Table 16 Survival outcomes by liver metastasis (fH)

	No. of patients	Postoperative survival rate (%)					SE of 5YSR	DD	Lost to follow up	Alive	Main cause of death							
		1 year	2 year	3 year	4 year	5 year					L	P	H	M	R	OC	OD	UK
fH0	10665	89.9	82.6	78.1	74.9	72.7	0.5	55	1806	6171	249	956	216	143	268	144	482	230
fH1	305	42.6	24.6	15.3	12.2	11.8	2.0	7	28	28	8	48	130	15	25	5	10	8

f final finding

Table 17 Survival outcomes by peritoneal metastasis (fP)

	No. of patients	Postoperative survival rate (%)					SE of 5YSR	DD	Lost to follow up	Alive	Main cause of death							
		1 year	2 year	3 year	4 year	5 year					L	P	H	M	R	OC	OD	UK
fP0	10301	91.2	84.5	80.0	76.9	74.8	0.4	49	1771	6131	232	628	322	143	245	148	468	213
fP1	658	49.0	27.0	19.3	14.7	12.4	1.4	11	64	66	24	363	30	15	49	1	21	25

Table 18 Survival outcomes by peritoneal cytology (CY)

	No. of patients	Postoperative survival rate (%)					SE of 5YSR	DD	Lost to follow up	Alive	Main cause of death							
		1 year	2 year	3 year	4 year	5 year					L	P	H	M	R	OC	OD	UK
CY0	4109	88.6	78.9	73.0	68.9	66.4	0.8	24	671	2157	135	403	184	82	120	56	185	116
CY1	651	51.6	29.1	18.2	14.9	12.3	1.4	4	73	60	23	338	35	15	62	4	25	16

Table 19 Survival outcomes by distant metastasis (fM)

	No. of patients	Postoperative survival rate (%)					SE of 5YSR	DD	Lost to follow up	Alive	Main cause of death							
		1 year	2 year	3 year	4 year	5 year					L	P	H	M	R	OC	OD	UK
fM0	10752	89.4	82.0	77.3	74.2	72.1	0.5	59	1817	6159	233	932	331	140	278	149	479	234
fM1	215	46.7	27.3	23.6	19.7	18.0	2.8	3	21	30	25	72	15	16	16	2	14	4

Table 20 Survival outcomes by JGCA stage

	No. of patients	Postoperative survival rate (%)					SE of 5YSR	DD	Lost to follow up	Alive	Main cause of death							
		1 year	2 year	3 year	4 year	5 year					L	P	H	M	R	OC	OD	UK
Stage IA	4997	98.2	96.7	94.9	93.2	91.9	0.4	11	983	3646	6	11	8	3	14	87	181	58
Stage IB	1459	96.4	93.0	90.1	87.4	85.1	1.0	7	267	993	9	28	13	11	15	28	78	17
Stage II	1237	93.0	85.0	79.7	75.7	73.1	1.3	7	196	736	26	70	44	24	38	14	65	24
Stage IIIA	975	85.8	71.2	61.2	55.2	51.0	1.7	9	143	395	47	137	50	32	53	6	61	51
Stage IIIB	562	76.6	55.3	43.9	36.0	33.4	2.1	5	63	153	48	141	31	24	40	2	36	24
Stage IV	1649	53.9	32.2	22.4	18.3	15.8	1.0	22	161	206	122	626	199	62	135	11	71	56

unknown site ($n = 298$), and local recurrence including node metastasis ($n = 267$).

