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Risk Factors for Residual Tumors in Surgery Following Neoadjuvant Chemotherapy for Esophageal Cancer

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Neoadjuvant chemotherapy (NAC) followed by esophagectomy is considered the standard treatment for resectable advanced esophageal squamous cell carcinoma in Japan. The purpose of this study was to identify the risk factors for residual tumors in surgery following NAC. We herein described risk factors for residual tumors in surgery following neoadjuvant chemotherapy for thoracic esophageal cancer. We reviewed the medical records of patients in our institution selected by using the following criteria: (1) pathologically confirmed squamous cell carcinoma or adenosquamous carcinoma before treatment; (2) cT1 to cT3; and (3) receipt of thoracotomy performed between 2007 and 2010 with the intention of curative resection after NAC composed of 5-fluorouracil plus cisplatin. The patients were divided into the complete resection group (R0 group), and the macroscopic or microscopic residual tumor group [R(+) group]. A total of 88 patients were eligible (R0, 70 patients; R1, 9 patients; R2, 7 patients; and not resected, 2 patients). There were more cT3 cancers and clinical node-positive diseases in the R(+) group than in the R0 group. Multivariate analysis identified tumor depth (cT3) and tumor location (above the carina) as risk factors for residual tumor. Patients with cT3 esophageal cancer above the carina have a high risk of residual tumor in esophagectomy following NAC. In these patients, more intensive preoperative therapy will be required.

Key words: Esophageal cancer – Neoadjuvant chemotherapy – Residual tumor – Risk factor – Tumor location

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The radical treatment options for resectable advanced esophageal squamous cell carcinoma are esophagectomy and definitive chemoradiotherapy.[1] In Japan, esophagectomy with neoadjuvant chemotherapy (NAC) has been used as the standard treatment of clinical stage II or stage III (except for cT4) esophageal squamous cell carcinoma [TNM staging system of the Union for International Cancer Control (UICC), version 6 (Sobin and Wittekind[2])] since the completion of the JCOG9907 study.[3,4] Our hospital also has employed NAC as the standard treatment for the aforementioned malignancies since 2007, as well as for cervical lymph node metastases and for squamous cell carcinomas located primarily within the abdominal esophagus (Ae), because the previously mentioned combined therapy may be effective. In Japan, NAC with 5-fluorouracil (5-FU) and cisplatin (CDDP) was approved as the standard treatment for these diseases, but the overall 5-year survival rate was 55%,[4] suggesting that a more effective treatment regimen was needed.

It is well known that the factors determining the prognosis of esophageal cancer resection are residual tumor classification (R classification), tumor depth, the presence or absence of lymph node metastases, preoperative and/or postoperative adjuvant chemotherapy, and histology.[5–8] Furthermore, it has been proven that NAC decreases the local residual tumor rate and improves local tumor control.[3,8–10]

This study aimed to clarify the relationship between clinicopathologic background factors and R classification in patients with esophageal squamous cell carcinoma who underwent cancer resection after NAC based on a review of their medical records.

Patients and Methods

Of the patients with esophageal cancer who were treated in Shizuoka Cancer Center, we included in the study: (1) those with thoracic and abdominal esophageal cancer; (2) those with pathologically confirmed squamous cell carcinoma or adenosquamous carcinoma based on pretreatment biopsy; (3) those with cT1 to cT3, cN0 to cN3, cM0, or cM1 lesions because of metastasis to the cervical lymph nodes [based on TNM staging system of the UICC, version 7 (Sobin *et al*[11])]; and (4) those who underwent esophagectomy after NAC with 5-FU and CDDP. Their background factors were identified in their medical records and retrospectively compared. NAC was performed as the standard treatment in accordance with the method used in the JCOG9907 study, namely, a course of 5-FU 800 mg/m^2 (from days 1–5, continuous infusion for 120 hours) and CDDP 80 mg/m^2 (day 1) every 3 weeks.[4]

The extent of disease was evaluated by using upper gastrointestinal endoscopy, contrast examination of the gastrointestinal tract, contrast computed tomography (the neck to the abdomen), fludeoxyglucose–positron emission tomography, and neck ultrasound before starting treatment. Preoperative clinical staging was evaluated on the basis of the various clinical laboratory test findings after discussion with an endoscopist, diagnostic imaging specialist, gastroenterologist, and digestive surgeon.

