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Dukes' classification as a useful staging system in resectable squamous cell carcinoma of the esophagus

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Abstract Dukes' classification for colorectal cancer is simple and has been widely used as a valuable prognostic indicator. It has been used as an assessment of gastric cancer, but it has not been evaluated for esophageal cancer. Of 251 patients with primary squamous cell carcinoma of the thoracic esophagus between February 1981 and April 1999, 155 patients underwent esophagectomy with a curative intent. Clinicopathologic characteristics of those 155 patients were retrospectively investigated according to the Dukes', tumor node metastasis (TNM) and Japanese staging systems. Dukes' classification showed a clear correlation between tumor stage and survival. The 3-year and 5-year survival rates of 64 Dukes' A cases were excellent (97.4% and 93.7%), good for 12 Dukes' B (75% and 75%), and poor for 79 Dukes' C (50.5% and 43.4%), respectively ($P<0.05$; Dukes' A vs B, $P<0.0001$; Dukes' A vs C, $P<0.10$; Dukes' B vs C). TNM stage classification also showed a good correlation between tumor stage and survival, but there were no significant differences between stage 0, I and stage IIA cases ($P=0.2678$) and between stage III and stage IV cases ($P=0.8298$). In the Japanese staging system, there were no significant differences among stage 0, stage 1, and stage 2 cases ($P=0.4093$). Dukes' classification was significantly correlated with tumor size, Borrmann type, histological type, and vessel invasion. Subdivision of Dukes' C according to the number of positive lymph nodes (1–4 vs ≥ 5) showed a clearer correlation with survival rather than other subdivisions, such as the metastatic lymph node ratio (<1.0 vs >1.0) or the site of lymph node metastasis. Dukes' classification, which incorporates the number of positive lymph nodes, correlates well with tumor progression and provides a simple

useful staging system after curative esophagectomy for esophageal cancer. Dukes' A tumor could be proposed as a criterion of early esophageal carcinoma.

Keywords Esophageal cancer · Dukes' classification · Lymph node metastasis · Long-term result

Introduction

Dukes' classification for colorectal cancer is simple, easy to interpret, and has been widely used as one of the most valuable prognostic indicators [4, 5, 16]. It can also be a satisfactory assessment of gastric cancer [1, 2]. Most physicians and surgeons use it as a gold standard staging system for clinical use. In the various staging systems for esophageal cancer, Skinner et al. [15] in 1986 proposed a staging system similar to the modified Dukes' system. The TNM classification determined by the International Union Against Cancer (UICC) [20] is currently the most popular in North American and European countries, and the Japanese staging system by the Japanese Society for Esophageal Disease [7] is popular in Japan. These two staging systems [7, 20] adopted locations of the lymph nodes as a subdivision of the pN category, instead of the number of involved nodes. For example, the TNM classification defined pN1 as regional lymph node metastasis and pM1 as distant metastasis, and the Japanese staging system divided the locations of lymph node metastasis into four categories according to the primary lesion.

The presence or absence of lymph node metastasis is a well-known prognostic indicator of esophageal cancer. Among the node-positive patients, the number of the metastatic nodes clearly influenced the survival. Generally, patients with a large number of diseased nodes have a worse survival rate than those with a few metastatic nodes [3, 11, 12]. Although Dukes' did not originally point out the significance of the number of involved nodes for rectal cancer [5], the TNM classification [20]

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Fig. 1 Scheme of the Dukes', TNM, and Japanese staging systems

Mucosa									
M mucosa									
Submucosa									
Muscularis propria									
Adventitia									
Lymph node metastasis									
TNM	TisN0	T1N0	T2N0	T2N1	T3N0	T3N1	T3N1M1	T4N1	T4N1M1
Japanese	TisN0	T1N0	T2N0	T2N2	T3N0	T3N2	T3N3M0	T4N2	T4N4M0
Dukes (present study)	A	A	A	CI	B	CI	CII	CI	CII

of gastric cancer and colorectal cancer were fully revised in 1997 and adopted the number of involved lymph nodes as a category of pN. In the present study, we assessed the predictability of modified Dukes' classification according to the number of positive lymph nodes for tumor progression and long-term prognosis in esophageal carcinoma patients.

