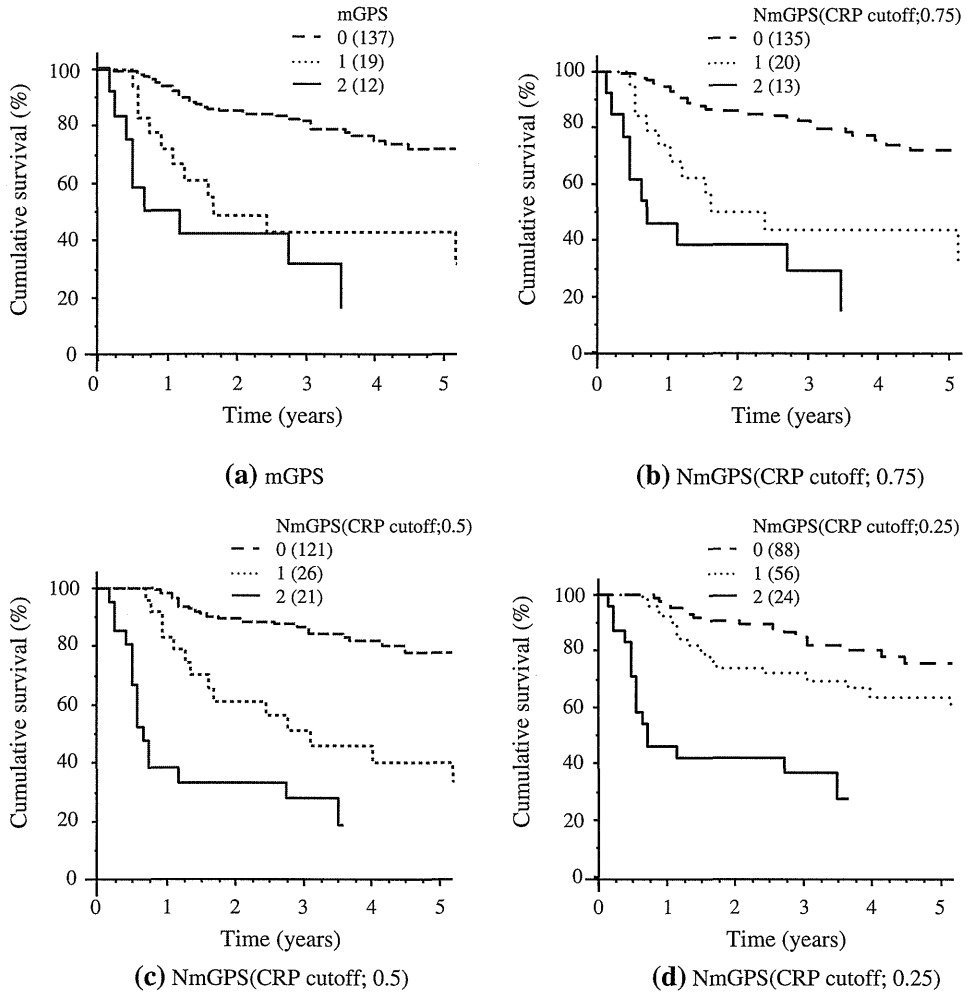

Fig. 1 **a** The cancer-specific survival curves based on the modified Glasgow Prognostic Score (mGPS). The 3-year cancer-specific survival rates of patients with a mGPS of 0 (*dashed line*), 1 (*dotted line*) and 2 (*solid line*) were 81.7, 42.8 and 31.3 %, respectively. There were statistically significant differences between the survival rates of patients with a mGPS of 0 and 1 ($p = 0.0002$), and between patients with a mGPS of 0 and 2 ($p < 0.0001$). There was no significant difference between the survival rates of patients with a mGPS of 1 and 2 ($p = 0.1860$). **b** The cancer-specific survival curves based on the new modified Glasgow Prognostic Score (NmGPS [CRP cutoff; 0.75 mg/dL]). The 3-year cancer-specific survival rates of patients with a NmGPS (CRP cutoff; 0.75 mg/dL) of 0 (*dashed line*), 1 (*dotted line*) and 2 (*solid line*) were 82.3, 43.6 and 28.8 %, respectively. There were statistically significant differences between the survival rates of patients with a NmGPS (CRP cutoff; 0.75 mg/dL) of 0 and 1 ($p = 0.0001$), and between patients with a NmGPS (CRP cutoff; 0.75 mg/dL) of 0 and 2 ($p < 0.0001$). There was no significant difference between the survival rates of patients with a NmGPS (CRP cutoff; 0.75 mg/dL) of 1 and 2 ($p = 0.1171$). **c** The cancer-specific survival curves based on the new modified Glasgow Prognostic Score (NmGPS [CRP cutoff; 0.5 mg/dL]). The 3-year cancer-specific survival rates of patients with a NmGPS (CRP cutoff; 0.5 mg/dL) of 0 (*dashed line*), 1 (*dotted line*) and 2 (*solid line*) were 86.5, 51.0 and 27.8 %, respectively. There were statistically significant differences between the survival rate of patients with a NmGPS (CRP cutoff; 0.5 mg/dL) of 0 and 1 ($p < 0.0001$), of 0 and 2 ($p < 0.0001$), and between patients with a NmGPS (CRP cutoff; 0.5 mg/dL) of 1 and 2 ($p = 0.0099$). **d** The cancer-specific survival curves based on the new modified Glasgow Prognostic Score (NmGPS [CRP cutoff; 0.25 mg/dL]). The 3-year cancer-specific survival rates of patients with a NmGPS (CRP cutoff; 0.25 mg/dL) of 0 (*dashed line*), 1 (*dotted line*) and 2 (*solid line*) were 85.1, 71.9 and 36.5 %, respectively. There were statistically significant differences between the survival rates of patients with a NmGPS (CRP cutoff; 0.25 mg/dL) of 0 and 2 ($p < 0.0001$), and between patients with a NmGPS (CRP cutoff; 0.25 mg/dL) of 1 and 2 ($p < 0.0001$), but not between those with a NmGPS (CRP cutoff; 0.25 mg/dL) of 0 and 1 ($p = 0.0685$)

cutoff; 0.5 mg/dL) 1 and 2 ($p = 0.0099$) (Fig. 1c). The 3-year cancer-specific survival rates of patients with NmGPS (CRP cutoff; 0.25 mg/dL) 0, 1 and 2 were 85.1, 71.9 and 36.5 %, respectively. There were statistically significant differences between the survival of patients with NmGPS (CRP cutoff; 0.25 mg/dL) 0 and 2 ($p < 0.0001$) and between patients with NmGPS (CRP cutoff; 0.25 mg/dL) 1 and 2 ($p < 0.0001$), but not between patients with NmGPS (CRP cutoff; 0.25 mg/dL) 0 and 1 ($p = 0.0685$) (Fig. 1d). Only NmGPS (CRP cutoff; 0.5 mg/dL) was able to divide into three independent patient groups in the survival curves.

Table 2 The Akaike information criterion (AIC) for the prognostic scoring systems

Prognostic score	AIC
mGPS	1059.0
NmGPS (CRP cutoff; 0.75 mg/dL)	1055.8
NmGPS (CRP cutoff; 0.5 mg/dL)	1044.9
NmGPS (CRP cutoff; 0.25 mg/dL)	1054.1

mGPS modified Glasgow Prognostic Score, *NmGPS* new modified Glasgow Prognostic Score

The AIC of the mGPS, NmGPS (CRP cutoff; 0.75 mg/dL), NmGPS (CRP cutoff; 0.5 mg/dL) and NmGPS (CRP cutoff; 0.25 mg/dL) were 1059.0, 1055.8, 1044.9 and 1054.1, respectively (Table 2). The NmGPS (CRP cutoff; 0.5 mg/dL) showed a smaller AIC than the mGPS and other NmGPS, so we selected the NmGPS (CRP cutoff; 0.5 mg/dL) as the optimal prognostic score and compared the mGPS with the NmGPS (CRP cutoff; 0.5 mg/dL) with respect to the clinicopathological features and prognostic