The tumor staging was described according to the TNM staging system of the UICC, version 7.[11] The resected specimens were pathologically evaluated in accordance with the General Rules for the Esophageal Cancer Study, version 10.[12,13]

The patients in this study were divided into the R0 group (no residual tumor), the R1 group (microscopic residual tumor), the R2 group (macroscopic residual tumor), and the nonresection group (resection was decided against because of the diagnosis of an unresectable tumor after opening the chest) according to the R classification, and the last 3 groups were combined to create the R(+) group.

The effects of NAC were classified using RECIST version 1.0, and the primary focus was classified as an unmeasurable lesion in accordance with the General Rules for the Esophageal Cancer Study (version 10).[12,13]

Statistical analysis was performed by using IBM SPSS statistics version 19 (SPSS Inc, an IBM company, Chicago, Illinois). Continuous and categoric data were analyzed by using Fisher exact test and Mann-Whitney *U* test, respectively. A P value <0.05 indicated a significant difference. The predictive factors for residual tumor were identified and analyzed by using logistic regression analysis when R(+) was used as the criterion variable.

Results

A total of 88 patients were included in this study. Of these patients, the preoperative biopsy identified squamous cell carcinoma in 86 and adenosquamous carcinoma in 2. Concerning R classification, the number of patients in the R0, R1, R2, and nonresection groups was 70, 9, 7, and 2, respectively, and the number of patients in the R(+) group was 18 (20.5%). Table 1 shows the backgrounds of the

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Table 1 Clinical characteristics of the patients

	All (n = 88)	R0 (n = 70)	R(+) (n = 18)	*P* value
Age, y, mean ± SD	63.7 ± 7.4	64.0 ± 7.0	62.4 ± 8.7	0.420[a]
Sex, n (%)				
Male	79 (89.8)	62 (88.6)	17 (94.4)	0.679[b]
Female	9 (10.2)	8 (11.4)	1 (5.6)	
Tumor location				
Ut	14 (15.9)	6 (8.6)	8 (44.4)	
Mt	46 (52.3)	36 (51.4)	10 (55.6)	
Lt	20 (22.7)	20 (28.6)	0 (0)	
Ae	8 (9.1)	8 (11.4	0 (0)	
Mt + Lt + Ae	74 (84.1)	64 (91.4)	10 (55.6)	0.001[b]
Cycles of chemotherapy				
One cycle	4 (4.5)	4 (5.7)	0 (0)	0.577[b]
Two cycles	84 (95.5)	66 (94.3)	18 (100)	
cT category				
cT1a	1 (1.1)	1 (1.4)	0 (0)	
cT1b	7 (8.0)	7 (10.0)	0 (0)	
cT2	16 (18.2)	15 (21.4)	1 (5.6)	
cT3	64 (72.7)	47 (67.1)	17 (94.4)	
cT1–cT2	24 (27.3)	23 (32.9)	1 (5.6)	0.019[b]
cN category				
cN0	26 (29.5)	25 (35.7)	1 (5.6)	
cN1	45 (51.1)	32 (45.7)	13 (72.2)	
cN2	17 (19.3)	13 (18.6)	4 (22.2)	
cN3	0 (0)	0 (0)	0 (0)	
cN1–cN3	62 (70.5)	45 (64.3)	17 (94.4)	0.018[b]
cM1 (LYM)	9 (10.2)	6 (8.6)	3 (16.7)	

[a]Mann-Whitney *U* test.

[b]Fisher exact test.