Patients and methods

Between February 1981 and April 1999, 206 patients with primary squamous cell carcinoma of the thoracic esophagus underwent an esophagectomy, 5 patients received an endoscopic mucosal resection, and the remaining 40 patients had palliative treatments at the Second Department of Surgery, Shimane Medical University. Of 206 patients surgically resected, 155 (75.2%) underwent R0 [20] esophagectomy according to the pathological examination of the resected specimen, and those were enrolled in this study.

The majority of these patients underwent a right transthoracic subtotal esophagectomy along with a three-field lymph node dissection, including the cervical (bilateral supraclavicular regions), mediastinal (periesophagus and around the trachea, including around bilateral recurrent laryngeal nerves), and abdominal (perigastric region and around the celiac axis) lymph nodes. Reconstruction was usually carried out with a gastric tube through the retrosternal route and esophagogastrostomy was done in the neck under cervical incision and laparotomy.

According to protocol, 106 patients received preoperative and/or postoperative radiochemotherapy. Of the remaining 49 patients, 26 with superficial esophageal cancer did not receive any adjuvant treatment, 4 refused any adjuvant treatment, and the remaining 19 patients did not receive any adjuvant treatment due to complication in 15 and miscellaneous causes in 4.

The classification of the Dukes' system was divided into three categories using an original system [5]. Dukes' A cases are those in which the carcinoma is limited to the wall, there being no extension into the surrounding tissues and no metastasis in lymph

nodes, Dukes' B cases are those in which the carcinoma has spread through direct continuity to the surrounding tissues but has not yet invaded the regional nodes, and Dukes' C cases are those in which metastases are present in the lymph nodes. Since original Dukes' C cases consisted of various kinds of node-positive patients, Dukes' C cases were further subdivided according to the number of positive lymph nodes.

Clinicopathologic characteristics of those 155 patients were retrospectively investigated according to the Dukes', TNM [20], and Japanese staging system [7] (Fig. 1). The outcome of patients was examined, and those who clearly died of recurrences were regarded as tumor-related deaths. In calculating the 5-year disease-specific survival rate, patients who were alive and who died of causes unrelated to esophageal cancer were counted as being alive at end point. The survival rates of all 155 patients were estimated using the Kaplan-Meier method [8], and the statistical analysis was carried out using the log rank test to test for equality of the survival curves. Statistical differences were analyzed using the χ^2 test. The level of significance was $P < 0.05$.

Results

Outcomes

At the time of this analysis, 77 patients were alive and free of cancer, and the remaining 78 patients were dead. Of those 78 deaths, the causes of death were recurrences of esophageal cancer in 37 and other causes in 41. The other causes are: in-hospital death mostly within 90 days after esophagectomy in 14 patients (in-hospital mortality 9.0%), pneumonia in six, severe emaciation in four, cerebrovascular attack in four, other malignancies in five, heart-related problems in three, age-related death in two, gastric tube ulcer perforation in one, cholecystitis in one, and unknown causes in one.

Long-term survival of Dukes' and other classifications

The 1-, 3-, and 5-year overall survival rates for all 155 patients were 73.8%, 51.7%, and 42.8%, respectively, and those disease-specific survival rates were 88.3%, 71.8%, and 66.3%, respectively.

According to criteria of the Dukes', TNM, and Japanese staging systems, the long-term survival rates were calculated (Fig. 2). Dukes' classification showed a clear correlation between tumor stage and survival. The 3-year and 5-year disease-specific survival rates of Dukes' A cases were excellent (97.4% and 93.7%), good for Dukes' B cases (75% and 75%), and poor for Dukes' C cases (50.5% and 43.4%), respectively ($P<0.05$; Dukes' A vs Dukes' B, $P<0.0001$; Dukes' A vs Dukes' C, $P<0.10$; Dukes' B vs Dukes' C; Fig. 2A). Of 64 Dukes' A cases, two died of recurrences of esophageal cancer, whereas two of 12 Dukes' B and 33 of 79 Dukes' C cases succumbed to recurrent esophageal diseases. The 3-year and 5-year overall survival rates of Dukes' A cases, moreover, were also good (73.3% and 63%), moderately good for Dukes' B cases (55% and 55%), and poor for Dukes' C cases (33.5% and 26.1%), respectively.