The proportion of male patients was 69.6% and their 5YSR was lower than that of female patients ($P < 0.01$; Table 5; Fig. 5). The proportion of patients who were more than 80 years old was 7.0%, and their 5YSR was 48.7% (Table 6; Fig. 6). Upper-third gastric cancer accounted for 21.4% of the cases, and the 5YSR (65.3%) of patients with cancer at this site was lower than that for the middle- and lower-third cancers ($P < 0.001$; Table 7; Fig. 7). The

Table 21 Survival outcomes by JGCA stage (4 classifications)

	No. of patients	Postoperative survival rate (%)					SE of 5YSR	DD	Lost to follow up	Alive	Main cause of death							
		1 year	2 year	3 year	4 year	5 year					L	P	H	M	R	OC	OD	UK
Stage I	6456	97.8	95.8	93.8	91.9	90.3	0.4	18	1250	4639	15	39	21	14	29	115	259	75
Stage II	1237	93.0	85.0	79.7	75.7	73.1	1.3	7	196	736	26	70	44	24	38	14	65	24
Stage III	1537	82.4	65.4	54.9	48.2	44.5	1.3	14	206	548	95	278	81	56	93	8	97	75
Stage IV	1649	53.9	32.2	22.4	18.3	15.8	1.0	22	161	206	122	626	199	62	135	11	71	56

Table 22 Survival outcomes by TNM stage

	No. of patients	Postoperative survival rate (%)					SE of 5YSR	DD	Lost to follow up	Alive	Main cause of death							
		1 year	2 year	3 year	4 year	5 year					L	P	H	M	R	OC	OD	UK
Stage IA	4795	98.2	96.7	94.8	93.1	91.8	0.4	11	951	3489	6	11	9	3	13	81	175	57
Stage IB	1495	95.9	92.5	89.4	86.9	84.6	1.0	7	290	995	11	29	19	8	19	28	77	19
Stage II	1333	92.1	84.2	77.4	72.9	70.5	1.3	10	201	769	34	92	45	28	47	13	77	27
Stage IIIA	874	83.6	67.3	57.6	51.6	46.6	1.8	7	134	318	51	138	58	21	49	9	51	45
Stage IIIB	352	76.2	51.4	38.6	32.3	29.9	2.6	3	39	85	35	101	20	14	20	1	21	16
Stage IV	1638	55.3	33.2	23.9	19.0	16.6	1.0	21	157	219	120	605	186	79	128	11	68	65

Table 23 Survival outcomes by TNM stage (4 classifications)

	No. of patients	Postoperative survival rate (%)					SE of 5YSR	DD	Lost to follow up	Alive	Main cause of death							
		1 year	2 year	3 year	4 year	5 year					L	P	H	M	R	OC	OD	UK
Stage I	6290	97.7	95.7	93.5	91.7	90.1	0.4	18	1241	4484	17	40	28	11	32	109	252	76
Stage II	1333	92.1	84.2	77.4	72.9	70.5	1.3	10	201	769	34	92	45	28	47	13	77	27
Stage III	1226	81.4	62.7	52.1	46.0	41.8	1.5	10	173	403	86	239	78	35	69	10	72	61
Stage IV	1638	55.3	33.2	23.9	19.0	16.6	1.0	21	157	219	120	605	186	79	128	11	68	65

Table 24 Survival outcomes by approaches

	No. of patients	Postoperative survival rate (%)					SE of 5YSR	DD	Lost to follow up	Alive	Main cause of death							
		1 year	2 year	3 year	4 year	5 year					L	P	H	M	R	OC	OD	UK
Laparotomy	10532	88.3	80.4	75.6	72.4	70.2	0.5	59	1757	5869	251	1002	345	154	289	147	487	231
Thoraco-laparotomy	112	70.5	56.0	47.6	43.7	40.7	4.7	3	8	39	14	19	11	6	7	0	4	4
Laparoscopic	396	99.2	98.9	98.6	97.7	97.4	0.9	0	87	300	0	0	0	0	1	2	3	3
Others	2	100.0	50.0	50.0	50.0	50.0	35.4	0	0	1	0	0	0	0	0	0	1	0

proportion of patients with type 4 cancer was 7.0%, and their 5YSR was markedly low, at 20.4% ($P < 0.001$; Table 8; Fig. 8). In regard to the histological type, the 5YSR of patients with undifferentiated type, including poorly differentiated adenocarcinoma, signet-ring cell carcinoma, and mucinous adenocarcinoma, was 64.6%. The undifferentiated type showed a poorer prognosis than the differentiated type ($P < 0.001$; Tables 9, 10). The grade of venous invasion (v0–v3) and that of lymphatic invasion (ly0–ly3) showed significant correlations with prognosis ($P < 0.001$; Tables 11, 12).