Table 3 The relationships between the mGPS and the clinicopathological features

Variable	mGPS 0 (n = 137)	mGPS 1 (n = 19)	mGPS 2 (n = 12)	p
Age, years				0.6128
≤65	66 (48.2 %)	7 (36.8 %)	5 (41.7 %)	
>65	71 (51.8 %)	12 (63.2 %)	7 (58.3 %)	
Sex				0.5084
Male	108 (78.8 %)	16 (84.2 %)	11 (91.7 %)	
Female	29 (21.2 %)	3 (15.8 %)	1 (8.3 %)	
Depth of tumor invasion				<0.0001
T0/1/2	81 (59.1 %)	3 (15.8 %)	2 (16.7 %)	
T3/4	56 (40.9 %)	16 (84.2 %)	10 (83.3 %)	
Lymph node metastasis				0.0101
N0	61 (44.5 %)	7 (36.8 %)	0 (0 %)	
N1/2/3	76 (55.5 %)	12 (63.2 %)	12 (100 %)	
Distant metastasis				<0.0001
M0	137(100 %)	19 (100 %)	10 (83.3 %)	
M1	0	0	2 (16.7 %)	
Histological type				0.2552
Differentiated	99 (72.3 %)	14 (73.7 %)	6 (50.0 %)	
Undifferentiated	38 (27.7 %)	5 (26.3 %)	6 (50.0 %)	
Lymphatic invasion				0.4047
0	57 (41.6 %)	6 (31.6 %)	3 (25.0 %)	
1, 2, 3	80 (58.4 %)	13 (68.4 %)	9 (75.0 %)	
Venous invasion				0.0043
0	77 (56.2 %)	3 (15.8 %)	6 (50.0 %)	
1, 2, 3	60 (43.8 %)	16 (84.2 %)	6 (50.0 %)	
Maximum tumor size, mm				0.0004
≤40	80 (58.4 %)	4 (21.1 %)	2 (16.7 %)	
>40	57 (41.6 %)	15 (78.9 %)	10 (83.3 %)	
Lymph node dissection				0.2819
Two fields	47 (34.3 %)	10 (52.6 %)	5 (41.7 %)	
Three fields	90 (65.7 %)	9 (47.4 %)	7 (58.3 %)	
Neoadjuvant therapy				0.0436
Yes	13 (9.5 %)	2 (10.5 %)	4 (33.3 %)	
No	124 (90.5 %)	17 (89.5 %)	8 (66.7 %)	
Adjuvant therapy				0.6440
Yes	62 (45.3 %)	8 (42.1 %)	7 (58.3 %)	
No	75 (54.7 %)	11 (57.9 %)	5 (41.7 %)	
TNM stage				0.0013
0, I, II	70 (51.1 %)	6 (31.6 %)	0	
III, IV	67 (48.9 %)	13 (68.4 %)	12 (100 %)	
Residual tumor				<0.0001
R0	136 (99.3 %)	16 (84.2 %)	7 (58.3 %)	
R1/2	1 (0.7 %)	3 (15.8 %)	5 (41.7 %)	

mGPS modified Glasgow Prognostic Score, *T* tumor, *N* node, *M* metastasis, *R* residual tumor

Table 4 The univariate prognostic factors for esophageal cancer (including the mGPS)

Variable	*p*	HR	95 % CI
Sex (male)	0.4597	1.312	0.639–2.694
Age (>65 years)	0.1343	1.550	0.873–2.751
mGPS (2)	<0.0001	5.664	2.717–11.809
Depth of tumor invasion (T3, 4)	<0.0001	3.801	2.057–7.025
Lymph node metastasis			
N1	0.0215	3.064	1.179–7.962
N2	0.0165	3.476	1.256–9.625
N3	<0.0001	10.200	4.575–22.739
Distant metastasis (M1)	<0.0001	3.745	2.165–6.476
Histological type (undifferentiated)	0.4363	0.765	0.390–1.501
Lymphatic invasion (1, 2, 3)	0.0047	2.541	1.332–4.850
Venous invasion (1, 2, 3)	0.0021	2.453	1.383–4.351
Tumor size (>40 mm)	0.0013	2.750	1.484–5.098
Lymph node dissection (three fields)	0.6601	1.142	0.632–2.064
Neoadjuvant therapy	0.5469	1.302	0.552–3.069
Adjuvant therapy	0.0020	2.468	1.392–4.374
Residual tumor (R1, 2)	<0.0001	17.248	7.826–38.016

mGPS modified Glasgow Prognostic Score, *HR* hazard ratio, *CI* confidence interval, *T* tumor, *N* node, *M* metastasis

Table 5 The multivariate prognostic factors for esophageal cancer (including the mGPS)

Variable	*p*	HR	95 % CI
mGPS (2)	0.0449	2.726	1.021–7.112
Depth of tumor invasion (T3, 4)	0.1884	1.718	0.767–3.848
Lymph node metastasis			
N1	0.1074	2.620	0.811–8.464
N2	0.0625	2.729	0.949–7.847
N3	0.0178	3.964	1.269–12.383
Distant metastasis (M1)	0.2256	1.569	0.757–3.250
Lymphatic invasion (1, 2, 3)	0.3861	0.711	0.329–1.538
Venous invasion (1, 2, 3)	0.0464	2.274	1.016–5.912
Tumor size (>40 mm)	0.5015	1.293	0.611–2.737
Adjuvant therapy	0.2073	1.589	0.773–3.266
Residual tumor (R1, 2)	0.0152	3.605	1.280–10.149

mGPS modified Glasgow Prognostic Score, *HR* hazard ratio, *CI* confidence interval, *T* tumor, *N* node, *M* metastasis

significance. The relationships between mGPS and clinicopathological features are summarized in Table 3.

Statistically significant associations were detected between the prognostics scores and the tumor depth ($p < 0.0001$), lymph node metastasis ($p = 0.0101$), distant metastasis ($p < 0.0001$), venous invasion ($p = 0.0043$), maximum tumor size ($p = 0.0004$), neoadjuvant therapy ($p = 0.0436$), advanced stage ($p = 0.0013$) and residual tumor R1/2 ($p < 0.0001$). The univariate analysis demonstrated that a mGPS of 2 ($p < 0.0001$), the depth of tumor invasion ($p < 0.0001$), lymph node metastasis (N1) ($p = 0.0215$), N2 ($p = 0.0165$), N3 ($p < 0.0001$), distant metastasis ($p < 0.0001$), lymphatic invasion ($p = 0.0047$), venous invasion ($p = 0.0021$), the maximum tumor size ($p = 0.0013$), neoadjuvant therapy ($p = 0.0020$) and R1/2 status ($p < 0.0001$) were associated with a worse prognosis (Table 4). The multivariate analysis demonstrated that a mGPS of 2 ($p = 0.0449$), lymph node metastasis (N3) ($p = 0.0178$), venous invasion ($p = 0.0464$) and R1/2 tumors ($p = 0.0152$) were independently associated with a worse prognosis (Table 5).

The relationships between the NmGPS (CRP cutoff; 0.5 mg/dL) and clinicopathological features are summarized in Table 6. Similar statistically significant differences were detected regarding the depth of tumor invasion ($p < 0.0001$), lymph node metastasis ($p = 0.0008$), distant metastasis ($p = 0.0008$), venous invasion ($p = 0.0015$), maximum tumor size ($p < 0.0001$), neoadjuvant therapy ($p = 0.0007$), adjuvant therapy ($p = 0.0166$), advanced stage ($p < 0.0001$) and R1/2 status ($p < 0.0001$). In the univariate analysis, a NmGPS (CRP cutoff; 0.5 mg/dL) of 2 was associated with a worse prognosis ($p < 0.0001$) (Table 7). The multivariate analysis demonstrated that a NmGPS (CRP cutoff; 0.5 mg/dL) of 2 ($p = 0.0002$), lymph node metastasis (N3) ($p = 0.0201$), venous invasion ($p = 0.0190$) and R1/2 status ($p = 0.0209$) were independently associated with a worse prognosis (Table 8).

Discussion

We evaluated the associations between the serum CRP and serum albumin levels with the clinicopathological features and cancer-specific survival of patients with ESCC. Moreover, we established a prognostic scoring system more sensitive than the mGPS, with a lower CRP cutoff value. This study is the first to evaluate a new, optimal mGPS, and to compare it with the mGPS for patients with ESCC. In fact, the NmGPS (CRP cutoff; 0.5 mg/dL) could indicate more aggressive tumor biology, in terms of the depth of tumor invasion, presence of lymph node metastasis, distant metastasis, venous invasion, the maximum tumor size, advanced stage and R1/2 status. The number of patients with a mGPS of 2 was very small (7.1 %), in contrast to the number of patients with a mGPS 0 or 1. Moreover, there were no significant differences between the survival curves of patients with a mGPS of 1 and 2. Therefore, the mGPS was unable to be separated into three independent patient groups. On the other hand, when patients were classified based on the NmGPS (CRP cutoff; 0.5 mg/dL), there were significant differences between

Table 6 The relationships between the NmGPS (CRP cutoff; 0.5 mg/dL) and the clinicopathological features