TNM stage classification also showed a correlation between tumor stage and survival, but there were no significant differences between 40 stage 0, I and 34 stage IIA cases ($P=0.2678$) and between 33 stage III and 29 stage IV cases ($P=0.8298$; Fig. 2B). The Japanese staging system showed also a correlation between tumor stage and survival, but there were no significant differences among stage 0, 1, and 2 ($P=0.4093$; stage 0 vs stage 1; Fig. 2C). Thus, both in the TNM and Japanese staging systems, there were no significant differences between subdivisions of the early stages.

Moreover, because adjuvant radiochemotherapies administered before and after surgery consisted of various regimens in the present study, this finding might make interpretation of our results difficult. Thus, 34 patients who received adjuvant radiochemotherapies before surgery were excluded from the analysis. The long-term results of 121 patients without any preoperative treatments were analyzed. The 3-year and 5-year disease-specific survival rates of Dukes' A cases were also excellent ($n=54$; 96.9% and 92.3%), good for Dukes' B cases ($n=6$; 75% and 75%), and poor for Dukes' C cases ($n=61$; 52.5% and 46.1%), respectively. These survival curves were similar to those shown in Fig. 2A and, thus, preoperative adjuvant treatments did not influence the survival rate. Moreover, there was no survival difference between the patients who received pre- or postoperative adjuvant treatments.

Clinicopathologic features according to the modified Dukes' classification (subdivision of Dukes' C cases by the number of positive lymph nodes)

Clinical features according to the modified Dukes' classification by the number of positive lymph nodes (CI, 1–4; CII, ≥ 5) are shown in Table 1. Age, gender, and