There was a high incidence of early-stage cancer, as indicated in Tables 13 and 14 and Figs. 9 and 10. The proportion of pathological T1 (pT1; mucosal or submucosal) cancer was 51.2%. The 5YSR of this population was 90.8%, and the primary cause of death was not cancer recurrence ($n = 96$), but other diseases ($n = 207$).

Table 25 Survival outcomes by operative procedures

	No. of patients	Postoperative survival rate (%)					SE of 5YSR	DD	Lost to follow up	Alive	Main cause of death							
		1 year	2 year	3 year	4 year	5 year					L	P	H	M	R	OC	OD	UK
Distal gastrectomy	6684	91.6	85.5	81.6	79.1	77.2	0.5	33	1173	4096	133	412	191	75	129	90	267	118
Total gastrectomy	3377	80.0	67.5	60.6	56.1	53.7	0.9	25	512	1427	124	612	154	75	155	32	179	107
Proximal gastrectomy	446	95.2	90.0	88.3	84.3	82.3	1.9	1	60	312	4	9	6	11	6	9	21	8
Pylorus-preserving	277	96.7	95.2	94.4	92.0	90.4	1.8	2	32	220	1	2	3	0	2	5	6	6
Local excision/ segmental resection	339	95.1	94.1	89.1	84.9	82.7	2.2	2	69	218	4	4	2	0	5	10	20	7
Mucosal resection	138	94.4	89.5	84.3	80.8	78.0	3.8	0	31	81	1	1	1	0	1	9	8	5

Table 26 Survival outcomes by lymph node dissection (D)

	No. of patients	Postoperative survival rate (%)					SE of 5YSR	DD	Lost to follow up	Alive	Main cause of death							
		1 year	2 year	3 year	4 year	5 year					L	P	H	M	R	OC	OD	UK
D0	812	79.1	72.7	69.2	65.1	63.7	1.8	8	153	394	17	85	25	4	30	28	52	24
D1	2371	85.1	76.9	72.9	70.4	68.3	1.0	19	340	1326	48	236	83	31	74	46	137	50
D1+α	1368	91.3	85.8	82.2	79.6	77.5	1.2	5	292	799	26	69	40	15	28	17	68	14
D1+β	605	94.8	90.7	87.2	84.9	83.5	1.6	2	122	391	5	25	10	5	6	5	26	10
D2	5403	90.7	82.8	77.5	74.0	71.8	0.6	28	840	3147	134	523	166	81	142	53	183	134
D3	391	78.9	62.7	54.6	50.5	46.8	2.6	0	30	161	30	82	23	18	15	2	20	10

α, Lymph node No. 7 irrespective of the location of lesions, and additionally No. 8a in patients with lesions located in the lower third of the stomach; β, Lymph nodes No. 7, 8a, 9

Table 27 Survival outcomes by involvement of the resection margins

	No. of patients	Postoperative survival rate (%)					SE of 5YSR	DD	Lost to follow up	Alive	Main cause of death							
		1 year	2 year	3 year	4 year	5 year					L	P	H	M	R	OC	OD	UK
PM− and DM−	10550	89.5	82.3	77.7	74.6	72.5	0.5	56	1784	6086	232	881	338	136	258	143	466	226
PM+ and/ or DM+	332	58.5	39.4	32.2	24.5	22.3	2.4	6	34	59	22	119	12	19	31	5	20	11

PM proximal margin, *DM* distal margin

Peritoneal washing cytology (CY) was carried out for 3481 of 5857 patients with T2, T3, and T4 cancer (59.4%). The 5YSR of cytology-positive patients (CY1) was 12.3%, which corresponded with that of the patients with peritoneal metastasis (P1) (Tables 17, 18).

