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Is lymph node dissection for neuroendocrine carcinoma of the stomach effective as it is for adenocarcinoma?

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ABSTRACT

Background: We evaluated the significance of lymph node dissection for gastric neuroendocrine carcinoma (NEC) by calculating the therapeutic value index for each station.
Methods: This study included 2164 advanced gastric cancer patients (common-type [Common-GC], n = 2125; and gastric NEC [NEC-GC], n = 39). Clinicopathological data were collected, and survival, type of recurrence, and the index for each type of gastrectomy were determined.
Results: NEC-GC was characterized by an older population (P = 0.009), upper tumor location (P = 0.021), frequent venous invasion (P < 0.001), and less neural invasion (P = 0.043). NEC-GC tended to be more frequent in men (P = 0.152), and to be associated with total gastrectomy (P = 0.177) and M1 cases (P = 0.167).
The five-year overall survival rates of the Common-GC and NEC-GC groups were 73.8% (95% confidence interval: 71.8–75.6) and 54.7% (37.5–68.9), respectively (P = 0.016).
Both groups showed similar index values in each station. Regarding the index of the peri-gastric nodal station (D1 station)/stations away from the stomach (D2 station), although the index of the D1 station was similar in the two groups (41.3 and 43.1), the index of the D2 station in the NEC-GC group was approximately half that of the Common-GC group (10.0 and 5.3).
The total recurrence rates of the two groups were similar (P = 0.871). However, the rates of hematogenous and lymphatic recurrence tended to be higher in the NEC-GC group (P = 0.132 and P = 0.152).
Conclusions: The therapeutic efficacy of the D1 station was similar in Common-GC and NEC-GC but that of the D2 station was worse in NEC-GC. Gastrectomy with D2 dissection would be less effective for NEC-GC.

Introduction

Neuroendocrine carcinoma (NEC) is a high-grade neuroendocrine neoplasm with aggressive behavior and a poor prognosis. The digestive organs are the dominant primary site of NEC, but NEC of the stomach is rare [1,2]. Gastric NEC is treated as a special type of gastric cancer in the Japanese Classification of Gastric Cancer [3]. Histologically, NECs are heterogeneous tumors, that include both small cell NEC and large cell NEC [2]. In addition, gastric NEC often coexists with adenocarcinoma components [2].

Although the standard treatment for gastric NEC has not been established yet, primary surgery is often selected for localized gastric NEC because there is a general consensus that complete local resection is necessary for the curative treatment of solid tumors. When surgeons select gastrectomy, the next question is the extent of nodal dissection. In Japan, gastrectomy with systematic lymph node dissection has been performed based on the treatment for common gastric adenocarcinoma [3,4]. However, it remains unclear whether nodal dissection is as effective for NEC as it is for gastric adenocarcinoma.

The efficacy of dissection could be evaluated based on the proportion of patients with nodal metastasis who survived for more than five years as a result of nodal dissection. This theory was proposed by Sasako et al. and was named the therapeutic index [5]. In gastric NEC, frequent nodal metastasis may work to increase the therapeutic index, but frequent hematogenous recurrence may

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offset the efficacy of nodal dissection.

In this background, the present study evaluated the therapeutic index of each nodal station of advanced gastric NEC in comparison to each nodal station of common gastric adenocarcinoma. This is the first report to discuss the efficacy of nodal dissection in gastric NEC.

Patients and methods

This was a retrospective, single center, observational study. We reviewed clinical data obtained from hospital records, such as general patient information, the histopathological characteristics of the tumors, and data concerning treatment and follow-up. This study was approved by the ethical committee of National Cancer Center Hospital (No. 2017-077).

Patients

This study included 2164 advanced gastric cancer patients, consisting of 2125 cases of common-type gastric cancer (Common-GC) and 39 cases of gastric cancer that included an NEC component (NEC-GC). All patients received gastrectomy with nodal dissection at our department between January 2000 and July 2015, in accordance with the Japanese Gastric Cancer Treatment Guidelines, version 4 [6]. All tumors met the following criteria: (1) advanced gastric cancer (pT2-pT4), (2) histologically proven common-type adenocarcinoma or NEC or adenocarcinoma including an NEC component, (3) underwent total, distal, proximal, or pylorus-preserving gastrectomy with D1 or more nodal dissection, (4) R0 resection or R1 resection due to cy + only was achieved, (5) M0 or M1 due to cy + only, and (6) no preoperative therapy was added.