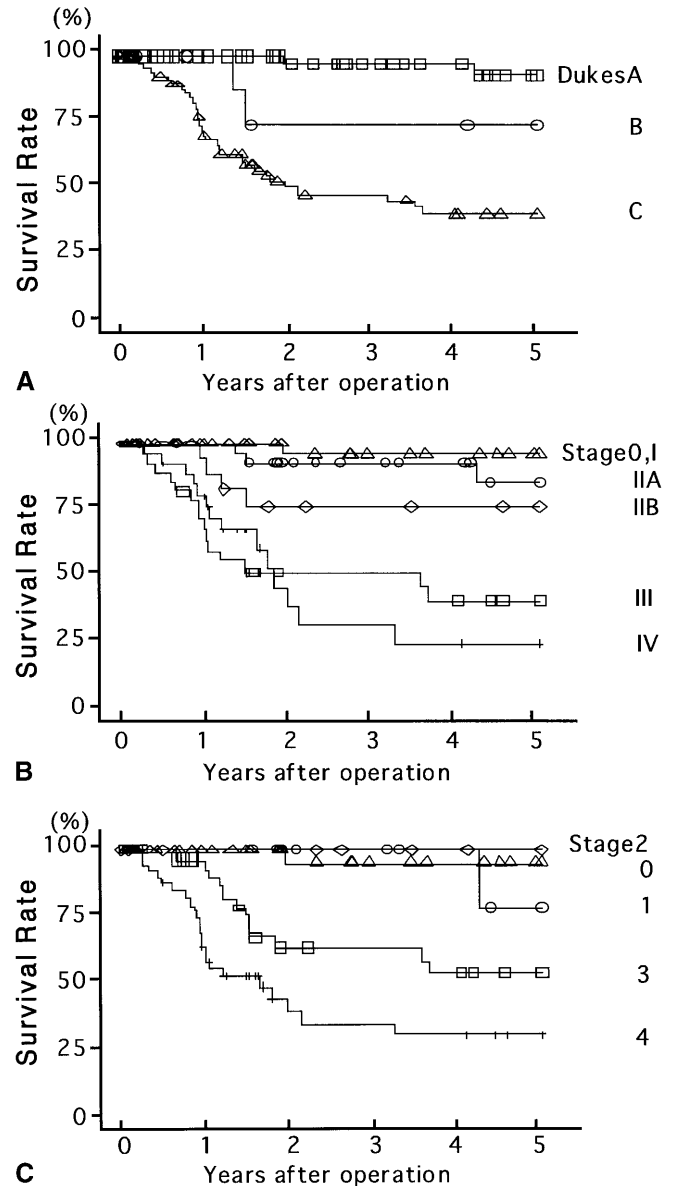


Fig. 2 Cumulative disease-specific survival curves according to the Dukes' (A), TNM (B), and Japanese (C; $n=155$) classifications. The 1-, 3-, and 5-year survival rates were 100%, 97.4%, and 93.7% for Dukes' A, 100%, 75%, and 75% for Dukes' B, and 77.4%, 50.5%, and 43.4% for Dukes' C, respectively ($P<0.05$; Dukes' A vs B, $P<0.0001$; Dukes' A vs C, $P<0.10$; Dukes' B vs C; A). There were no significant differences between stage 0, I and stage IIA cases ($P=0.2678$) and between stage III and stage IV ($P=0.8298$) using the TNM classification (B). There were no significant differences among the stage 0, 1, and 2 ($P=0.4093$; stage 0 vs 1) using the Japanese classification (C)

tumor location were not different between the groups. The mean tumor size was significantly different between Dukes' A (3.2 ± 1.9 cm) and Dukes' B cases (5.3 ± 2.0 cm; $P<0.001$) and between Dukes' CI (4.4 ± 1.6 cm) and Dukes' CII cases (5.7 ± 1.8 cm; $P<0.002$), and tumor size was commonly less than 3 cm in Dukes' A (56%), commonly 3.1–6 cm in Dukes' B (67%), and sometimes 6.1 cm or more in Dukes' CI (14%) and Dukes' CII

Table 1 Clinical features according to the Dukes' classification (subdivision of the Dukes' C cases by the number of positive lymph nodes, *CI* 1–4; *CII* ≥5). Numbers in parentheses are percentages; *NS* not significant

Variable	Dukes' A (n=64)	Dukes' B (n=12)	Dukes' CI (n=50)	Dukes' CII (n=29)	P value
Gender					
Male	59 (92)	12 (100)	44 (88)	28 (97)	NS
Female	5 (8)	0	6 (12)	1 (3)	
Age (years)					
<60	17 (27)	2 (17)	11 (22)	10 (34)	NS
60–69	31 (48)	6 (50)	19 (38)	14 (48)	
≥70	16 (25)	4 (33)	20 (40)	5 (17)	
Tumor location					
Upper	6 (9)	1 (8)	6 (12)	4 (14)	NS
Middle	38 (59)	6 (50)	31 (62)	11 (79)	
Lower	20 (31)	5 (42)	13 (26)	14 (48)	
Size of tumor (cm)					
≤3.0	36 (56)	1 (8)	9 (18)	0	<0.001
>3.0, <6.0	24 (38)	8 (67)	34 (68)	17 (59)	
>6.0	4 (6)	3 (25)	7 (14)	12 (41)	<0.001 (A vs B, C1, C2)
Mean±SD	3.2±1.9	5.3±2.0	4.4±1.6	5.7±1.8	
Borrmann classification					
0	38 (59)	0	11 (22)	1 (3)	<0.001
I	6 (9)	1 (8)	4 (8)	2 (7)	
II	12 (19)	4 (33)	14 (28)	12 (42)	
III	8 (13)	7 (58)	21 (42)	14 (48)	

Table 2 Pathologic features according to the Dukes' classification (subdivision of the Dukes' C cases by the number of positive lymph nodes, *CI* 1–4; *CII* ≥5). Numbers in parentheses are percentages; *NS* not significant