Variable	NmGPS (0.5) 0 ($n = 121$)	NmGPS (0.5) 1 ($n = 26$)	NmGPS (0.5) 2 ($n = 21$)	p
Age, years				0.7471
≤65	56 (46.3 %)	10 (38.5 %)	10 (47.6 %)	
>65	65 (53.7 %)	16 (61.5 %)	11 (52.4 %)	
Sex				0.1744
Male	96 (79.3 %)	24 (92.3 %)	15 (71.4 %)	
Female	25 (20.7 %)	2 (7.7 %)	6 (28.6 %)	
Depth of tumor invasion				<0.0001
T0/1/2	78 (64.5 %)	5 (19.2 %)	3 (14.3 %)	
T3/4	43 (35.5 %)	21 (80.8 %)	18 (85.7 %)	
Lymph node metastasis				0.0008
N0	58 (47.9 %)	9 (34.6 %)	1 (4.8 %)	
N1/2/3	63 (52.1 %)	17 (65.4 %)	20 (95.2 %)	
Distant metastasis				0.0008
M0	121 (100 %)	26 (100 %)	19 (90.5 %)	
M1	0	0	2 (9.5 %)	
Histological type				0.1994
Differentiated	87 (71.9 %)	21 (80.8 %)	12 (57.1 %)	
Undifferentiated	34 (28.1 %)	5 (19.2 %)	9 (42.9 %)	
Lymphatic invasion				0.1399
0	53 (43.8 %)	8 (30.8 %)	5 (23.8 %)	
1, 2, 3	68 (56.2 %)	18 (69.2 %)	16 (76.2 %)	
Venous invasion				0.0015
0	72 (59.5 %)	6 (23.1 %)	8 (38.1 %)	
1, 2, 3	49 (40.5 %)	20 (76.9 %)	13 (61.9 %)	
Maximum tumor size, mm				<0.0001
≤40	79 (65.3 %)	6 (23.1 %)	4 (19.0 %)	
>40	42 (34.7 %)	20 (76.9 %)	17 (81.0 %)	
Lymph node dissection				0.4501
Two fields	44 (36.4 %)	12 (46.2 %)	6 (28.6 %)	
Three fields	77 (63.6 %)	14 (53.8 %)	15 (71.4 %)	
Neoadjuvant therapy				0.0007
Yes	11 (9.1 %)	2 (7.7 %)	8 (38.1 %)	
No	110 (90.9 %)	24 (92.3 %)	13 (61.9 %)	
Adjuvant therapy				0.0166
Yes	52 (43.0 %)	11 (42.3 %)	16 (76.2 %)	
No	69 (57.0 %)	15 (57.7 %)	5 (23.8 %)	
TNM stage				<0.0001
0, I, II	68 (56.2 %)	8 (30.8 %)	0	
III, IV	53 (43.8 %)	18 (69.2 %)	21 (100 %)	
Residual tumor				<0.0001
R0	121 (100 %)	23 (88.5 %)	15 (71.4 %)	
R1/2	0 (0 %)	3 (11.5 %)	6 (28.6 %)	

NmGPS new modified Glasgow Prognostic Score, *T* tumor, *N* node, *M* metastasis, *R* residual tumor

groups separated by one point (NmGPS [CRP cutoff; 0.5] 0 vs 1: $p < 0.0001$, NmGPS [CRP cutoff; 0.5 mg/dL] 1 vs 2: $p = 0.0099$). In the multivariate analysis of cancer-specific survival, a NmGPS (CRP cutoff; 0.5 mg/dL) of 2 was found to be a more independent prognostic indicator of a worse prognosis than a mGPS of 2. Moreover, we evaluated the quality of the prognostic scoring system using the AIC. The results of that evaluation suggested that the system using the NmGPS (CRP cutoff; 0.5 mg/dL) had higher quality than the mGPS and other NmGPS. These findings demonstrate that the NmGPS (CRP cutoff; 0.5 mg/dL) is more sensitive than the mGPS in patients with ESCC.

It is known that Asian countries, especially Japan, Korea and China, have the highest rates of esophageal cancer in the world [3], and people in Japan, Korea and China may be closely related in terms of genetics [19]. Shah et al. [20] reported that the mean CRP value of East Asians was less

Table 7 The univariate prognostic factors for esophageal cancer (including the NmGPS [CRP cutoff; 0.5 mg/dL])

Variable	*p*	HR	95 % CI
Sex (male)	0.4597	1.312	0.639–2.694
Age (>65 years)	0.1343	1.550	0.873–2.751
NmGPS (CRP cutoff; 0.5 mg/dL) (2)	<0.0001	7.807	4.215–14.461
Depth of tumor invasion (T3, 4)	<0.0001	3.801	2.057–7.025
Lymph node metastasis			
N1	0.0215	3.064	1.179–7.962
N2	0.0165	3.476	1.256–9.625
N3	<0.0001	10.200	4.575–22.739
Distant metastasis (M1)	<0.0001	3.745	2.165–6.476
Histological type (undifferentiated)	0.4363	0.765	0.390–1.501
Lymphatic invasion (1, 2, 3)	0.0047	2.541	1.332–4.850
Venous invasion (1, 2, 3)	0.0021	2.453	1.383–4.351
Tumor size (>40 mm)	0.0013	2.750	1.484–5.098
Lymph node dissection (three fields)	0.6601	1.142	0.632–2.064
Neoadjuvant therapy	0.5469	1.302	0.552–3.069
Adjuvant therapy	0.0020	2.468	1.392–4.374
Residual tumor (R1, 2)	<0.0001	17.248	7.826–38.016

NmGPS new modified Glasgow Prognostic Score, *HR* hazard ratio, *CI* confidence interval, *T* tumor, *N* node, *M* metastasis

Table 8 The multivariate prognostic factors for esophageal cancer (including the NmGPS [CRP cutoff; 0.5 mg/dL])

Variable	*p*	HR	95 % CI
NmGPS (CRP cutoff; 0.5 mg/dL) (2)	0.0002	4.437	2.000–9.844
Depth of tumor invasion (T3, 4)	0.2794	1.583	0.688–3.642
Lymph node metastasis			
N1	0.1379	2.236	0.772–6.476
N2	0.1119	2.553	0.804–8.108
N3	0.0201	3.731	1.229–11.323
Distant metastasis (M1)	0.3020	1.470	0.707–3.054
Lymphatic invasion (1, 2, 3)	0.3928	0.710	0.323–1.558
Venous invasion (1, 2, 3)	0.0190	2.286	1.145–4.563
Tumor size (>40 mm)	0.5685	1.251	0.579–2.702
Adjuvant therapy	0.0949	1.807	0.902–3.618
Residual tumor (R1, 2)	0.0209	3.230	1.194–8.737

NmGPS new modified Glasgow Prognostic Score, *HR* hazard ratio, *CI* confidence interval, *T* tumor, *N* node, *M* metastasis

than half the mean CRP value of people in other countries. Regarding the cause of the low CRP in East Asia, it was suggested that the haplotype map (HapMap) frequencies of CRP polymorphisms known to be associated with the CRP concentration might differ by ancestry; but for the most part, the difference in CRP is still unexplained [20]. Therefore, it could be that the low CRP cutoff value, we identified reflects the low mean CRP value of East Asians.

The mechanism responsible for the association between a systemic inflammatory response (SIR) and a poor outcome in patients with advanced cancer is not well understood. However, there is increasing evidence that there is a relationship between SIR and cancer survival. Cancer cells might influence the tumor microenvironment through the upregulation of inflammatory pathways by producing proinflammatory mediators, such as cytokines, chemokines, cyclooxygenase-2 (COX-2), prostaglandins, inducible nitric oxide synthase and nitric oxide [21]. These proinflammatory mediators markedly promote tumor progression, invasion and metastasis [21]. Interleukin-6 (IL-6) is a proinflammatory cytokine associated with angiogenesis, and it induces both the development and progression of cancer [22]. CRP is produced by hepatocytes in response to inflammatory cytokines, particularly interleukin-6, which is present in the tumor microenvironment [23]. Because the SIR is also associated with lymphocytopenia and an impaired T-lymphocytic response within the tumor microenvironment, it reflects compromised cell-mediated immunity [23].

Hypoalbuminemia often develops secondary to an ongoing SIR [24]. In addition, the occurrence of a SIR and the associated nutritional decline may influence the

tolerance of and compliance with active treatment [11]. Therefore, the combination of an elevated serum CRP level and hypoalbuminemia reflects both SIR and the progressive nutritional decline of the patient with advanced cancer, and can predict the malignant potential of the tumor and a worse prognosis of cancer patients.

CRP and albumin are routinely evaluated parameters. The GPS is simpler and cheaper than other techniques such as computed tomography, magnetic resonance imaging and positron emission tomography. Therefore, because we can easily predict the prognosis of cancer patients using the NmGPS (CRP cutoff; 0.5 mg/dL), we can take appropriate measures to care for postoperative patients to improve their survival.

In conclusion, we developed a simple and sensitive prognostic scoring system for patients with esophageal squamous cell carcinoma based on the GPS. This scoring system may also be useful for predicting the prognosis of patients with other carcinomas.

Conflict of interest M. Nakamura and the co-authors have no conflict of interest to declare.

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ORIGINAL ARTICLE

Atrial fibrillation after esophageal cancer surgery: an analysis of 207 consecutive patients

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Abstract
Purpose The aim of this study was to identify perioperative risk factors that are associated with postoperative atrial fibrillation (AF) and the outcomes of different pharmacological interventions in esophageal cancer patients who underwent transthoracic esophagectomy.
Methods This study included 207 patients who underwent a transthoracic esophagectomy for esophageal cancer resection by a single surgeon from January 1, 2004, through December 31, 2010.
Results Postoperative AF occurred in 19 patients (9.2 %), all of whom received antiarrhythmic drug therapy at the early stage. Antiarrhythmic treatment was effective in 12 cases (63.2 %). In this study, landiolol hydrochloride, an ultrashort-acting β_1-selective β-blocker, was the first-line therapy for postoperative AF. A multivariate logistic regression analysis showed that postoperative AF was significantly associated with the use of an ileo-colon for reconstruction after esophagectomy ($P = 0.0023$, odds ratios [OR] = 13.6) and with the presence of tachycardia with a heart rate of >100 bpm on postoperative day (POD) 1 ($P = 0.0004$, OR = 18.4).
Conclusions Postoperative AF is associated with the use of a colon conduit for reconstruction after esophagectomy and with tachycardia with a heart rate >100 bpm on POD 1. Identifying patients at high risk for postoperative AF will allow for more direct application of pharmacological methods of prophylaxis.