Evaluation of the tumor

Tumors were evaluated according to the Union for International Cancer Control tumor–node–metastasis classification, 8th edition [7]. Lymph node stations were numbered according to the definition of the Japanese Gastric Cancer Association (Table 1) [3]. Then, peri-gastric lymph node stations (No. 1 to No. 7) were defined as D1 station and stations away from the stomach (No.8a to 12a) were defined as D2 station (Table 1). ND1 and ND2 were defined as follows: ND1, positive for lymph node metastasis up to D1 station; ND2; positive for lymph node metastasis beyond D1 station and up to D2 station.

Therapeutic value index of lymph node dissection

We introduced the therapeutic value index presented by Sasako et al., in 1995 to evaluate the impact of each dissected lymph node station [5]. The index, which was defined as a percentage, was calculated by multiplying the incidence of lymph node metastasis to the station by the 5-year survival rate of patients.

Statistical analysis

All data are presented as the median and total ranges, unless otherwise stated. Student's t-test and the chi-squared test were used to compare the proportions of patients. Overall survival (OS) was measured from the date of the operation to the date of death or the last follow-up examination. The OS rates were calculated by the Kaplan-Meier method and compared by a log-rank test. All statistical analyses were performed using the freely available software program, EZR version 1.51 [8].

Results

Study population

Three thousand twenty-eight patients who underwent gastrectomy for advanced gastric cancer between January 2000 and July 2015 were screened for this study, and 2164 patients were judged to be eligible, and divided into the common-type gastric cancer group (Common-GC, N = 2125) and the gastric cancer including an NEC component (NEC-GC, N = 39) (Fig. 1). Among NEC-GC group, NEC component was dominant (NEC dominant) in 31 cases, and adenocarcinoma component was dominant (NEC minor) in 8 cases.

Background characteristics and histopathological findings

The background characteristics and histopathological findings are shown in Table 2. In comparison to the Common-GC group, the NEC-GC group showed the following characteristics: older population ($P = 0.009$), upper tumor location in the stomach ($P = 0.021$), frequent venous invasion ($P < 0.001$), and less neural invasion ($P = 0.043$).

In the Common-GC group, 28.6% of the patients received adjuvant chemotherapy, which—in almost all cases—was S-1 or a regimen containing S-1. On the other hand, in the NEC-GC group, 7 patients (17.9%) received adjuvant chemotherapy. One patient

Table 1
Lymph node stations.

D1 station	
No. 1	Right paracardial nodes
No. 2	Left paracardial nodes
No. 3	Lesser curvature nodes
No. 4sa	Left greater curvature nodes along the short gastric arteries
No. 4sb	Left greater curvature nodes along the left gastroepiploic artery
No. 4d	Right greater curvature nodes along the right gastroepiploic artery
No. 5	Suprapyloric nodes
No. 6	Infrapyloric nodes
No. 7	Nodes at the root of the left gastric artery
D2 station	
No. 8a	Nodes along the common hepatic artery
No. 9	Nodes at the celiac artery
No. 10	Nodes around the splenic hilum
No. 11p	Nodes along the proximal splenic artery
No. 11d	Nodes along the distal splenic artery
No. 12a	Nodes along the proper hepatic artery