Variable	Dukes' A (n=64)	Dukes' B (n=12)	Dukes' CI (n=50)	Dukes' CII (n=29)	P value
Histological type					
Good	30 (47)	8 (67)	10 (20)	9 (31)	<0.01
Moderate	24 (37)	3 (25)	31 (62)	15 (52)	
Poor	10 (16)	1 (8)	9 (18)	5 (17)	
Depth of invasion					
pTis, T1	40 (62)	0	11 (22)	1 (3)	<0.001
pT2	24 (38)	0	20 (40)	9 (31)	
pT3, T4	0	12 (100)	19 (38)	19 (66)	
Lymph node metastasis					
N0	64 (100)	12 (100)	0	0	<0.001
N1	0	0	36 (72)	14 (48)	
Distant(M)	0	0	14 (28)	15 (52)	
Lymph vessel invasion					
Absent	32 (50)	5 (42)	3 (6)	0	<0.001
Present	32 (50)	7 (58)	47 (94)	29 (100)	
Blood vessel invasion					
Absent	37 (58)	4 (33)	13 (26)	2 (7)	<0.001
Present	27 (42)	8 (67)	37 (74)	27 (93)	

cases (41%). Ulcerative tumors (Borrmann II and III) were more common in Dukes' CI and CII than the in Dukes' A and B cases ($P<0.0001$).

Pathologic characteristics according to the modified Dukes' classification are shown in Table 2. Well-differentiated tumors were more common in Dukes' A and B cases than others ($P<0.001$). The frequency of adventitial invasion [depth of invasion (pT)3/T4] was

more common in Dukes' CII (66%) than Dukes' CI (38%). The level of lymph node metastasis was significantly different between Dukes' CI and CII cases; about one-fourth of Dukes' CI tumors (28%) showed pM1, whereas more than half of Dukes' CII (52%) had pM1. Lymph vessel ($P<0.001$) and blood vessel ($P<0.001$) invasion were significantly more common in Dukes' CI and CII than in the Dukes' A and B cases.

