidence of postoperative pneumonia in the CRT group. Radiotherapy techniques that decrease the volume of the lung receiving low radiation doses may significantly reduce the risk of pulmonary complications [18].

Bosset et al. [25] reported a higher postoperative mortality in patients given multimodality therapy compared to those given surgery alone (17% compared to 5%). Adelstein et al. [26] reported an 18% postoperative mortality in their phase II study of preoperative concurrent chemoradiotherapy for esophageal carcinoma (12 of 67

patients died). Noguchi et al. [10] also reported a higher postoperative mortality rate (20.8%; 5 of 24) in patients given preoperative CRT. Preoperative CRT improves local tumor control compared to preoperative CTx alone, but it is associated with substantial perioperative mortality and morbidity [15].

There are several factors that increase the risk of postoperative pneumonia after neoadjuvant CRT. The first factor might be intrathoracic adhesion and the decrease in pulmonary compliance caused by radiotherapy, which could disturb the secretion discharge from the lung in cases complicated by pulmonary disease. The second factor could be due to a selection bias in the cases that are mostly T4 in the CRT group, and they might already have immunological dysfunction for some other reason, possible systemic metastasis, or so on. Another factor is suspected from our results in the study that show that the normal bone marrow response of releasing band cells from the postmitotic marrow pool was impaired by CRT just after surgery (until POD1 or POD2), and this might lead to later occurrence of pulmonary complications. This is also supported by the facts observed in this study that CRP tended to be higher in the CRT group than in the non-CRT group (Fig. 2); on the other hand, neutrophil counts tended to be lower in the CRT group than in the non-CRT group, although it was not statistically significant (Fig. 3). Heidecke et al. [14] reported that T lymphocytes from patients having undergone CRT exhibited a significantly reduced proliferative response following stimulation in vitro. However, our results in the study show that lymphocyte counts did not differ between CRT and non-CRT groups during the study period.

The bone marrow is the site of proliferation, terminal differentiation, and maturation of neutrophilic granulocytes. Inflammatory stimuli increase the rate of neutrophil

production from the precursors in the bone marrow, shorten their maturation time, decrease the time neutrophils residing in the marrow, and cause immature neutrophils to enter the circulation [27]. We usually observe an increase in the number of circulating band cells as bone marrow stimulation after major surgery. However, our results suggest that the marrow response to release band cells into the circulation was disturbed by CRT.

In conclusion, preoperative CRT might be a risk factor for postoperative pneumonia in patients with esophageal carcinoma undergoing esophagectomy. The normal bone marrow response after esophagectomy could be impaired by CRT, which might contribute to an increase of later pulmonary complications.

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大動脈浸潤食道癌の集学的治療中に発症した大動脈食道瘻に対して予防的大動脈ステントグラフトが有用であった1例

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田中　慶太*2　成瀬　好洋*　　竹井　亮二*3

はじめに

高度進行食道癌に対する化学放射線療法 (chemoradiotherapy, 以下 CRT) は有用な治療法である反面, 照射量の増加とともに遅延性胸水や肺臓炎, 心不全, 心嚢水などの合併症が増加することも報告されてきている。そのなかでも致死的な合併症の一つとして食道大動脈瘻 (aortoesophageal fistula, 以下 AEF) がある。我々は治療の過程で AEF が予見された症例に対して, 大動脈ステントグラフト (aortic stent graft, 以下 ASG) を留置することで AEF を回避しえた症例を経験したので報告する。

I. 症例供覧

患　者：54歳, 男性
主　訴：嚥下困難
既往症：慢性副鼻腔炎
アルコール暦：ワイン½〜1本/日
喫煙歴：なし
家族歴：特記すべきことなし。
現病歴：上記主訴で近医を受診し精査施行し