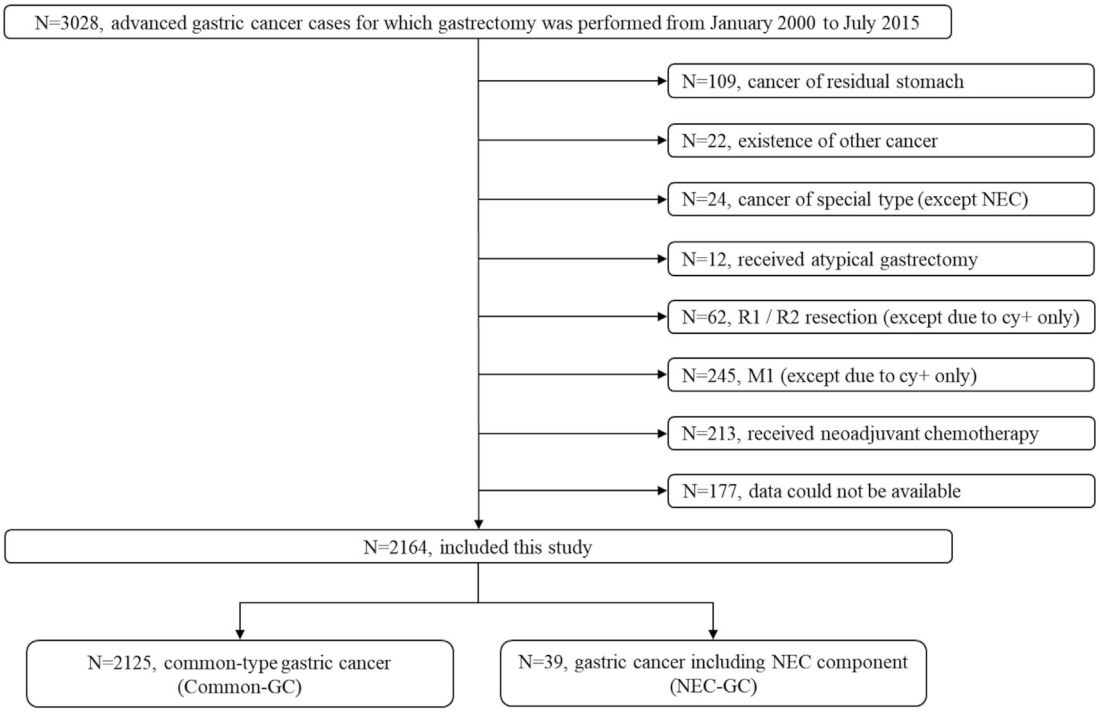

Fig. 1. Flow diagram of the 3028 patients who underwent gastrectomy for advanced gastric cancer between January 2000 and July 2015.

Table 2
Background characteristics of the patients in the common-type gastric cancer and gastric neuroendocrine carcinoma groups.

Characteristics		Common-GC (N = 2125)	NEC-GC (N = 39)	P value
Age (years)	Median (range)	65 (21–92)	70 (35–86)	0.009*
Gender	Female/Male	694/1431	8/31	0.152+
Tumor size (mm)	Median (range)	55 (6–300)	55 (15–150)	0.658*
Tumor location	L/M/U	685/871/569	11/10/18	0.021+
Type of gastrectomy	DG/PPG/TG/PG	1111/97/880/37	16/0/22/1	0.177+
pT category (UICC TNM 8th)	T2/T3/T4	570/739/816	10/18/11	0.290+
pN category				
according to UICC TNM 8th	N0/N1/N2/N3	751/445/404/525	10/13/8/8	0.249+
according to LN station	N0/ND1/ND2	751/937/437	10/21/8	0.397+
M category	M0/M1 (by CY1 only)	1995/130	34/5	0.167+
pStage (UICC TNM 8th)	I/II/III/IV	307/814/873/131	4/16/14/5	0.322+
Histological type	Differentiated/Undifferentiated	836/1289	–	
	NEC dominant/NEC minor	–	31/8	
Lymphatic invasion	-/+	730/1395	13/26	1+
Venous invasion	-/+	1120/1005	7/32	<0.001+
Neural invasion	-/+	1143/967	28/11	0.043+
Adjuvant chemotherapy	No/Yes	1518/607	32/7	0.201+

Common-GC, common-type gastric cancer; NEC-GC, gastric neuroendocrine carcinoma; DG, distal gastrectomy; PPG, pylorus-preserving gastrectomy; TG, total gastrectomy; PG, proximal gastrectomy; UICC, Union for International Cancer Control; ND1, positive for lymph node metastasis up to D1 station; ND2, positive for lymph node metastasis beyond D1 station and up to D2 station.
*; P values were evaluated by Student's t-test.
+; P values were evaluated by the chi-squared test.

received irinotecan plus cisplatin therapy; the other 6 patients received S-1 therapy.

Survival

The median follow-up period of the survivors of the Common-GC group was 85.8 months, while that of the NEC-GC group was 84.8 months; both exceeded 5 years. The 5-year overall survival (5y-OS) rates are shown in Fig. 2. The OS rate of the NEC-GC rates was significantly poorer than that of the Common-GC rates (P = 0.016). Although the number of NEC-GCs at each N stage was limited, in ND2, NEC-GC was associated with a poorer survival in comparison to Common-GC (P = 0.069), while no difference in survival was evident in ND1 (P = 0.763). Among NEC-GC group, there were no significant difference in the OS curves between NEC dominant and NEC minor (P = 0.116).