Keywords Esophageal cancer · Atrial fibrillation · Esophagectomy

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Introduction

A transthoracic esophagectomy for the resection of esophageal carcinoma is associated with a high incidence of complications, including postoperative pneumonia, anastomotic leakage and cardiac events. Postoperative atrial fibrillation (AF) is a common arrhythmia after esophagectomy (10–60 %) and is associated with increased morbidity and mortality rates [1–6]. Considerable progress has been made toward decreasing surgical complications, such as anastomotic leakage, because of the standardization of surgical techniques [7]. However, the continued high rate of postoperative AF may be related to the use of extensive lymphadenectomy [8, 9]. Several studies have reported on the use of pharmacological therapies, such as diltiazem, amiodarone and landiolol, to prevent AF after general thoracic surgery, but their effectiveness remains controversial [10–13]. Therefore, the identification of high-risk populations will allow for targeted use, and will resolve questions about the efficacy of the drugs, potentially leading to successful prevention of AF.

Previous studies identified several risk factors predicting the development of AF after esophagectomy, including advanced age, male sex, a history of cardiac disease and a history of chronic obstructive pulmonary disease (COPD) [2, 4, 14]. However, these studies examined only small numbers of patients with esophageal cancer, and the risk

factors are consequently not clearly understood. Furthermore, these studies included patients who had various surgical procedures, such as the Lewis Tanner operation, transhiatal approach and three-phase lymph node dissection. We routinely perform right transthoracic esophageal resection with two-field (the mediastinum and the abdomen) or three-field (plus bilateral cervix) lymph node dissection and anastomosis with the cervical esophagus in the cervical wound for patients with thoracic esophageal cancer. For these reasons, our study was conducted to identify perioperative risk factors that are associated with postoperative AF, and to assess the outcomes of different pharmacological interventions in esophageal cancer patients who underwent transthoracic esophagectomy.

Patients and methods

Between January 1, 2004, and December 31, 2010, a total of 232 consecutive patients underwent surgery for thoracic esophageal carcinoma at Wakayama Medical University Hospital. This study included 207 patients who underwent transthoracic esophagectomy for esophageal cancer resection by a single surgeon. The patients who underwent esophagectomy with an additional laryngectomy ($n = 2$) or pneumonectomy ($n = 2$) were excluded. Two patients who underwent a nonresective operation (bypass surgery, 1 patient; diagnostic thoracotomy, 1 patient) were also excluded. In addition, 14 patients who underwent palliative esophagectomy were excluded. Five patients who had preoperative AF, defined as a sustained or repetitive arrhythmia documented by electrocardiography (ECG) that required antiarrhythmic therapy [14], were also excluded. Follow-up data were obtained from the database, which included the patients' background, surgical details and tumor characteristics. The tumor invasion (T) and lymph node status (N) were classified by the UICC criteria [15]. Informed consent was obtained from all of the patients in accordance with the guidelines of the Ethics Committee on Human Research of Wakayama Medical University Hospital. Data regarding the patients' age, sex, tumor location, tumor level (TNM stage), cardiac disease, hypertension, preoperative cardiac function test results, preoperative pulmonary function test results, diabetes and treatment with concurrent combined chemotherapy/chemoradiotherapy were analyzed. Patients with conditions such as angina pectoris and previous myocardial infarction were classified as having cardiovascular disease. Poor cardiac function was defined as an ejection fraction <60 %, as measured by echocardiography. Patients with abnormal pulmonary function on spirograms (vital capacity ration [%VC] < 70 % or forced expiratory volume in 1 s [FEV_1]/forced vital capacity [FVC] < 60 %) were classified as having pulmonary disease as a comorbidity [16]. Diabetes mellitus was noted if the patient had a fasting blood glucose concentration >126 mg/dL or was receiving antidiabetic therapy [17]. We administered neoadjuvant chemotherapy with cisplatin and 5-fluorouracil for Stage II–III esophageal cancer. This regimen employed in the Japan Clinical Oncology Group (JCOG) 9907 [18] study is now standard in Japan. In our institute, neoadjuvant chemoradiotherapy (NACRT) has been used to treat localized esophageal carcinoma (cT3–4 tumors). We therefore performed NACRT in the modified JCOG 9906 study with cisplatin and 5-fluorouracil plus concurrent radiotherapy [19].

In our institute, traditional open right transthoracic esophageal resection with two- or three-field lymph node dissection is usually performed for patients with thoracic esophageal cancer. After anterolateral thoracotomy, esophagectomy with regional lymphadenectomy is performed. Our two-field lymph node dissection includes total mediastinal, perigastric and celiac lymphadenectomy. Three-field lymph node dissection adds removal of the lymph nodes in the supraclavicular and cervical paratracheal regions to the two-field approach. In January 2009, we adopted minimally invasive thoracoscopic esophageal resection when the tumor is cT1–2 [20, 21]. In brief, the patient is placed in a prone position, five trocars are placed along the medial edge of the scapula, and thoracoscopic esophagectomy with regional lymphadenectomy is performed. In cases in which a patient has lower third thoracic esophageal cancer with poor cardiac function or has had a previous right thoracotomy, we perform left transthoracic esophageal resections. If the lesion is located in the middle or upper third of the thorax, we use hand-assisted laparoscopic surgery for mobilization of the stomach and abdominal lymph node dissection and gastric tube formation [22].

A gastric conduit through the retrosternal route or through the posterior mediastinum is usually used to construct the anastomosis with the cervical esophagus. In patients with previous gastrectomy or concomitant gastric cancer, the right ileo-colon is used. The esophageal anastomosis is then established in an end-to-side fashion in the cervical wound.

All patients underwent perioperative respiratory rehabilitation, and 125 mg of methylprednisolone was administered intravenously at the beginning of the thoracotomy and again at the end of the surgery [23, 24]. All patients were admitted to the intensive care unit immediately after the operation. All patients began standing and walking on postoperative day (POD)1. Epidural analgesia was used routinely for postoperative pain management for 1 week. All patients having a postoperative cardiac diagnosis by ECG remained under continuous monitoring for at least 72 h after surgery.

In this study, postoperative complications were analyzed according to the Clavien–Dindo classification and the thoracic morbidity and mortality (TM&M) system [25, 26]. In this study, complications higher than Grade II were regarded as clinically significant postoperative complications. Grade II refers to any complication that requires pharmacological treatment or minor intervention only; Grade III means any complication that requires surgical, radiological or endoscopic intervention or multiple therapies (Grade IIIa indicates that intervention does not require general anesthesia; Grade IIIb indicates that intervention requires general anesthesia) and Grade IV indicates any complication requiring intensive care unit management and life support. Surgical mortality (Clavien–Dindo classification Grade V) included in-hospital deaths within 30 days after surgery.

Postoperative AF was defined as an absent P wave before the QRS complex, with irregular ventricular rhythm on the rhythm strips [1, 14]. Leakage at the anastomosis site was determined by the leakage of contrast medium by upper gastrointestinal series after surgery. An intra-abdominal abscess (including bile leakage) was defined as intra-abdominal fluid collection, identified by ultrasonography or computed tomography (CT), with positive cultures. The diagnosis of postoperative pneumonia was made via CT and an elevated white blood cell count and serum C-reactive protein (CRP) level. Respiratory failure was defined as the need for intubation and mechanical ventilation in patients. The diagnosis of postoperative pneumothorax and diaphragmatic hernia was made via chest CT. Postoperative deterioration of liver function was defined by a serum aspartate aminotransferase level more than two times the upper limit of the normal level within 14 days after the operation. The diagnosis of postoperative vocal code paralysis was made via bronchoscopy, which is a routine examination in our group (POD1).

The StatView 5.0 software package (Abacus Concepts, Inc., Berkeley, CA) was used for all statistical analyses. Quantitative results are expressed as medians and ranges. A statistical analysis was performed using Fisher's test. A P value <0.05 was considered to be significant. The univariate and multivariate logistic regression analyses were performed to identify risk factors influencing the development of postoperative AF. Risk factors with a univariate $P < 0.10$ were included in the multivariate analysis. Risk factors with a multivariate $P < 0.05$ were defined as independent risk factors.

Results

Table 1 shows the detailed characteristics of the 207 patients, including 167 males and 40 females, with a median age of 66 years. The tumor was located in the upper third of the thorax in 16 patients (7.7 %), middle third of the thorax in 151 patients (72.9 %) and lower third of the thorax in 40 patients (19.3 %), and the median tumor size was 39 mm. The primary tumors were squamous cell carcinoma (193; 93.2 %), adenocarcinoma (10; 4.8 %) and others (4; 1.9 %). Twenty-five (12.1 %), 34 (16.4 %), 54 (26.1 %), 55 (26.6 %) and 39 (18.8 %) patients had TNM Stage 0, I, II, III and IV, respectively.