The 5YSRs of the patients stratified by the JGCA staging system were 91.9% for stage IA, 85.1% for stage IB, 73.1% for stage II, 51.0% for stage IIIA, 33.4% for stage IIIB, and 15.8% for stage IV. These JGCA 5YSRs seemed to correlate well with the TNM 5YSRs (Tables 20, 21, 22, 23; Figs. 12, 13).

In regard to the operative procedure, the proportion of patients who underwent laparoscopic gastrectomy was 3.6%, and their 5YSR was 97.4%. Laparoscopic surgery

Table 28 Survival outcomes by curative potential of gastric resection

	No. of patients	Postoperative survival rate (%)					SE of 5YSR	DD	Lost to follow up	Alive	Main cause of death							
		1 year	2 year	3 year	4 year	5 year					L	P	H	M	R	OC	OD	UK
Resection A	7038	97.5	94.9	92.5	90.4	88.7	0.4	20	1309	5006	41	72	52	31	49	108	271	99
Resection B	2593	85.0	70.7	62.1	56.3	53.1	1.0	20	364	1108	121	380	151	72	119	31	157	90
Resection C	1420	50.3	28.7	19.7	15.5	13.4	1.0	22	145	145	98	567	152	55	128	10	65	55

Resection A, no residual disease with high probability of cure satisfying all of the following conditions: T1 or T2; N0 treated by D1, 2, 3 resection or N1 treated by D2, 3 resection; M0, P0, H0, CY0, and proximal and distal margins >10 mm; *Resection B*, no residual disease but not fulfilling criteria for "Resection A"; *Resection C*, definite residual disease

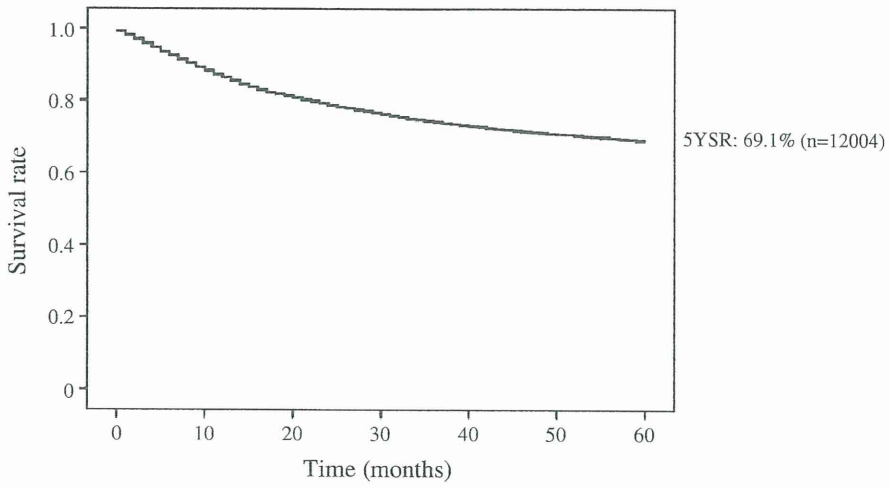

Fig. 3 Kaplan–Meier survival for all 12004 patients with primary gastric cancer. *5YSR* 5-year survival rate