Calculated therapeutic value index for each nodal station

The incidence of nodal metastasis, the 5y-OS rates of patients with metastasis, and the calculated therapeutic index for each group are described in Table 3. Both groups seemed to show similar index values in each station. Focusing on the index of D1/D2 station, the index of D1 station of the two groups seemed equivalent, while

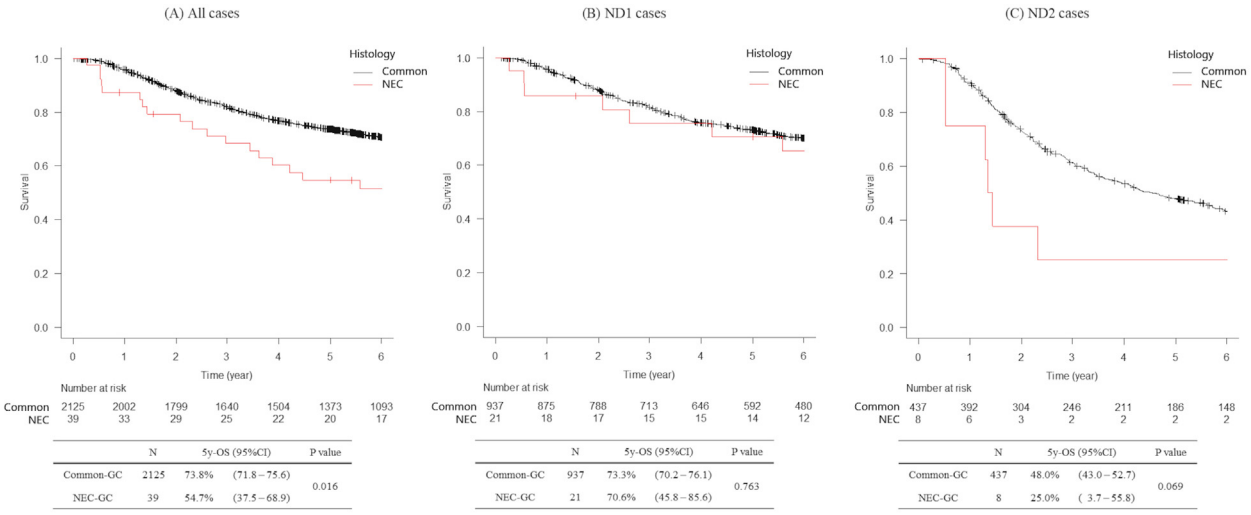

Fig. 2. Overall survival (OS) of the common-type gastric cancer and gastric neuroendocrine carcinoma groups.

Table 3
The incidence of nodal metastasis, the 5-year survival rates and the calculated therapeutic value index in the common-type gastric cancer and gastric neuroendocrine carcinoma groups.

Station	Metastatic rate (%)				5-year survival rate of patients with metastasis (95% confidence interval)				Therapeutic value index	
	Common-GC		NEC-GC		Common-GC		NEC-GC		Common-GC	NEC-GC
No. 1	419/1696	(19.8)	12/38	(31.6)	55.7	(50.6−60.4)	33.3	(10.3−58.8)	11.0	10.5
No. 2	141/785	(15.2)	4/24	(16.7)	47.1	(38.4−55.4)	50.0	(5.8−84.5)	7.2	8.3
No. 3	941/1177	(44.4)	22/37	(59.5)	62.6	(59.3−65.6)	53.6	(30.9−71.8)	27.8	31.9
No. 4sa	91/796	(10.3)	1/19	(5.3)	35.2	(25.3−45.3)	0	NA	3.6	0
No. 4sb	126/1912	(6.2)	0/38	(0)	46.7	(37.6−55.3)	NA	NA	2.9	NA
No. 4d	519/1569	(24.9)	5/38	(13.2)	55.1	(50.6−59.4)	40.0	(5.2−75.3)	13.7	5.3
No. 5	150/1731	(8.0)	4/36	(11.1)	48.3	(39.7−56.4)	0	NA	3.9	0
No. 6	443/1636	(21.3)	3/38	(7.9)	56.2	(51.2−60.8)	0	NA	12.0	0
No. 7	358/1754	(17.0)	9/39	(23.1)	49.9	(44.3−55.1)	33.3	(7.8−62.3)	8.5	7.7
No. 8a	202/1887	(9.7)	2/37	(5.4)	48.0	(40.7−55.0)	0	NA	4.6	0
No. 9	172/1891	(8.3)	4/35	(11.4)	39.9	(32.4−47.4)	25.0	(0.9−66.5)	3.3	2.9
No. 10	63/591	(9.6)	2/13	(15.4)	42.1	(29.6−54.2)	0	NA	4.1	0
No. 11p	146/1871	(7.2)	3/36	(8.3)	41.1	(32.9−49.2)	33.3	(0.9−77.4)	3.0	2.8
No. 11d	54/718	(7.0)	1/16	(6.3)	41.7	(28.4−54.5)	0	NA	2.9	0
No. 12a	27/1615	(1.6)	0/30	(0)	34.2	(17.0−52.2)	NA	NA	0.6	NA
D1 station	1350/2125	(63.5)	29/39	(74.4)	65.0	(62.3−67.5)	57.9	(37.9−73.5)	41.3	43.1
D2 station	437/2104	(20.8)	8/38	(21.1)	48.0	(43.0−52.7)	25.0	(3.7−55.8)	10.0	5.3