た。胸部上部中部食道癌と診断され, 精査加療目的で当院を紹介された。

入院時現症：身長 162 cm, 体重 57 kg。頸部に表在リンパ節は触れなかった。腹部は平坦かつ軟で腫瘤を触知しなかった。嗄声もなかった。

入院時検査所見：白血球 5,200 /μl, 赤血球 346×10⁴/μl, Ht 34.3%, Hb 11.7 /dl, CEA 1.3μg/l, SCC 4.5 ng/ml。貧血と SCC の上昇以外, 有意な異常は認められなかった。

上部消化管内視鏡：門歯より 32〜37 cm に潰瘍を伴う易出血性の隆起性病変が認められ, 3 型食道癌と診断した (図 1a, b)。

生検では moderately differentiated squamous cell carcinoma が認められた。

超音波内視鏡：門歯より 33 cm で狭窄のためスコープは通過しない。可視範囲では大動脈および左気管支との可動性は消失し, 大動脈浸潤と判断した。また, 上縦隔リンパ節転移も認められた (図 1c)。

気管支鏡：気管膜様部は外部より圧排され, 呼吸性移動は消失していることから気管浸潤が疑われた。洗浄細胞診では class Ⅲ であった (図 1d)。

上部消化管造影：胸部中部食道を中心に病変長 10 cm の深い潰瘍を伴う隆起性病変が認められた。軸変異を伴うことから T4 が疑われた (図 2a)。

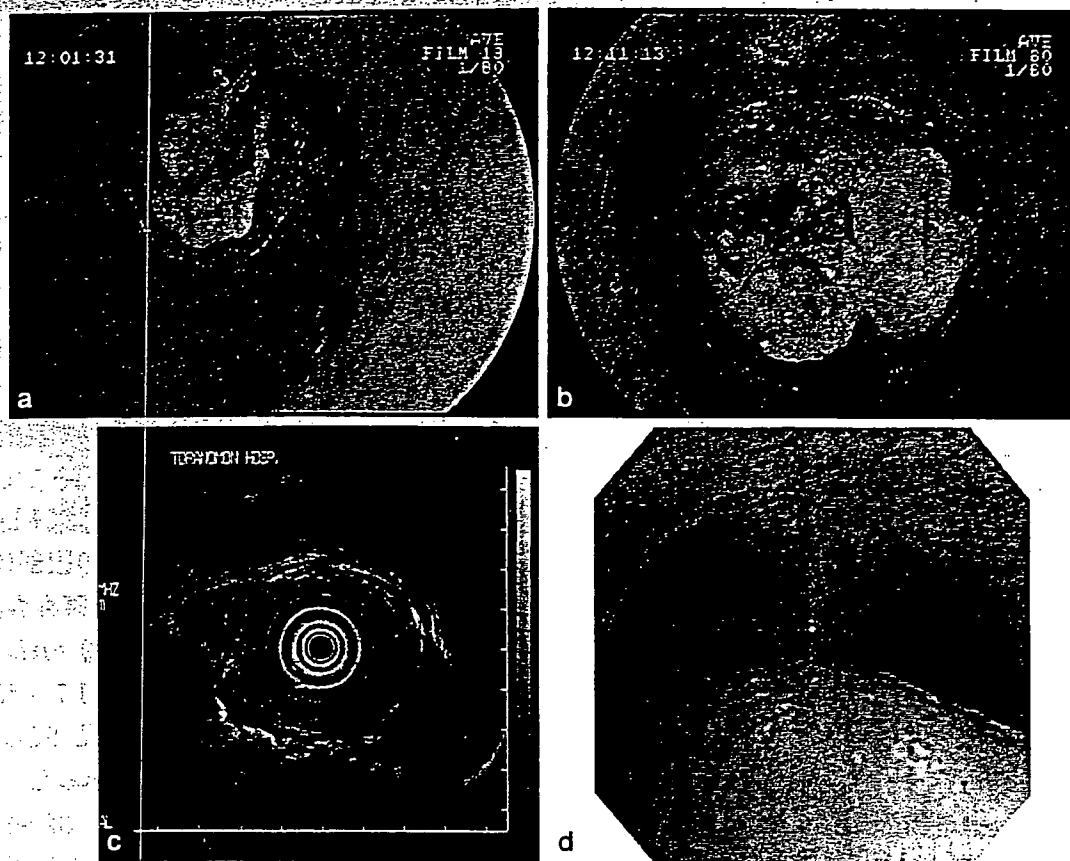胸部造影 CT：胸部上部食道から胸部中部食道にかけて全周性に食道壁の肥厚が認められた。腫瘍が胸部大動脈には 1/3 周以上接しており, 大動脈と腫瘍の間に介在組織の消失がある