Table 2 shows the surgical data. A total of 171 patients (82.6 %) underwent an open right transthoracic esophageal resection. Twenty-eight patients (13.5 %) received a minimally invasive thoracoscopic esophageal resection [21]. Eight patients underwent a left transthoracic esophageal resection. One hundred thirteen patients received a radical three-field lymphadenectomy (total mediastinum, abdomen and cervix), and 88 patients received a two-field lymphadenectomy (total mediastinum and abdomen). After esophagectomy, the stomach was used for reconstruction in 182 patients, the ileo-colon was used in 24 patients and the

Table 1 Clinicopathological features of the patients ($n = 207$)

Age, years (median, range)	66 (43–85)
Sex (male/female)	167/40
Tumor location (Ut/Mt/Lt)	16/151/40
Tumor size, mm (median, range)	39 (3–90)
Pathology (SCC/adenocarcinoma/other)	193/10/4
Depth of invasion[a] (T0/Tis/T1/T2/T3/T4)	2/6/83/35/79/2
TNM stage[a] (0/I/II/III/IV)	25/34/54/55/39
NAC (%)	53 (25.6)
NACRT (%)	14 (6.8)

Ut upper third of the thorax, *Mt* middle third of the thorax, *Lt* lower third of the thorax, *SCC* squamous cell carcinoma, *NAC* neoadjuvant chemotherapy, *NACRT* neoadjuvant chemoradiotherapy

[a] UICC TNM 7th edition

Table 2 Surgical data ($n = 207$)

Approach (right thoracotomy/thoracoscope/left thoracotomy)	171/28/8
Lymph node dissection (3-field/2-field/1-field)[a]	113/88/6
Conduit (stomach/colon/jejunum)	182/24/1
Route of reconstruction (retrosternal/posterior mediastinum)	148/59
Median length of operation, min (range)	525 (310–776)
Median blood loss, mL (range)	437 (45–3,100)
Blood transfusion (%)	54 (26.1)
Curative resection[b] (%)	192 (92.8)

[a] Three-field indicates bilateral cervical regions, the mediastinal space and the abdomen; two-field indicates the mediastinum and the abdomen and one-field indicates the abdomen and the middle/low mediastinum

[b] UICC TNM R0

jejunum was used in one patient. The median duration of the operation was 525 min, and the median blood loss was 437 mL.

The details of the postoperative complications for esophagectomy (more than Grade II morbidity) are listed in Table 3. One or more complications were experienced by 61 patients (29.5 %). AF and pneumonia, classified as Grade II, only required medical therapy (e.g. beta-blockers for AF, or antibiotics for pneumonia). Seventeen patients with lateral vocal cord paralysis were followed through swallowing rehabilitation until recovery. Five patients with bilateral vocal cord paralysis required tracheostomy. Anastomotic leakage was observed in eight patients (3.9 %), six with minor leaks and two with leaks requiring additional drainages. Three patients with respiratory failure required 1–14 days of ventilation and tracheostomy early in the series, and subsequently required 1 month to recover. Diaphragmatic hernias occurred in two patients after esophagectomy with gastric pull-up (one patient with a retrosternal gastric tube, one patient with an intrathoracic gastric tube). These two patients underwent diaphragmatic hernia repair in open surgery. In our series of 207 patients who underwent esophagectomy, no surgical mortality occurred.

Table 3 Postoperative complications ($n = 207$)

Complications	No. (%)	Clavien–Dindo classification[a] (n)		
		Grade II	Grade IIIa	Grade IIIb
Any	61 (29.5)			
Atrial fibrillation	19 (9.2)	19		
Vocal cord paralysis[b]	22 (10.6)	17	5	
Pneumonia	12 (5.8)	12		
Anastomotic leakage	8 (3.9)	6	2	
Pneumothorax	6 (2.9)	6		
Wound infection	5 (2.4)	5		
Respiratory failure	3 (1.4)			3
Chylothorax	2 (1.0)	2		
Cervical lymphatic leakage	2 (1.0)	2		
Enteritis	2 (1.0)	2		
Diaphragmatic hernia	2 (1.0)			2
Deterioration of liver function	1 (0.5)	1		
Bile leakage	1 (0.5)		1	
Intra-abdominal abscess	1 (0.5)		1	
Mortality	0 (0)			

[a] Surgical complications were classified into five categories by the Clavien–Dindo classification

[b] Including transient paralysis

Other complications related to the esophagectomy (more than Grade II morbidity) affected 63.2 % of the patients who had postoperative AF (12/19) compared with 16.0 % of the patients without AF (30/188) ($P < 0.0001$, Table 4). We found that postoperative complications were more common in patients with postoperative AF.

Table 5 shows the details of the patients with postoperative AF. All patients were male, and had a median age of 69 years. In all cases, the postoperative AF occurred within 48 h after surgery. In 12 of the 19 patients (63.2 %), AF was found after patients were up and walking postoperatively. The median duration of postoperative AF was 3.7 days (range 0.5–14 days). All 19 patients received antiarrhythmic drug therapy in the early stage, and 12 patients (63.2 %) responded positively. Successful treatment was defined as a heart rhythm change to a sinus rhythm within 72 h of the start of treatment. In our institute, landiolol hydrochloride, an ultrashort-acting β_1-selective β-blocker has been used as the first-line therapy against postoperative AF since 2002 [12].

The univariate and multivariate analyses were performed to identify risk factors for postoperative AF. Table 6 shows the results of the analysis of the 31 variables that were univariately examined as potential risk factors for the 19 patients with postoperative AF vs the 188 patients without postoperative AF. Nine of the 31 factors differed significantly between these groups ($P < 0.10$). Of the preoperative factors, patients having hypertension ($P = 0.0003$) and having other arrhythmia ($P = 0.0064$) were found to be significant. In terms of the intraoperative factors, ileo-colon use for reconstruction ($P < 0.0001$), reconstruction through the retrosternal route ($P = 0.0870$) and a long operation ($P = 0.0058$) were selected as significant predictors. Among the various postoperative factors, dopamine use ($P = 0.0484$), the onset of other complications ($P < 0.0001$), tachycardia ($P < 0.0001$) and fever ($P = 0.0041$) were selected. The multivariate logistic regression analysis indicated that postoperative AF was significantly associated with the use an ileo-colon for reconstruction after esophagectomy ($P = 0.0023$) and the presence of tachycardia with a heart rate of >100 bpm on POD1 ($P = 0.0004$), with odds ratios of 13.6 (95 % confidence interval [CI], 2.5–72.4) and 18.4 (95 % CI, 3.7–92.0), respectively.

Table 4 Correlation between the onset of postoperative atrial fibrillation and other complications in patients after esophagectomy ($n = 207$)

Other complications	Atrial fibrillation		
	Yes ($n = 19$)	No ($n = 188$)	P value
Yes ($n = 42$)	12	30	<0.0001
No ($n = 165$)	7	158	

We found that postoperative AF was significantly associated with the use of a colon conduit for reconstruction and with tachycardia on POD1 (Table 6). Therefore, we examined the incidence of postoperative AF in patients with these factors. As shown in Table 7, the incidence of postoperative AF in patients with both colon conduit use for reconstructions after esophagectomy and those who had tachycardia with a rate >100 bpm on POD1 was 100 % (4/4), while the incidence of postoperative AF in patients without these two factors was only 2.4 % (4/168).

Discussion

Major pulmonary complications and surgical sepsis are common morbidities in patients with AF after esophagectomy [6]. The association of postoperative AF with mortality has also been documented after lung surgery [27] and after major noncardiac operations [14]. In the present study, postoperative complications were also frequently observed in patients with AF.

We speculate that AF after esophagectomy is caused by an inflammatory response following surgical trauma to the sympathovagal nerve fibers supplying the heart [2, 28, 29]. It has been reported that advanced age and a history of cardiac disease are predisposing factors for postoperative AF [6]. Ma et al. [2] reported that AF was associated with postoperative hypoxia, a history of COPD, thoracic–gastric dilatation, an age older than 65 years, male sex and a history of cardiac disease. Stippelet al [30] reported that an elevated body temperature was the most important predisposing factor for AF. Interestingly, Hou et al. [1] described that an elevated level of perioperative N terminal (NT)-pro B-type natriuretic peptide (BNP) is an independent predictor of AF. Thus, previous studies have shown different results.

We found that the use of colonic interposition for esophageal replacement after esophagectomy was a predictor of postoperative AF. This association has not been

Table 5 Summary of patients with postoperative atrial fibrillation

Patient no.	Age	Sex	Onset of an AF	Situation at the onset	Duration of AF (days)	Drugs	Other complications
1	72	M	POD2	Resting	0.5	Digoxin	None
2	68	M	POD2	Resting	0.5	Digoxin	Pneumonia
3	71	M	POD2	Resting	2	Digoxin	None
4	68	M	POD2	Resting	4	Digoxin	Pneumothorax
5	85	M	POD2	After walking	6	Digoxin Landiolol Verapamil	Enterocolitis
6	77	M	POD2	After walking	10	Landiolol Pilsicainide Verapamil	Respiratory failure
7	71	M	POD1	After walking	4	Digoxin Landiolol Verapamil	Pneumonia
8	68	M	POD1	Resting	1	Landiolol	Vocal cord paralysis
9	52	M	POD2	Resting	0.5	Pilsicainide	Vocal cord paralysis
10	64	M	POD2	After walking	1	Landiolol	None
11	72	M	POD2	After walking	3	Landiolol Disopyramide	None
12	76	M	POD2	After walking	2	Landiolol	Anastomotic leakage
13	75	M	POD2	After walking	14	Landiolol	Anastomotic leakage Intra-abdominal abscess
14	67	M	POD2	Resting	3	Landiolol	None
15	65	M	POD2	After walking	6	Pilsicainide	Vocal cord paralysis
16	71	M	POD1	After walking	2	Landiolol	None
17	65	M	POD1	After walking	2	Landiolol	Pneumothorax
18	59	M	POD1	After walking	7	Landiolol	None
19	62	M	POD2	After walking	2	Pilsicainide	Vocal cord paralysis