Table 2 Criteria for the effectiveness of neoadjuvant chemotherapy

	R0 (n = 70)	R(+) (n = 18)	*P* value
RECIST, n (%)			
Without a target lesion	42 (60.0)	5 (27.8)	0.018[a]
With target lesions	28 (40.0)	13 (72.2)	
CR	0 (0)	0 (0)	
PR	11 (39.3)	5 (38.5)	1.000[a,b]
SD	16 (57.1)	8 (61.5)	
PD	1 (3.6)	0 (0)	
Pathologic criteria for the effects of chemotherapy, n (%)[c]			
Not resected	0	2	
Resected	70	16	
Grade 0	8 (11.4)	7 (43.8)	
Grade 1a	31 (44.3)	5 (32.3)	
Grade 1b	19 (27.1)	4 (25.0)	
Grade 2	10 (14.3)	0 (0)	
Grade 3	2 (2.9)	0 (0)	
Grades 0–1a	39 (55.7)	12 (75.5)	0.259[a]
Grades 1b–3	31 (44.3)	4 (25.0)	

[a]Fisher exact test.

[b]Comparing the PR group with the group including SD and PD.

[c]Criteria set by the Japan Esophageal Society were used.[11] Grade 0, no recognizable cytologic or histologic therapeutic effect; grade 1a, viable cancer cells account for two thirds or more of the tumor tissue; grade 1b, viable cancer cells account for at least one third but less than two thirds of the tumor tissue; grade 2, viable cancer cells account for less than one third of the tumor tissue, whereas other cancer cells are severely degenerated or necrotic; and grade 3, no viable cancer cells are evident.

patients according to R classification. The primary lesions of all 18 patients in the R(+) group were located within the upper thoracic (Ut) and middle thoracic (Mt) esophagus, and there were no residual tumors for which their primary lesions were located within the lower thoracic (Lt) and Ae. When each factor was evaluated groupwise, the number of cT3 cancers and number of primary lesions within the Ut were significantly greater in the R(+) group, whereas the number of cN0 cancers was smaller in this group. The primary tumor sites were compared, and the number of tumors within the Ut was significantly greater in the R(+) group. When these sites were divided into 2 groups (Ut/Mt and Lt/Ae), the number of tumors in Ut/Mt was significantly greater in the R(+) group ($P < 0.001$, Fisher exact test).

The treatment effects were compared between the R0 and R(+) groups (Table 2). Target lesions according to RECIST criteria were observed in 41 of 88 patients (46.6%), including 28 (40.0%) in the R0 group and 13 (72.2%) in the R(+) group, and the proportion of the patients with target lesions was significantly greater in the R(+) group. Furthermore, the objective response rates of the patients with target lesions were 39.3% in the R0 group and 38.5% in the R(+) group, with no significant difference observed. The pathologic response rate in accordance with the General Rules for the Esophageal Cancer Study was compared between the nonresponders, including grades 0 to 1a, and the responders, including grades 1b to 3, which indicated that there was a tendency that the number of responders was greater in the R0 group, but there was no significant difference between the groups.

Because the Ut was a significantly more common primary tumor site in the R(+) group than in the R0 group (Table 1), all patients were divided into 2 groups according to the primary tumor site (Ut and others) to investigate the background factors (Table 3). There were no significant differences in the background factors between the groups.

Furthermore, multivariate analysis was performed by using residual tumor as a criterion to identify the predictive factors for residual tumor, which was divided into (1) Ut/Mt–Ae, (2) cT3/cT1–2, and (3) cN1–3/cN0. As a result, the predictive

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Table 3 Patient characteristics according to tumor location

	Ut (n = 14)	Mt, Lt, Ae (n = 74)	*P* value
Age, y, mean ± SD	64.4 ± 9.2	63.5 ± 7.0	0.697[a]
Sex, n (%)			
Male	13 (92.9)	67 (90.5)	1.000[b]
Female	1 (7.1)	7 (9.5)	
cT category, n (%)			
cT1–cT2	4 (28.6)	20 (27.0)	1.000[b]
cT3	10 (71.4)	54 (73.0)	
cN category, n (%)			
cN0	3 (21.4)	23 (31.1)	0.543[b]
cN1–cN3	11 (78.6)	51 (68.9)	
Cycles of chemotherapy, n (%)			
One cycle	1 (7.1%)	3 (9.5%)	0.507[b]
Two cycles	13 (92.9%)	71 (95.9%)	
RECIST, n (%)			
Without a target lesion	5 (35.7)	42 (43.2)	0.242[b]
With target lesions	9 (64.3)	32 (56.8)	
PR	2 (35.7)	14 (43.8)	0.441[b]
SD + PD	7 (64.3)	18 (56.3)	
Pathologic criteria for the effects of chemotherapy, n (%)[c]			
Tumor resected	13	73	
Grades 0–1a	9 (69.2)	42 (57.5)	0.547[b]
Grades 1b–3	4 (30.8)	31 (42.5)	
Factors leading to residual tumor, n (%)			
Proximal margin	3 (21.4)	2 (2.7)	
Adjacent organs	4 (28.6)	8 (10.8)	
Trachea/bronchus	4 (28.6)	5 (6.8)	
Aorta	0 (0)	2 (2.7)	
Pericardium	0 (0)	3 (4.1)	
Unknown	0 (0)	1 (1.4)	
Unresectable node metastasis	1 (7.1)	0 (0)	