図 1
a) b) 入院時上部消化管内視鏡所見
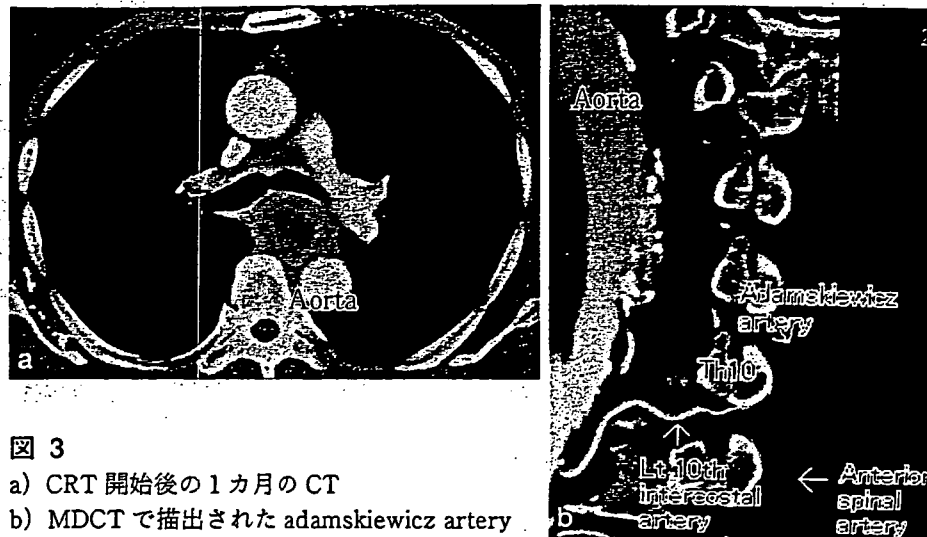c) 同，上部消化管超音波内視鏡所見
d) 同，気管支鏡所見

図 2
a) 入院時上部消化管造影
b) 同，CT

図 3
a) CRT 開始後の 1 カ月の CT
b) MDCT で描出された adamskiewicz artery

ことから大動脈浸潤と判断した。また左主気管支への直接浸潤も疑われた（図 2b）。

　頸部超音波検査所見：No.101，106recR のリンパ節に転移が認められた。

　臨床病期：cT4（Ao Tr）N2M0　Stage IV a

1. 治療方針

　大動脈および左主気管支への浸潤を伴う食道癌と判断し，CRT の方針とした。この状況でCRT を施行すれば腫瘍壊死に伴う致死的な食道大動脈瘻の危険性があり，CRT と並行して，ASG 留置を施行する方針とした。治療方針に関しては，本人と家族に十分な説明を行ったうえで同意を得てから開始した。

2. 治療内容

　照射は根治照射とし，照射範囲はリンパ節転移領域に対して両鎖骨上から腹部までの前後対向 2 門 T 字照射で 34Gy，さらに主病巣への斜入照射 28Gy を追加し，総線量は 62Gy とした。CRT と併用する化学療法のレジメンは low-dose FP 療法（5-FU 200 mg/m² day1-5/week. Cisplatin 4 mg/m² day1-5/week）とし，照射スケジュールと合わせて月曜から金曜日までの 5 日投与の 2 日休薬のサイクルで 6 週間の投与を開始した。CRT 開始後 1 カ月，総線量 34Gy の時点で治療効果判定を行ったところ，SD で