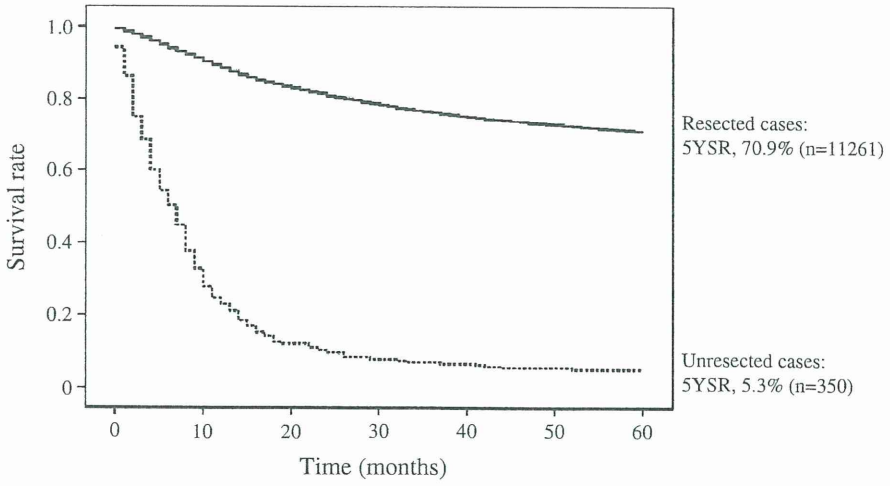

Fig. 4 Kaplan–Meier survival for resected cases and unresected cases

was carried out mainly in patients with early gastric cancer. Only 1.0% of the patients were treated by thoraco-laparotomy, and their 5YSR was 40.7%. Thoraco-laparotomy was carried out in patients with gastric cardia cancer invading the esophagus (Table 24). Thirty percent of the patients underwent total gastrectomy, and their 5YSR was 53.7%. The proportion of patients treated by modified surgery such as proximal gastrectomy, pylorus-preserving gastrectomy, segmental gastrectomy, and local resection was 9.4% (Table 25). D0, D1, D1+α, and D1+β dissections were carried out in 7.4, 21.7, 12.5, and 5.5% of the patients, respectively. According to the JGCA gastric cancer treatment guidelines [7, 8], D1+α dissection with modified gastrectomy was indicated for T1(M)N0 tumors and T1(SM)N0 differentiated tumors <1.5 cm in diameter, while D1+β dissection with modified gastrectomy was indicated for T1(SM)N0 undifferentiated tumors, T1(SM)N0 differentiated tumors larger than 1.6 cm,