Common-GC, common-type gastric cancer; NEC-GC, gastric neuroendocrine carcinoma; NA, not available.

that of D2 station in the NEC-GC group was only approximately half of that in the Common-GC group.

Type of first recurrence

The types of first recurrence in each group is are in Table 4. The total recurrence rates of the two groups did not differ to a statistically significant extent (P = 0.871). However, the rates of hematogenous and lymphatic recurrence in the NEC-GC group tended to be higher than those in the Common-GC group (P = 0.132 and P = 0.152, respectively).

Discussion

This study examined the therapeutic efficacy of nodal dissection for gastric NEC in comparison to common-GC. To our knowledge, this is the first report to examine the therapeutic efficacy of lymph node dissection for gastric NEC. The present study demonstrated

Table 4
Type of first recurrence in each group.

	Common-GC (N = 2125)		NEC-GC (N = 39)		P value
	N	%	N	%	
Whole recurrence	601	28.3	12	30.8	0.871
Dissemination	302	14.2	5	12.8	0.988
Hematogenous	201	9.5	7	17.9	0.132
Lymphatic	127	6.0	5	12.8	0.152
Local	9	0.4	0	0	1

Common-GC, common-type gastric cancer; NEC-GC, gastric neuroendocrine carcinoma.
※There were some overlapping cases. P values were evaluated by the chi-squared test.

that the therapeutic value index of peri-gastric lymph nodes in common GC and NEC-GC was similar, while that of the regional nodes away from the stomach was worse in the gastric NEC group. This result suggested that gastrectomy with D2 lymph node dissection would be less effective for gastric NEC than it is in common GC.

We introduced the therapeutic value index to evaluate the therapeutic efficacy of lymph node dissection for each station. The index consists of the product of the metastatic incidence of each station and the prognosis of patients with metastasis to the station [5]. This study showed that common GC and NEC-GC had similar metastatic rates for both the D1 and D2 stations and similar 5-year survival rates when the patients had metastasis at D1 station; however, the survival rate of the NEC-GC group was approximately half that of the common-GC group, and the index of the NEC-GC group was approximately half that of the common-GC group.

Why was the survival of gastric NEC patients only worse than that of common-type patients when the D2 station was positive? The precise mechanisms are unclear. Interestingly, the frequency of whole and peritoneal recurrence was similar in both types of disease; however, hematogenous and lymphatic metastasis were more frequently observed in the gastric NEC group than in the common-type group. One review article pointed out the clinicopathological similarity between gastric NEC and pulmonary small cell carcinoma, that is, there were high frequency of hematogenous and lymphatic metastasis in gastric NEC cases [9]. And one study article also showed the high frequency of liver and distant lymph node recurrence in gastric NEC [2]. Our results were compatible with these articles. This suggested that recurrence other than dissemination occurred simultaneously by multiple routes in gastric-NEC. Positivity of the D2 station would be a marker for invisible micro-metastasis at the distant organs or distant lymph nodes in gastric NEC. The idea of the regional lymph nodes might differ between gastric NEC and the common type.