AF atrial fibrillation, *POD* postoperative day, *M* male

Table 6 Results of the univariate and multivariate analyses of risk factors influencing the postoperative atrial fibrillation

Risk factors	Categories	Univariate analysis	Multivariate analysis	
		P value	*P* value	Odds ratio (95 % CI)
Preoperative factors				
Sex	Male	0.9668		
	Female			
Age (years)	≥70	0.2932		
	<70			
BMI (kg/m^2)	≥25	0.9666		
	<25			
Cancer location	Ut	0.9793		
	Mt/Lt			
NAC	Yes	0.5326		
	No			
NACRT	Yes	0.4979		
	No			
History of cardiovascular disease	Yes	0.1864		
	No			
History of hypertension	Yes	0.0003	0.0648	3.660 (0.923–14.510)
	No			
History of pulmonary disease	Yes	0.2573		
	No			
History of diabetes mellitus	Yes	0.7009		
	No			
Ejection fraction (%)	<60	0.5659		
	≥60			
R(L)BBB, PVC or AV block	Yes	0.0064	0.1410	3.289 (0.674–16.057)
	No			
Intraoperative factors				
Approach	Thoracotomy	0.1068		
	Thoracoscope			
Lymphadenectomy	3-Field	0.1099		
	2-Field			
Conduit	Colon	<0.0001	0.0023	13.580 (2.546–72.426)
	Gastric tube/jejunum			
Route of reconstruction	Retrosternal	0.0870	0.3277	2.727 (0.366–20.338)
	Posterior mediastinum			
Thoracic duct resection	Yes	0.9786		
	No			
Duration of operation (min)	≥600	0.0058	0.6799	1.384 (0.295–6.484)
	<600			
Blood loss (mL)	≥500	0.1917		
	<500			
Blood transfusion	Yes	0.2674		
	No			
Curative resection[a]	Yes	0.7278		
	No			
Postoperative factors				
Dopamine use	Yes	0.0484	0.6966	0.746 (0.171–3.249)
	No			

Table 6 continued

Risk factors	Categories	Univariate analysis	Multivariate analysis	
		P value	*P* value	Odds ratio (95 % CI)
Sivelestat use	Yes	0.3785		
	No			
Complications other than AF	Yes	<0.0001	0.0516	4.920 (1.924–16.710)
	No			
Sinus heart rate in POD 1 (bpm)	≥100	<0.0001	0.0004	18.401 (3.680–92.003)
	<100			
Hemoglobin in POD1 (g/dL)	<8	0.9764		
	≥8			
WBC on POD 1 (/μL)	≥10,000	0.2379		
	<10,000			
CRP on POD 1 (mg/dL)	≥10	0.8663		
	<10			
PaO_2 on POD 1 (mm Hg)	<100	0.5042		
	≥100			
Highest CVP on POD 1 (mm Hg)	<5	0.6214		
	≥5			
Highest fever on POD1 (°C)	≥37	0.0041	0.1261	3.053 (0.730–12.757)
	<37			

CI confidence interval, *BMI* body mass index, *NAC* neoadjuvant chemotherapy, *NACRT* neoadjuvant chemoradiotherapy, *Ut* upper third of the thorax, *Mt* middle third of the thorax, *Lt* lower third of the thorax, *R(L)BBB* right(left) bundle branch block, *PVC* premature ventricular contraction, *AV block* atrioventricular block, *AF* atrial fibrillation, *POD* postoperative day, *WBC* white blood cell, *CRP* C-reactive protein, *CVP* central venous pressure

[a] UICC TNM R0

Table 7 Incidence of postoperative atrial fibrillation in patients with two risk factors, colon conduit use for reconstructions and sinus tachycardia with a rate >100 bpm on POD1

Risk categories[a]	AF cases	(%)
Risk 0		
Without colon conduit, HR < 100 bpm	4/168	2.4
Risk 1–1		
Without colon conduit, HR ≥ 100 bpm	6/15	40.0
Risk 1–2		
With colon conduit, HR < 100 bpm	5/20	25.0
Risk 2		
With colon conduit, HR ≥ 100 bpm	4/4	100.0

POD postoperative day, *HR* heart rate, *AF* atrial fibrillation

[a] Risk 0 indicates the patients without colon conduit use for reconstruction after esophagectomy and with a heart rate <100 bpm on POD1. Risk 1–1 indicates the patients without colon conduit use for reconstruction but with tachycardia with a heart rate >100 bpm. Risk 1–2 indicates the patients with colon conduit use for reconstruction who had a heart rate <100 bpm. Risk 2 indicates the patients with both colon conduit use for reconstruction and tachycardia

demonstrated in the previous studies. In general, transthoracic esophagectomy produces an excessive inflammatory response, which may lead to the development of systemic inflammatory response syndrome and postoperative morbidities [24]. In particular, colonic reconstruction after esophagectomy is a more complex procedure, with increased morbidity compared with gastric transposition [31]. The blood loss is greater and the length of the operation is longer in the colonic reconstruction group, reflecting the complexity of the operation [31]. Therefore, it is suggested that esophagectomy with reconstruction using a colonic conduit is accompanied by much greater surgical stress, which might translate to a high incidence of postoperative AF.

In this study, sinus tachycardia with a rate >100 bpm on POD1 was the most significant risk factor for postoperative AF. The peak incidence of postoperative AF was on POD1 or 2, which is consistent with the findings of previous studies [2, 4]. A previous report in patients undergoing pulmonary surgery also showed similar results [14]. In our institute, esophageal cancer patients are consistently up and walking on POD1 or 2 after esophagectomy, and as a result, the greatest incidence of AF was found after walking. We suspect that the increases in heart rate during walking may have triggered the AF. We previously found that a perioperative physiotherapy and pulmonary rehabilitation program improves the exercise capacity and early

ambulation in patients undergoing esophagectomy [23]. Therefore, we consider early mobilization to be essential for patients that have undergone esophagectomy; however, it is also important to control the heart rate on POD1 and 2 in order to prevent AF after esophagectomy.

Intraoperative fluid therapy decisions may also influence the postoperative AF. Our surgical team and anesthetist kept the infusion rates between 6 and 8 mL/kg/h during esophagectomy, and the intraoperative urine output was kept between 0.5 and 1 mL/kg/h. Therefore, we consider that the water balance during the operation had no influence on the postoperative AF in our series of patients.

Prophylactic therapy may be performed for high-risk groups, including patients who undergo esophagectomy with reconstruction using a colon conduit and/or patients with sinus tachycardia after esophagectomy, to prevent the occurrence of postoperative AF. Indeed, the incidence of postoperative AF in patients with colon conduit use for reconstructions and tachycardia on POD1 was 100 %. The current commonly cited guidelines do not provide a specific recommendation for anticoagulation in the postoperative period for general thoracic surgeries [32]. Early attention to heart rate control and possible conversion back to normal sinus rhythm is a well-accepted principle of current patient care [32]. We consider landiolol hydrochloride to be a first-line therapy against postoperative AF [12]. Landiolol is a drug which acts as a highly cardioselective, ultrashort-acting β_1-selective β-blocker. It is often used as an anti-arrhythmic agent in Japan. Because of its extremely short half-life in the blood (<4 min), landiolol is outstanding in terms of its immediate efficacy and adjustability. Recent randomized controlled studies using landiolol have reported significant reductions in AF after cardiac surgery compared with placebo [12]. Another randomized controlled study clearly demonstrated that the mortality and the perioperative incidence of cardiovascular events could be reduced by the use of β-blockers in patients who underwent major noncardiac surgery [33]. Therefore, we may reduce not only the incidence of AF, but also other postoperative complications after esophagectomy, with the use of landiolol. While several medications have been used for postoperative AF prophylaxis without risk discrimination, a better understanding of the mechanisms responsible for postoperative AF could help in the design of novel prophylactic or therapeutic measures targeting those who are at the greatest risk. Clinical trials of the prophylactic use of landiolol to prevent postoperative AF are now planned in patients at high risk who undergo transthoracic esophagectomy.

Conflict of interest None.