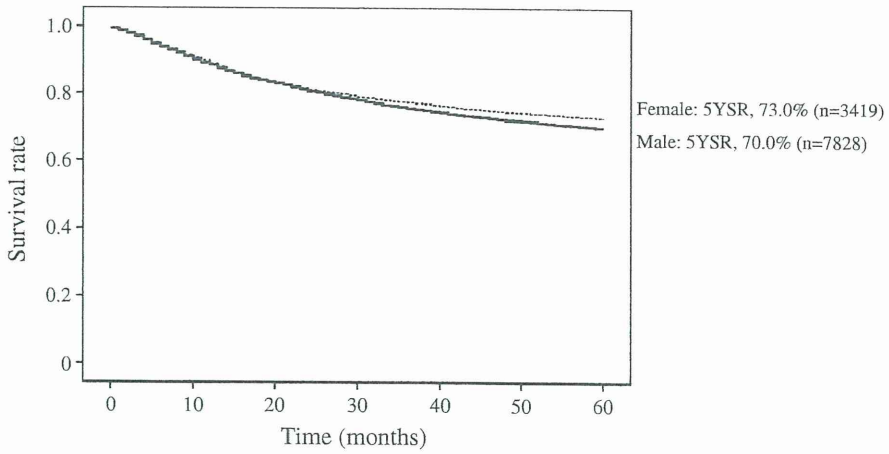

Fig. 5 Kaplan–Meier survival of the resected cases stratified by sex

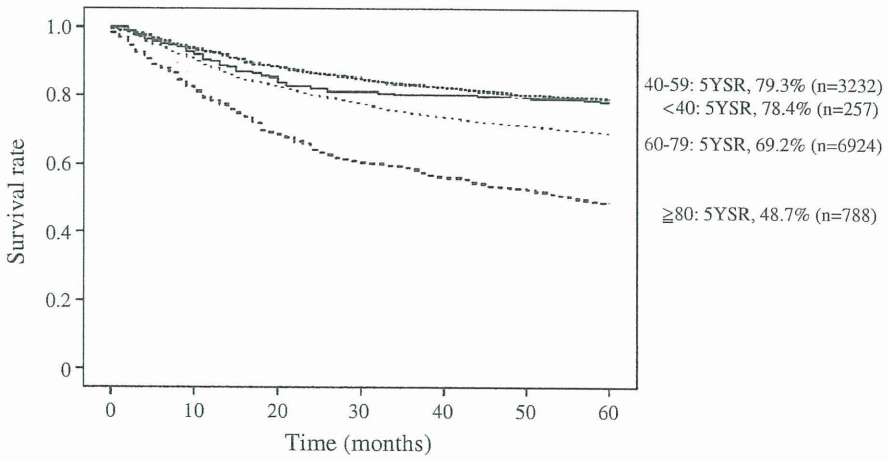

Fig. 6 Kaplan–Meier survival of the resected cases stratified by age

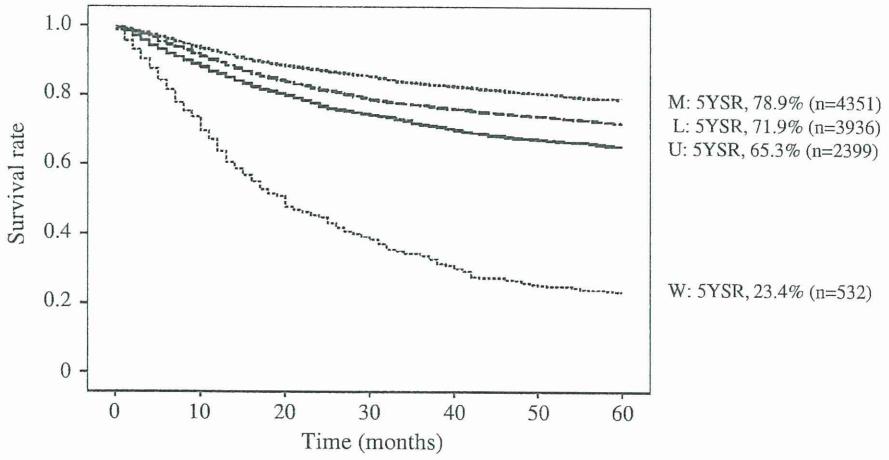

Fig. 7 Kaplan–Meier survival of the resected cases stratified by tumor location. *W* whole stomach, *M* middle third, *L* lower third, *U* upper third of stomach

T1(M)N1 tumors, and T1(SM)N1 tumors <2.0 cm. D0 and D1 dissections were carried out mainly in patients with non-curative factors or poor surgical risks. D2 lymph node dissection was carried out in 49.3% of the patients and the risk of direct death in those with D2 gastrectomy was 0.5% (28/5403; Table 26).

The curative potential of gastric resection was an important prognostic factor. The proportion of patients with a high probability of cure (resection A) was 63.7%, and their 5YSR was 88.7%. On the other hand, the proportion of patients with definite residual tumor (resection C) was 12.8%, and their 5YSR was 13.4% (Table 28; Fig. 14).

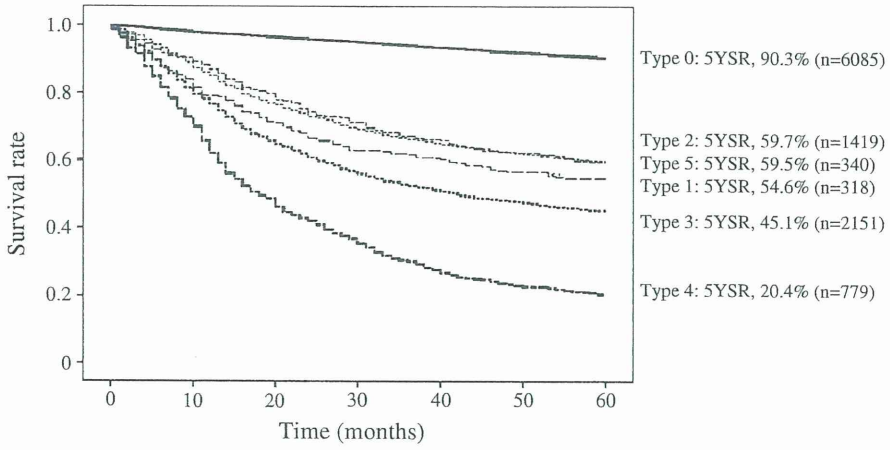

Fig. 8 Kaplan–Meier survival of the resected cases stratified by macroscopic type