あった。効果判定には RECIST 基準（Response Evaluation Criteria in Solid Tumor）を用いた[1]。

　結果として治療効果はあるものの，腫瘍が壊死した部位と大動脈壁との距離が近接し，AEF 発症のリスクが高くなったため（図 3a），CRT を一時休止したうえで ASG を留置する方針とした。また，少量の吐血が認められるようになり，食道大動脈瘻前兆としての Sentinel bleeding の可能性が考えられた。縦隔造影 CT（MDCT）で ASG を留置する部位の Aorta 径と病変長を計測し，さらに前脊髄動脈に血流を供給する adamskiewicz artery を同定し，ステント留置予定部位の下端から 4 cm 頭側に離れていることを確認した（図 3b）。

3. 手術所見

　事前に清潔操作下でステントグラフトを作製した。Z ステント（Cook self-expanding Gianturco Z-stent 3 連 30×75 mm）に Ube woven graft（28 mm）を 5-0 タイクロンを用いてステントに縫着した。これを 2 個作製し，グラフト留置用のシースの中に収納した。全身麻酔下に仰臥位で右鼠径部に約 5 cm の皮膚切開をおき，右外長骨動脈を露出し，テーピングを行った。触診上，動脈硬化は認められなかった。
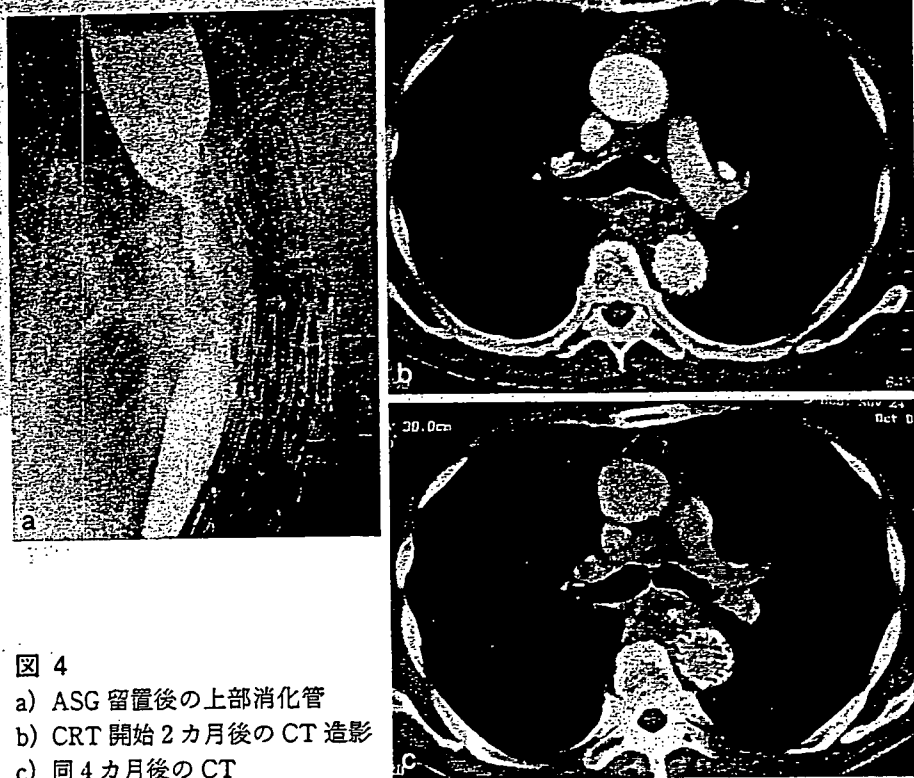
　ヘパリン 5,000 単位を静注後，右外長骨動脈の遠位側をクランプし，右外長骨動脈にシース