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7 ペプチドワクチンを用いた膵癌治療

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Key words ：ペプチドワクチン，免疫療法，PEGASUS-PC，immunocheckpoint

はじめに

膵癌は唯一切除が治癒の可能性を有する治療法であるが，いまだに切除不能症例が切除可能症例を上回り，その予後は不良である[1]。また，切除例においても高率に再発をきたし，術後の治療が予後延長において重要となっている。ゲムシタビン塩酸塩は5-FUとの比較試験結果から，膵癌化学療法における標準治療となったが[2]，さらなる治療成績の向上を探索する目的で多くの薬剤とのhead-to-headの比較試験ならびにゲムシタビン塩酸塩との併用が試みられた。上皮成長因子受容体（Epidermal Growth Factor Receptor；EGFR）に対する分子標的治療薬であるエルロチニブとゲムシタビン塩酸塩との併用が，はじめてゲムシタビン塩酸塩単剤と比較して生存において優越性を示した薬剤である[3]。しかし，生存に関するHazard比は0.82であるが，その生存期間中央値は併用群6.2ヵ月，ゲムシタビン塩酸塩単独群5.9ヵ月[3]とわずかであり，副作用や費用対効果を考えると新たな標準治療との結論には至らないのが現状である。大腸癌の予後が新規抗悪性腫瘍薬の登場により著しく改善していることからも，膵癌の予後改善には新薬の開発が急務であることは想像に難くない。最近，FOLFIRINOX療法が報告され，ゲムシタビン塩酸塩を含まないregimenではじめて全生存期間に対する優越性を証明できたこと（Hazard ratio for death，0.57；95% confidence interval，0.45-0.73；$P<0.001$）[4]から，膵癌化学療法も大きく飛躍していくものと考えるが，その副作用は有熱性好中球減少症をはじめとする重篤なものが認められ，残念ながら，全膵癌患者に対し施行できる治療法ではないことが問題点である。一方，免疫療法は，抗癌剤や分子標的治療薬とは異なり，副作用の点からも開発が望まれている治療法である。

Ⅰ．T細胞の癌細胞識別

T細胞は異物となる抗原を特異的に認識して排除するが，抗原受容体であるT細胞受容体は直接抗原を認識しないことが抗体とは異なるところである。抗原の分解物質であるペプチドが，主要組織適合性複合体（major histocompatibility complex；MHC）に結合し，免疫応答を誘導する。腫瘍関連抗原においては細胞傷害性T細胞（Cytotoxic T lymphocyte；CTL）が認識できる腫瘍抗原ペプチドが報告され[5]，それまでは漠然としていた腫瘍抗原が明らかとなり，理論的根拠に立脚した腫瘍抗原を標的とした癌ワクチン療法が考案されることになった。標的となる腫瘍細胞に特異的に発現している内因性抗原である腫瘍関連抗原は樹状細胞に取り込まれ，プロテアソームによるプロセシング作用を受けてペプチド断片となり，主要組織適合抗原（MHC，ヒトではHLA）クラスⅠ分子の$\alpha 1$，$\alpha 2$ドメインに結合し，ゴルジ体を介して細胞表面へ表出し，MHC（HLA）ーペプチド複合体によりペプチドがCD8陽性T細胞に提示され，CD8陽性T細胞を活性化することにより抗原

特異的なCTLが誘導される。ペプチドワクチン療法では腫瘍特異的CTLを誘導しうるペプチドを同定し，それを癌患者に投与することで，樹状細胞に取り込まれ，上述の作用機序により腫瘍特異的CTLが誘導される。腫瘍抗原の同定に伴って特異的T細胞の頻度やサブセットなどが生命予後と関連すること[6]からも，T細胞が癌細胞の消去を担っていることが推測される。乳癌に対する癌ペプチドワクチンが術後補助療法として再発抑制効果が報告された[7]が，膵癌には期待されたような臨床効果は見られなかった[8]。その原因として癌細胞の免疫逃避機構の存在が示唆される。

Ⅱ．免疫逃避機構

化学発癌モデルやウイルス発癌モデルとは異なり，自然発癌において腫瘍細胞は宿主免疫監視機構をすり抜け発育している。一定以上の腫瘍細胞量にまで成長した腫瘍細胞はヘテロな集団であり，さまざまな免疫逃避機構が推測される[9,10]。腫瘍細胞は遺伝子変異を起こしやすく腫瘍関連抗原の発現も不安定であり，CTLが認識できない細胞が存在する。腫瘍抗原だけでなくHLA class Ⅰの発現が低下するため，HLA-ペプチド複合体が形成されず，CTLが腫瘍細胞を認識できない。このHLA class Ⅰの発現が低下する現象は多くの癌腫で報告されており[11~13]，膵癌でも同様の報告がされている[10]。また，HLA class Ⅰ発現の低下・消失は患者生存率が低下し，再発も多いことがほかの癌腫で報告されている[14,15]。さらに癌微小環境における免疫抑制因子の存在が危惧される。腫瘍細胞や周囲の間質細胞から産生されるIL-10に代表される免疫抑制性サイトカインやTGF-β[16]，制御性T細胞により[17]，CTLは免疫抑制状態となる。また，腫瘍抗原の長期に渡る持続的暴露がT細胞の機能不全・exhaustionに陥る[18]。

Ⅲ．腫瘍新生血管を標的とした癌ワクチン療法

免疫逃避機構を克服するには，癌細胞自体を標的にするのではなく膵癌細胞の増殖や転移に必須で[19,20]，かつHLA class Ⅰ発現が安定している腫瘍新生血管を標的とする新しい発想での免疫療法を施行することとした。VEGF-Aはほとんどの腫瘍で発現が上昇しており，VEGFR1およびVEGFR2の二つのレセプター型チロシンキナーゼと結合する[21]。VEGFR1およびVEGFR2を介したシグナル伝達を遮断することで，血管新生の阻害や癌細胞の増殖。転移を抑制することが期待できる[22]。また，VEGFR2はVEGFR1よりVEGF-Aによる血管内非細胞の増殖や血管透過性などの主要なシグナル伝達を強く担うレセプターであり，VEGFR2のシグナル伝達を遮断することは腫瘍新生血管の阻害ならびに腫瘍細胞の浸潤・転移を抑制できる可能性を示唆している。当科で施行した医師主導型第Ⅰ相臨床試験で用いたペプチドはVEGFR2由来エピトープペプチド（VEGFR2-169，Elpamotide，エルパモチド）であり，VEGFR2を特異的に認識し，最も強い腫瘍新生血管を傷害するCTLを誘導することができる[23]。また，担癌患者からも特異的CTLが誘導できることが明らかになっている。VEGFR1由来ペプチドも同定されており，ペプチドをパルスした細胞に対し細胞傷害活性を有することが確認され，VEGFR1を内因性に発現した細胞においても特異的活性化CTLの誘導が確認できている[24]。さらに，VEGFR2はFOXP3highCD4$^+$Treg細胞に選択的に発現しており[25]，VEGFR2を標的とすることでTreg細胞の抑制に期待ができる。

Ⅳ．当科で行った第Ⅰ相臨床試験

HLA-A-*2402を有する切除不能膵癌患者を対象に医師主導型第Ⅰ相臨床試験，「切除不能進行再発膵癌に対する腫瘍新生血管を標的としたHLA-A*2402拘束性エピトープペプチドとgemcitabine併用による第Ⅰ相

表1 局所皮膚反応と臨床効果

	局所皮膚反応	
	陽性	陰性
PR+SD	12	0
PD	3	3

参考文献26から改変転載

表2 免疫応答と臨床効果

	ペプチド投与量（mg）		
	0.5 (n=6)	1.0 (n=6)	2.0 (n=6)
局所皮膚反応（+/−）	5	4	6
CTL反応（+/−）	3	4	4
臨床効果			
PR/SD/PD	0/4/2	0/4/2	1/3/2
全生存期間（日）	233	207	344

参考文献26から改変転載

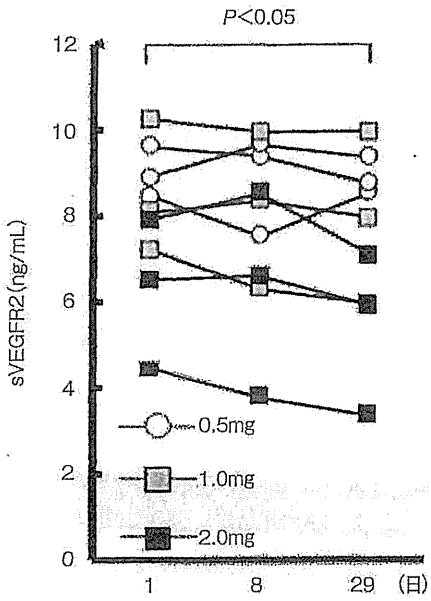

図1 ペプチドワクチン投与によるsVEGFR2抑制効果
参考文献26より改変転載

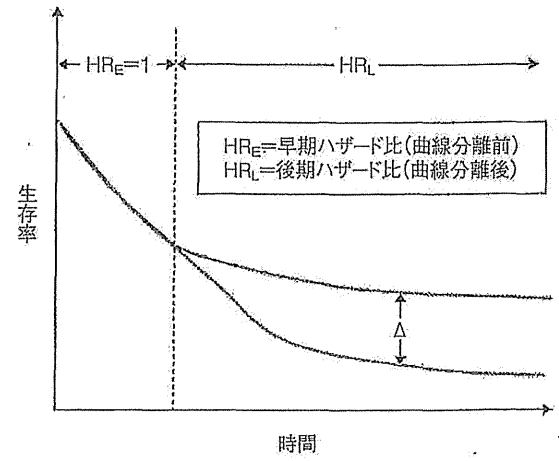

図2 癌ワクチン療法における生存曲線分離効果遅延

臨床試験」（ClinicalTrials. gov ID：NCT00622622）を施行した。種々の理由からdrop outした3名を除き，評価対象患者は18名で主要評価項目は安全性とした。注射部位反応やCTL反応解析などの免疫反応，臨床的反応を副次的評価項目とし推奨投与量を決定することとした。VEGFR2-169を0.5 mg，1.0 mg，2.0 mgの各コホート6名とし，週1回の投与とした。Gemcitabineは1,000 mg/m^{2}とし，通常投与と同じ3週投薬1週休薬とした。免疫学的解析ではVEGFR2-169特異的CTLが11例（61%）で誘導され，注射部位反応も15例（83%）に認められた（**表1**）。副作用は許容範囲内であり，投与量を規定する毒性は認めなかった。臨床的効果はペプチド投与部位の局所皮膚反応が陽性であった症例15例のうち12例（80%）がpartial responseまたはstable diseaseであったが，陰性であった症例3例すべてprogress diseaseであった（**表1**）。さらに2 mg投与群の生存期間が最も長かった（**表2**）。以上の結果から推奨投与量は2 mg/bodyとした[26]。また，ほかの第Ⅰ相臨床試験においても，重篤な副作用は認めず，血清sVEGFR2濃度はエルパモチド投与により有意に低下し，濃度依存性を示す傾向があった（**図1**）[27]。