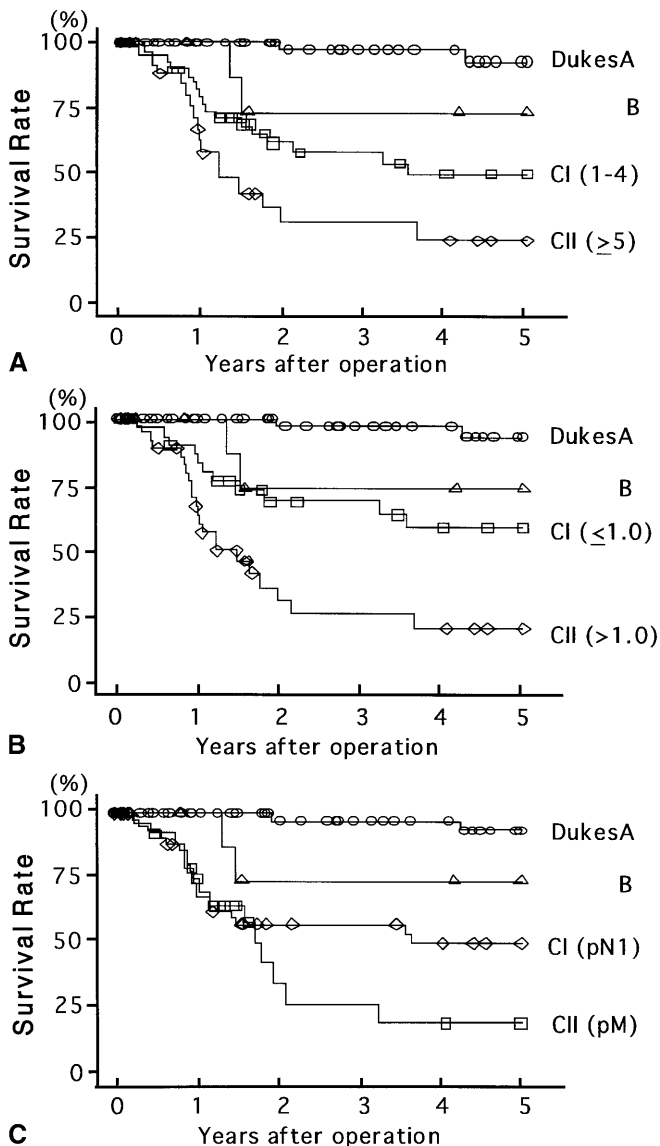


Fig. 3 Cumulative disease-specific survival curves of modified Dukes' C classification according to the number of positive lymph nodes (A), metastatic lymph node ratio (B), and level of positive lymph nodes (C) ($n=155$). The 1-, 3-, and 5-year survival rates according to the number of positive lymph nodes were 82.9%, 59.9%, and 52.2% for Dukes' CI (1-4) and were 68.7%, 34.7%, and 28.9% for Dukes' CII (≥ 5), respectively ($P<0.05$; Dukes' CI vs CII; A). According to the metastatic lymph node ratio, the survival curves between Dukes' B and Dukes' CI (≤ 1.0) were not different (B). According to the level of positive lymph nodes, the survival curves between Dukes' CI [regional lymph node metastasis (pN1)] and Dukes' CII [distant lymph node metastasis (pM)] were not different (C)

Long-term survival according to the subdivisions of Dukes' C classification

Because original Dukes' C cases consisted of various kinds of node-positive patients, Dukes' C cases were subdivided according to the number of positive lymph nodes, the metastatic lymph node ratio, and the level of positive nodes (Fig. 3). In modified Dukes' C classifica-

tion according to the number of positive lymph nodes (CI, 1-4 vs CII, ≥ 5), the 3-year and 5-year survival rates were 59.9% and 52.2% for Dukes' CI cases ($n=50$) and 34.7% and 28.9% for Dukes' CII cases ($n=29$), respectively ($P<0.05$; Fig. 3A). Seventeen patients of Dukes' CI and sixteen of Dukes' CII died of recurrent esophageal cancer. In this classification, the 5-year survival rates for each Dukes' A, B, CI, and CII were different step-wise (but not significant between Dukes' B and CI cases; $P=0.2720$).

According to the metastatic lymph node ratio (CI, ≤ 1.0 vs CII, >1.0), the survival rates between Dukes' CI ($n=38$) and CII cases ($n=41$) were significantly different ($P=0.0058$), but the survival rates of Dukes' CI were almost the same as that of Dukes' B cases ($P=0.4669$; Fig. 3B). Last, according to the level of positive lymph nodes (CI, pN1 vs CII, pM1), the survival rates between Dukes' CI ($n=50$) and CII ($n=29$) were not different ($P=0.2415$; Fig. 3C). Thus, the subdivision of Dukes' C according to the number of lymph nodes is the most accurate predictor of survival.

Discussion

Dukes [5] reported in 1932 a pathologic classification of the staging system of rectal cancer based on the degree of wall penetration and the presence or absence of lymph node metastasis. Until now, Dukes' classification of colorectal cancer has been one of the most simple and valuable prognosticators in the world [4, 16] and also can be satisfactorily applied to gastric cancer after curative gastrectomy [1, 2]. In the staging system for esophageal cancer, the TNM classification by the American Joint Committee on Cancer [20] is most popular in Western countries, whereas a Japanese classification by the Japanese Society for Esophageal Disease [7] is mostly preferred in Japan. As recent analyses of the molecular biology and oncogenes have progressed, these molecular markers will be combined in this staging system in the future. Thus, it might be important to determine whether or not Dukes' classification, which has fewer categories than the TNM and the Japanese classification, can be assessed for the staging system for esophageal cancer.

Under these circumstances, the Dukes', TNM, and Japanese classifications were evaluated as to whether these staging systems were valuable for predicting tumor progression and long-term survival after curative esophagectomy for esophageal cancer. Although the TNM and Japanese classifications showed a good correlation between survival rates, these two systems did not show any differences between the subdivisions of the early stages (stage 0, I, and IIA in the TNM system and stage 0, 1, and 2 in the Japanese system). These results showed that the Dukes' system in the present study combined early stages of TNM and Japanese classifications that have the same prognosis into the Dukes' A stage. Because the Dukes' classification, furthermore, correlated well with the tumor progression, it could be applied to esophageal cancer as a more simple and useful staging system.