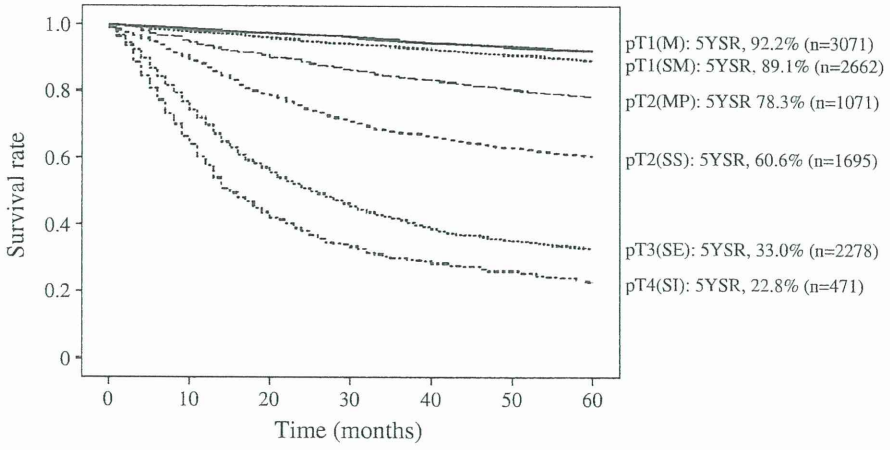

Fig. 9 Kaplan–Meier survival of the resected cases stratified by depth of tumor invasion. *M* mucosa or muscularis mucosa, *SM* submucosa, *MP* muscularis propria, *SS* subserosal, *SE* serosa, *SI* adjacent structures

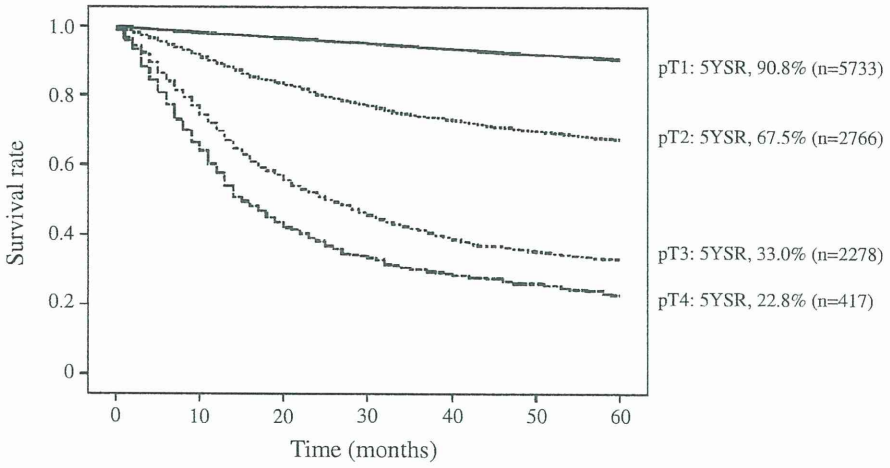

Fig. 10 Kaplan–Meier survival of the resected cases stratified by pT classification

Discussion

The data presented in this report were collected from 187 hospitals in Japan. The number of new patients who were diagnosed with gastric cancer in 2001 was estimated to be 107726 [9]. Accordingly, the 11261 patients registered by this program corresponded to approximately 10% of the population affected by gastric cancer in Japan. Even though these patients may not represent the average features of gastric cancer, this article is considered to be the largest report for the past 10 years clarifying the trends of gastric cancer.