[a]Mann-Whitney *U* test.

[b]Fisher exact test.

[c]Criteria set by the Japan Esophageal Society were used.[11] Grade 0, no recognizable cytologic or histologic therapeutic effect; grade 1a, viable cancer cells account for two thirds or more of the tumor tissue; grade 1b, viable cancer cells account for at least one third but less than two thirds of the tumor tissue; grade 2, viable cancer cells account for less than one third of the tumor tissue, whereas other cancer cells are severely degenerated or necrotic; and grade 3, no viable cancer cells are evident.

factors were (1) the primary tumor site (Ut) and (2) cT3 (Table 4).

The patients were divided into 2 groups according to the primary tumor site (Ut/Mt and Lt/Ae) to identify any differences based on age, sex, cT factor, cN factor, and the number of courses of NAC. The results indicated that there were no factors displaying significant differences according to the tumor site, suggesting that Mt and Ut might be risk factors for residual tumor.

In the R1 group, the numbers of patients with a positive proximal resection margin and a positive deep resection margin were 4 and 5, respectively. The organs adjacent to the deep resection margin were the tracheae (bronchi) in 2 patients, cardiac sac in 2 patients, aorta in 1 patient, and unknown in 1 patient (some cases overlapped). The macroscopic residual tumor sites in the R2 group were the tracheae (bronchi) in 5 patients, cardiac sac in 1 patient, lymph nodes in 1 patient, and proximal resection margin in 1 patient (some cases overlapped). In 2 patients of the nonresection group, it was decided that the lesions were unresectable because of the primary lesion's invasion into other organs, which were the tracheae (bronchi) in 2 patients, vertebrae in 1 patient, and cardiac sac in 1 patients (some cases overlapped).

Table 4 Multivariate analysis of the risk factors for residual tumor

	Odds ratio	95% Confidence interval	*P* value
Tumor location (Ut/Mt, Lt, Ae)	12.516	2.875–54.457	0.001
cT category (cT3/cT1–2)	13.375	1.374–130.197	0.026

Discussion

There are several reports on NAC for treating esophageal cancer. A meta-analysis of NAC for esophageal cancer indicated that NAC increased the survival rate of these patients. However, focusing on esophageal squamous cell carcinoma alone, the survival rate tended to be improved, but no significant differences were observed ($P = 0.18$).[14] Most of the aforementioned reports came from other countries, and the survival rate of the patients undergoing NAC alone was significantly different from that reported in Japan,[15] which gave rise to doubts about the generalizability of the aforementioned results in Japan. Therefore, a multicenter randomized control study (JCOG9907) was performed in Japan to evaluate the efficacy of NAC, and the study results demonstrated that NAC with 5-FU and CDDP increased the survival rate in medical institutions in Japan, where complete mediastinal lymph node dissection is applied as the standard surgical technique.[2,3]

As described previously, R classification is an important prognostic factor in patients undergoing esophageal cancer resection. The residual tumor rate after esophagectomy after NAC varied among reports[4,8,10,16,17] (Table 5) because there appeared to be larger differences in the background of patients and surgical techniques rather than the chemotherapy regimens. In the patients undergoing NAC in

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Table 5 Tumor residual rates in esophagectomy following NAC according to reported randomized control trials