One criticism, however, is that the number of Dukes' B (pT3N0 or pT4N0) cases was small (7.7%) in the present study. The incidence of Dukes' B cases has been reported to be 13–14% [6, 10, 11, 13], which was almost comparable with our incidence. Killinger et al. [10] reported that survival of T3N0 cases (almost equal to Dukes' B) was intermediate between that of T1N0 and T2N0 cases (equal to Dukes' A) and that of T1N1, T2N1, T3N1 cases (almost equal to Dukes' C). These results support that the division of Dukes' B cases from Dukes' A and C is reasonable and acceptable.

In 1997, the TNM classification for gastric cancer and colorectal cancer by UICC was fully revised according to the number of involved lymph nodes, but this staging system by the number of positive nodes was not applied for esophageal cancer [20]. Among the node-positive patients, the number of the metastatic nodes clearly influenced the survival after curative esophagectomy [3, 11, 12]. Generally, patients with a large number of diseased nodes have a worse survival than those with a few metastatic nodes (for example, 1–3 vs ≥ 4 [11], 1–4 vs ≥ 5 [12], 1–7 vs ≥ 8 [3]). In the present study, therefore, Dukes' C patients were subdivided between one to four and five or more involved lymph nodes. This subdivision significantly correlated well with tumor size, histological differentiation, pT, pN, and vessel invasion. Histological differentiation and blood and/or lymph vessel invasion have been reported to be correlated well with patients' survival [6, 14], and depth of invasion and lymph node metastasis consist of two major factors of the TNM [20] and Japanese staging system [7]. These findings support that the modified Dukes' classification according to the number of positive lymph nodes is useful for evaluating the tumor progression. From the view point of long-term survival, the subdivision of Dukes' C according to the number of positive nodes showed a clearer correlation with survival rather than other subdivisions according to the metastatic lymph node ratio and level of lymph node metastasis. Therefore, the number of positive lymph nodes should be included for the esophageal staging system, and the modified Dukes' classification according to the number of involved lymph nodes is useful for predicting patients' survival after curative esophagectomy for esophageal carcinoma.

Unlike the early gastric carcinoma patients (tumor invasion limited to the epithelium, muscularis mucosa, and submucosa regardless of the presence or absence of lymph node metastasis), the prognosis of superficial esophageal carcinoma patients is considered to be dismal once the regional lymph nodes are involved [9, 18, 21]. Sugimachi et al. [17] proposed that the criteria for early esophageal carcinoma was mucosal carcinoma (pTis, T1) regardless of the presence or absence of lymph node metastasis, and that a submucosal cancer should be excluded from the classification of early esophageal carcinoma. Using TNM classification [20], the pT1N0 tumor is classified as stage I and pT2N0 tumor as stage IIA. On the contrary, we have previously reported that

pT2N0 tumors yielded an excellent survival rate, such as pT1N0 diseases [19] and, in the present study, Dukes' A tumors (pTisN0, pT1N0, and pT2N0) showed an excellent survival rate, exceeding 90%. Likewise, Killinger et al. [10] compared the survival results in stage II esophageal carcinoma and revealed that the survival was not different between T1N0 and T2N0 (both 50% of 5-year survival rate, $P=0.83$). They concluded that the distinction between these subgroups was not warranted. Similarly, Skinner et al. [15] grouped submucosal (T1b) and T2 tumors in one group because the wall penetration held the same variable of survival when those patients had no lymph node metastasis. Because our survival data are better than those previously reported, we assume that Dukes' A tumor should be categorized as a group with an excellent prognosis and proposed as a criterion of early esophageal carcinoma.

In conclusion, the modified Dukes' classification, which incorporates the number of positive lymph nodes, correlates well with tumor progression and provides a simple useful staging system after curative esophagectomy for esophageal cancer. Dukes' A tumor could be proposed as a criterion of early esophageal carcinoma.

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