図 4
a) ASG 留置後の上部消化管
b) CRT 開始 2 カ月後の CT 造影
c) 同 4 カ月後の CT

を挿入して下行大動脈に誘導した。ステントグラフトの下端が Th10 の下端となるように 1 個留置した。さらに 1 個目のグラフトの頭側 1/3 と重なるように 2 個目のステントを留置した（図 4a）。その後大動脈造影を行って留置部位に問題ないことを確認した。シースを抜去して右外長骨動脈の近位側を遮断し，5-0 サージロンで縫合閉鎖し，右足背動脈の拍動を確認して手術終了とした。

4. 術後経過

ASG 留置後は数日間の高熱が認められたものの，脊髄麻痺などの問題は認められなかった。炎症反応の回復を待ったうえで CRT を再開した。化療のレジメンを DCF 療法（5-FU 500 mg/m² day1-5, Docetaxel 60 mg/m² day2, Cisplatin 50 mg/m² day2, 4 週 1 クール）療法に変更し，その後 CRT は完遂し，治療効果判定は PR であった。治療により腫瘍は縮小したが，大動脈ステントにより AEF は発症しな

かった。CRT 開始後 2 カ月と 4 カ月後の写真を示す（図 4b，c）。治療開始後 4 カ月まで再発は認められず，経口摂取も可能であった。

その後食道気管支瘻および食道縦隔瘻を形成したため食道バイパス術（胸骨後挙上胃再建，頸部食道胃吻合，残置食道・胃上部チューブ外瘻，腸瘻造設）を施行して，再び経口摂取可能となり治療開始 6 カ月で退院となった。その後肺炎による呼吸不全となり，治療開始 8 カ月で永眠された。治療後の剖検では食道癌局所再発，原発巣周囲のリンパ節再発，腫瘍壊死に伴う食道気管瘻が認められた（図 5a，b）。大動脈壁は壊死により脱落し，近傍には壊死に伴う膿瘍が認められた（図 5c，d）。しかし，炎症性細胞はほとんど認められず，感染による膿瘍とは判断できなかった。結果として瘻孔形成による大動脈穿孔を免れた状態であり，ASG の有用性が証明された。
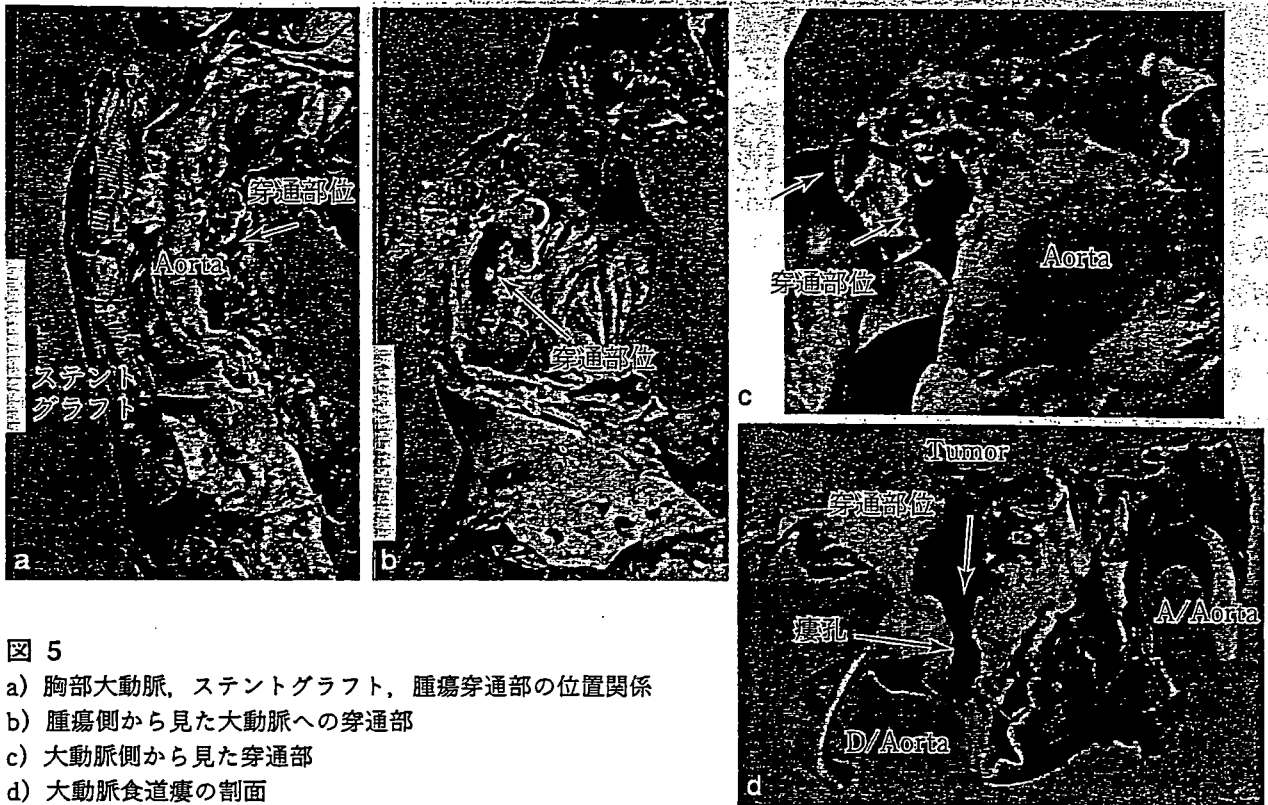
図 5
a) 胸部大動脈，ステントグラフト，腫瘍穿通部の位置関係
b) 腫瘍側から見た大動脈への穿通部
c) 大動脈側から見た穿通部
d) 大動脈食道瘻の割面