Author	Year started	Histologic type	Eligibility criteria	Chemotherapy schedule	Tumor residual rate, %
Boonstra *et al*[10]	1989	SCC	Resectable tumors (clinical stages I–III or IVa in lower esophageal cancers)	CDDP, 80 mg/m^2, day 1; VP-16, 100 mg/m^2, days 1 and 2, 200 mg/m^2, days 3 and 5; q3w, 2–4 cycles	39 (R1 + R2 + NR)
Kelsen *et al*[16]	1990	SCC, AD	cT1–3, cM0	CDDP, 100 mg/m^2, day 1; 5-FU, 1000 mg/m^2, days 1–5; q4w, 3 cycles	38 (R1 + R2 + NR)
Ancona *et al*[17]	1992	SCC	Clinical stages II–III (non-T4)	CDDP, 100 mg/m^2, day 1; 5-FU, 1000 mg/m^2, days 1–5; q3w, 2 cycles	6 (R1 + R2)
Allum *et al*[8]	1992	SCC, AD	Resectable tumors (cM0)	CDDP, 80 mg/m^2, day 1; 5-FU, 1000 mg/m^2, days 1–4; q3w, 2 cycles	14 (R2 + NR)
Ando *et al*[4]	2000	SCC	Clinical stages II–III (non-T4)	CDDP, 80 mg/m^2, day 1; 5-FU, 800 mg/m^2, days 1–5; q3w, 2 cycles	4 (R1 + R2)

AD, adenocarcinoma; NR, not resected; R1, microscopic tumor-positive margin; R2, macroscopic residual tumor; SCC, squamous cell carcinoma; VP-16, etoposide.

the JCOG9907 study, the proportion of patients achieving R0 was 96%, whereas the rate of the patients with residual tumors (R1 and R2) was 4%.[3] By contrast, the proportion of patients with residual tumors was approximately 20% at the time of completion of this study, which was significantly much different from the result of the JCOG9907 study. The reason might be because many patients with cervical lymph node metastases were included in this study, and thus the number of patients with advanced carcinoma was greater in this study than in the JCOG9907 study or because patients with cT4 esophageal cancer might have participated in this study.

This study result indicated that patients whose primary tumors were located within the Ut and those with cT3 esophageal cancer were likely to have residual tumors after surgery and NAC. Furthermore, 9 of 18 patients in the R(+) group had residual tumors in the tracheae (bronchi), which suggested that the lesions located within the Ut and/or Mt easily infiltrated into these organs because the Ut and Mt are anatomically adjacent to the tracheae (bronchi), without any septum. In terms of surgical technique, R0 was more likely to be achieved if the distal Mt and the Ae were detached to a great extent or if the tissues surrounding the lesion were resected together. However, detachment with the membranous part of the trachea or bronchi was anatomically difficult in the Ut to the proximal Mt, which might not permit achieving R0 and might result in a positive deep resection margin in patients with cT3 esophageal cancer. Igaki *et al*[18] reported that residual tumor was likely to be detected and the prognosis was poor in patients with cT3 esophageal cancer whose primary tumor was located within the Ut, which was consistent with the finding of this study. Several studies conducted in other countries also reported that patients with esophageal cancer located above the carina had a poor prognosis.[5,19,20] It was considered that the aforementioned anatomic structures might have an influence on the prognosis to some extent.

The rate of residual tumors observed in this study was substantially different from that in the JCOG9907 study, but the subgroup analysis result indicated that NAC did not sufficiently improve the prognosis of patients whose primary tumor was located within the Ut and those with cT3 esophageal cancer,[3] which was similar to the result of this study.

Our findings suggested that (1) the primary tumor site (Ut) and (2) the tumor depth staging (cT3) in patients with esophageal squamous cell carcinoma were the risk factors for residual tumor after surgery and NAC, and that the NAC regimen of 5-FU and CDDP was not sufficiently effective in these patients. To increase the proportion of patients who achieve R0 and the survival rate, NAC should be further modified. Currently, NAC using concurrent docetaxel/CDDP/5-FU[21] has been attempted in Japan to increase the survival rate. It is expected that these therapies may improve the treatment outcome.

Conclusion

The cT3 esophageal cancer mainly located within the Ut may have a higher risk of residual tumor after esophagectomy and NAC with 5-FU and CDDP. It is expected that further modification of such therapy will improve the treatment outcome.

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