V. 第Ⅱ/Ⅲ相臨床治験の意義—PEGASUS-PC 試験—

この医師主導型第Ⅰ相臨床試験の結果にて，pivotal に第Ⅱ/Ⅲ相臨床治験（PEGASUS-PC 試験）へと発展した。実薬と偽薬の割付比率は 2:1 で，153 例が登録された。主要評価項目である全生存期間では，実薬群と偽薬群で統計学的有意差は認められなかった。しかし，注射部位反応によるサブグループ解析を行ったところ，実薬群で皮膚反応を強く認めた 10 例の生存期間中央値が 16.0 ヵ月であるのに対し，偽薬ならびに実薬で皮膚反応のない群の生存期間中央値が約 8 ヵ月であった。すなわち，皮膚反応が一つのバイオマーカーになり得る可能性とペプチドワクチンにより生存期間が延長する responder が存在し，エルパモチドにより誘導された VEGFR-2 特異的 CTL の効果と考えられた。

PEGASUS-PC 試験では，全症例における生存期間の有意な延長は認めなかったが，PEGASUS-PC 試験は日本で初めてのペプチドワクチンによる膵癌に対する質の高い治験であるだけでなく，後の免疫療法の臨床試験のあり方の礎になると考えられる。とくに，免疫治療の特徴を評価する解析法要，すなわち，従来の抗悪性腫瘍薬とは全く異なった新しい解析方法で行われた点がほかの試験とは異なる斬新な試験ということができよう。通常，有効性は主に Kaplan-Meier 法により生存割合を算出し，log-rank 検定あるいは Willcoxon 検定によって治療群間の比較検定を行うことで，主要評価項目である生存期間あるいは無病生存期間の差により評価される。しかし，癌ペプチドワクチンにおいては，抗原特異的免疫応答を介した薬理薬効から遅発性の効果発現が想定されている（**図 2**）。このことを考慮し，観察期間後期に重み付けを置く Harrington-Fleming 法[28]による解析が行われ，独立行政法人医薬品医療機器総合機構（PMDA）がこれを許可したことは免疫療法の新時代を感じさせるものである。その反面，ペプチドワクチン療法に代表される免疫療法は，治療効果が得られるまでの時間が十分に得られない間に癌の進行による全身状態の悪化ならびに癌死亡に至ることが，免疫療法の有効性の証明を阻んでいるものと考える。

VI. ペプチドワクチンの効果発現の特性

ペプチドワクチンは生体の免疫反応を介した効果であるため，従来の抗腫瘍薬とは違った観点から評価をしなければならない。米国 FDA ではすでにガイダンスが発行されているが，日本には癌ワクチン療法のガイダンスはなく，日本バイオセラピィ学会が 2012 年 12 月に「がん治療用ペプチドワクチンガイダンス」を発行した（http://jsbt.org/guidance/）。統計検定においても，Harrington-Fleming 法[28]のような薬剤の特性に応じたハザード比の変化に対応した検定が必要である。また，腫瘍縮小効果は RECIST（Response Evaluation Criteria in Solid Tumours）での評価が一般的であるが，病勢進行（PD）の場合遅延性の効果については評価ができない。そこで PD 基準を修飾した irRC（immune-related response criteria）が提唱された[29,30]。irRC が生存期間延長効果と相関するかについては，今後のさらなる臨床研究が必要である。

VII. 複数のペプチドワクチンによる治療

PEGASUS-PC 試験では実薬群の中に強い皮膚反応を示す症例があり，生存期間が延長する可能性が示唆された。そこで，使用するペプチドの種類を増やすことで免疫能の改善する症例が増えることが期待される。Stage Ⅲ大腸癌では RNF43 と TOMM34 由来の HLA-A24 拘束性ペプチドと経口抗癌剤である UFT/LV を投与したところ，RNF43 と TOMM34 の双方に対する CTL 反応陽性群の生存期間中央値が 36.1 ヵ月であるのに対し，CTL 反応陰生群の生存期間中央値は 9.5 ヵ月と短かった（$p=0.0079$）[28]。標準治療不応進行食道癌では TTK，LY6K，IMP3 由来の HLA-A24 拘束性ペプチドを投与したところ，三つの抗原に対する CTL 陰性群に

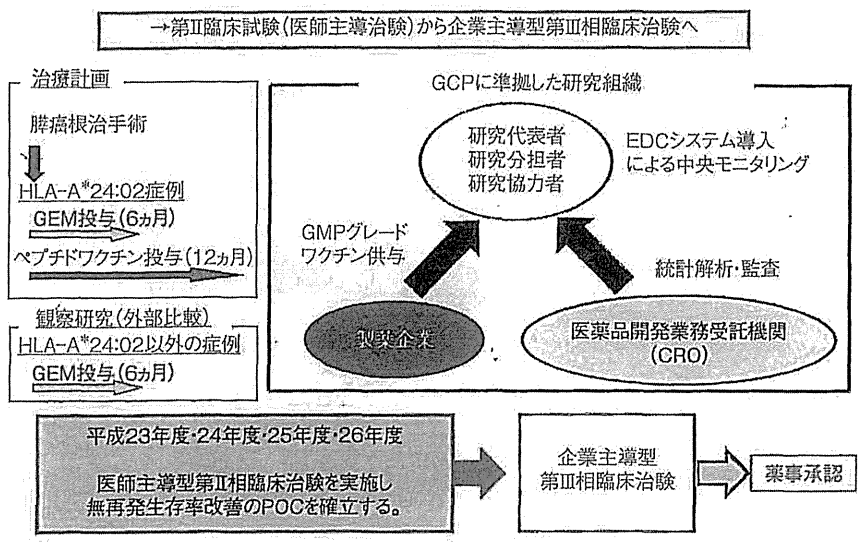

図3 膵癌に対する術後再発予防のための2方向性ペプチドワクチン療法の開発

比較して，陽性抗原数が増えるにつれ生存期間が延長し，TTK，LY6K，IMP3の3抗原すべてに反応を示した群のみに1年以上の長期生存例が見られた[31]。膵癌においても，腫瘍新生血管と腫瘍細胞を直接標的とする2方向性のワクチン療法として，VEGFR1，VEGFR2，KIF20Aに対する3種類のペプチドワクチンを混合したC01を用いた標準療法不応膵癌に対するプラセボ対照ランダム化第III相臨床治験（COMbined PEptide ThErapy for Pancreatic Cancer；COMPETE-PC試験）が全国40施設で実施された。しかし，対象症例が標準治療不応の進行膵癌であるため，生存期間に対する優越性を証明することはできず，中間解析において無効中止となった。これらの治験結果を詳細に層別化に基づく解析を進めることで，ペプチドワクチンの対象症例を絞り込めるものと考えられることから，詳細な報告が待たれる。

VIII. 医師主導治験：膵癌に対する術後再発予防のための2方向性新規ペプチドワクチン療法の開発

本来，免疫療法は再発予防に最も適した治療法である。そこで，現在われわれはC01ワクチンを用いた膵癌切除後の再発予防を目的とした多施設共同第II相臨床治験を医師主導型治験として実施している。本研究の結果を基に，企業主導型第III相治験へ展開し，薬事承認を目指すことを目的としている（**図3**）。

IX. ペプチドワクチン療法のbreak through

進行癌患者ではすでに免疫抑制状態に陥り，細胞傷害性T細胞なども疲弊している可能性がある。進行癌におけるT細胞の不適切な抗原刺激はT細胞の活性を抑制すること，すなわちanergyが示唆されていたが，このT細胞の抑制メカニズムとしてImmune checkpointが重要であることが明らかとなってきた。すなわち，Immune checkpointを介した不適切な細胞傷害性Tリンパ球の活性化により抗腫瘍効果を失う一方（**図4**），Immune checkpointに対する抗体でImmune checkpointをblockすると細胞傷害性Tリンパ球の抗腫瘍活性は回復することが明らかになった。これまでに，メラノーマ患者にImmune checkpointであるPD-1とCTLA-4の抗体を単独投与する第I相試験の結果，PD-1とCTLA-4に対する2種類の抗体を1 mg/kgまたは3 mg/kg投与する同時併用投与のcohortでは，40～53%のObjective Responseを認め，その効果は持続した[32]。

これらの効果により，FDAは2011年にCTLA-4抗体を転移性メラノーマに対する標準治療として承認し