II. 考　察

　CRT は放射線単独治療と比較すると，抗癌剤の放射線増感作用により，病変局所のコントロールという点で優れた治療成績が示され[2]，現在では進行食道癌に対する治療の一選択肢となっている。併用する抗癌剤は CDDP/5FU が主に用いられ[1]，放射線の総線量は 50～60Gy との報告が多い[4][5]。しかし，従来の化学療法や放射線単独治療と比較すると血液毒性，粘膜障害，潰瘍形成，壊死，穿孔などの点で強いといわれている[6]。とくに大動脈浸潤のある食道癌への CRT 治療過程において，腫瘍壊死から動脈壁の破綻を生じて出血を引き起こす大動脈食道瘻は致死的な合併症である[7]。今回我々は予防的に ASG を留置することでその合併症を回避し，CRT を完遂することが可能であった。元来 ASG は大動脈瘤の治療に使用されてきたが[8]，近年では動脈硬化による大動脈潰瘍の治療や，大動脈浸潤食道癌に対する術前 CRT に

おいて AEF 予防目的で留置する方法も報告されている[9]。

　ASG 留置前に把握しておかねばならないことは以下の 3 点である。① ASG 留置部位の Aorta 径，②留置する ASG の長さ，③ adamskiewicz artery の走行である。③については ASG 留置により adamskiewicz artery が閉塞した場合，脊髄麻痺が発症するリスクがあるため，当院では縦隔造影 CT を用いてその走行を把握するようにしている。また，ASG はキットとしての取り扱いはないため，事前に自分達で準備，作製する必要がある。挿入するステントは Cook self-expanding Gianturco Z-stent を使用し，これらを①清潔操作下に Ube woven Graft をステント周囲に体外で縫着，②全身麻酔下に右鼠径部から右腸骨動脈を露出して切開し，シースを用いてステントを誘導して大動脈内に留置，といった手順となる。挿入にはデリケートなカテーテル操作や適切な部位にステントを留置する技術，血管の cut down などの技術が必要とされるため，血管外科および放射線