Gastric NEC has been believed to be associated with aggressive behavior and a poor prognosis [1,2]. In this study, the overall survival of the gastric NEC group was significantly worse in comparison to the common type group. However, both types had similar survival rates when nodal metastasis was limited to the D1 station. This result suggested that gastric NEC is mostly a local disease and that nodal dissection works well as long as the cancer cells remain up to the lymph nodes close to the primary site. Thus, at least D1 nodal dissection would be justified for gastric NEC.

The present study was associated with several limitations. First, the cases of gastric NEC in this study were not entirely consistent with NEC in the current World Health Organization (WHO) classification. The concept of neuroendocrine neoplasm was first proposed in the WHO classification of the tumors of the digestive system 2010 [1], and these tumors were classified as neuroendocrine tumor (NET)-G1, G2, and NEC-G3, according to the Ki-67 index value. Then, in 2019, the WHO classification was updated and gastrointestinal NEC was reclassified into NET-G3 and NEC according to its histological differentiation [10]. On the other hand, in the Japanese classification of gastric carcinoma, NEC was described as endocrine cell carcinoma, a special type of gastric cancer [3]. This only provided a histomorphological description and did not describe the Ki-67 index. This study included cases between 2000 and 2015, with many cases treated before 2010. In old cases, especially before 2010, it is difficult to determine whether a case was NEC or NET-G3, mixed adeno-neuroendocrine carcinoma (MANEC)/mixed neuroendocrine-non-neuroendocrine neoplasm, or neither of them from the pathological reports published at that time. On the other hand, one report showed that the survival did not differ between NEC and MANEC or between pure NEC and NEC with an adenocarcinoma component [2]. In fact, also in this study, there was no significant difference in survival between NEC dominant and NEC minor. Thus, even in this study, the amount of the NEC component may not be necessarily be as important as previously considered.

Second, the number of gastric NEC patients was relatively small. The reliability of the results must therefore be taken into consideration. However, it seems difficult to accumulate more gastric NEC cases in a single institute. A multicenter study should be planned. The third issue is adjuvant chemotherapy for gastric NEC. Although a standard adjuvant chemotherapy has yet to be established, 7 of 32 patients received adjuvant chemotherapy. Six of the seven patients received S-1 therapy, and one received irinotecan plus cisplatin therapy in this cohort. The effects of these regimens are unknown but might have affected the results.

Conclusion

We showed that the therapeutic efficacy of dissection of the peri-gastric lymph nodes was similar in patients with common-type gastric cancer and patients with gastric NEC; however, the efficacy of patients who underwent dissection of the regional nodes away from the stomach was worse in the gastric NEC group. Gastrectomy with D2 lymph node dissection would be less effective for gastric NEC in comparison to common-type gastric cancer.

Disclosures

None of the authors have any financial relationships to disclose, and none of the authors have a personal or institutional financial interest in the materials or devices described in this article.

CRediT authorship contribution statement

Yukinori Yamagata: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data curation, Writing - original draft, Writing - review & editing, Visualization, Supervision, Project administration. **Takaki Yoshikawa:** Conceptualization, Methodology, Validation, Investigation, Resources, Writing - original draft, Writing - review & editing, Visualization, Supervision, Project administration. **Kenichi Ishizu:** Conceptualization, Investigation, Resources, Writing - review & editing. **Ayako Kamiya:** Conceptualization, Investigation, Resources, Writing - review & editing. **Takeyuki Wada:** Conceptualization, Investigation, Resources, Writing - review & editing. **Tsutomu Hayashi:** Conceptualization, Investigation, Resources, Writing - review & editing. **Sho Otsuki:** Conceptualization, Investigation, Resources, Writing - review & editing. **Hitoshi Katai:** Conceptualization, Investigation, Resources, Writing - review & editing.

Declaration of competing interest

Dr. Yamagata has nothing to disclose. Dr. Yoshikawa reports personal fees from ONO, personal fees from MSD, personal fees from Lilly, personal fees from TAIHO, personal fees from Chugai, personal fees from Nihon Kayaku, personal fees from BMS, personal fees from Daiichi Sankyo, personal fees from TERUMO, personal fees from Johnson and Johnson, personal fees from Pfizer, personal fees from Olympus, personal fees from Yakult, personal fees from Eizai, personal fees from Kyowa, personal fees from Covidien, outside the submitted work;.

Dr. Ishizu has nothing to disclose.

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Dr. Wada has nothing to disclose.

Dr. Hayashi has nothing to disclose.

Dr. Otsuki has nothing to disclose.

Dr. Katai has nothing to disclose.

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