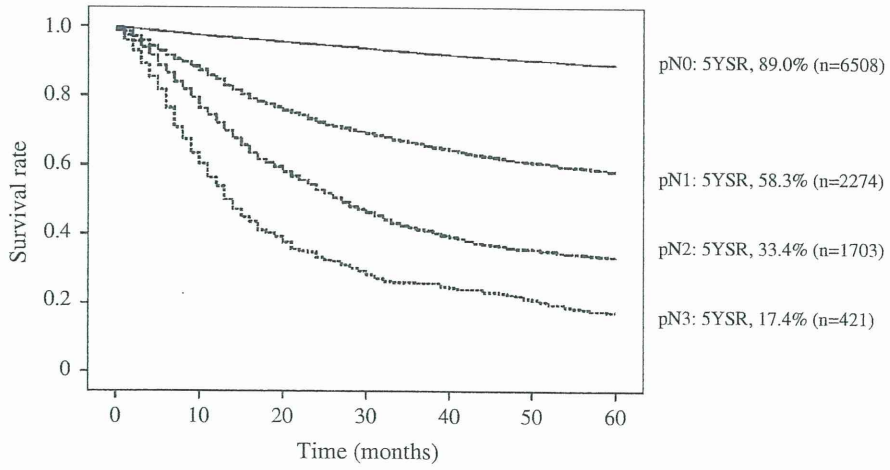

Fig. 11 Kaplan–Meier survival of the resected cases stratified by lymph node metastasis

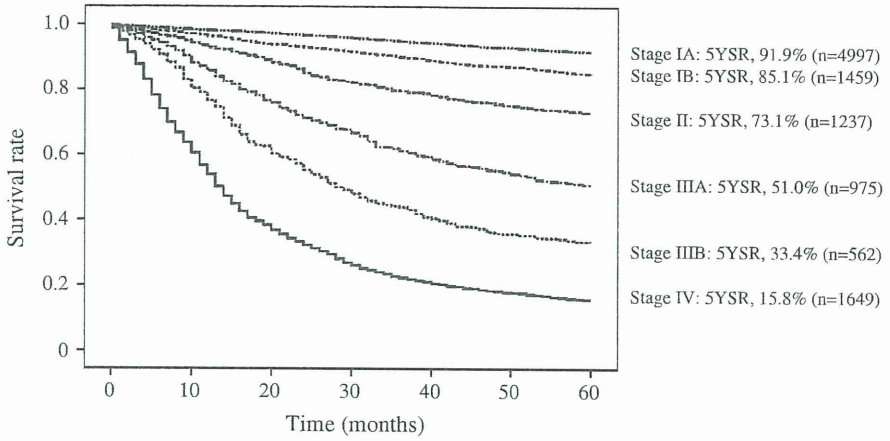

Fig. 12 Kaplan–Meier survival of the resected cases stratified by Japanese Gastric Cancer Association (JGCA) stage

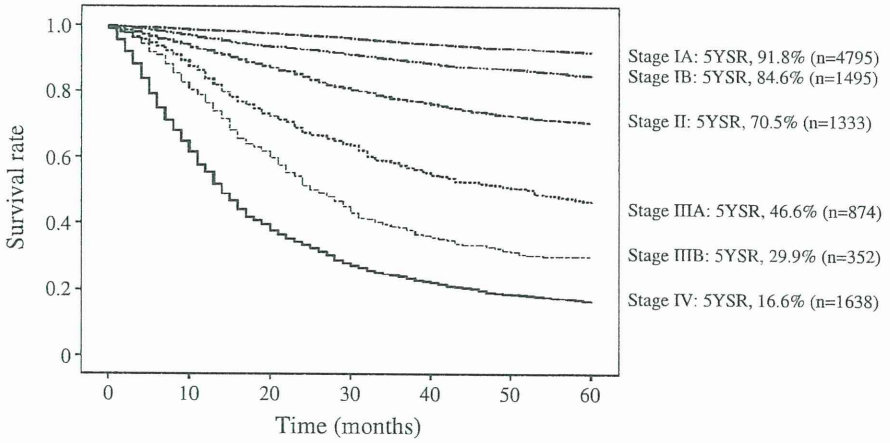

Fig. 13 Kaplan–Meier survival of the resected cases stratified by TNM stage

The reliability of the results in this report depends on the quality of data accumulated in the JGCA database. As the algorithms of the JGCA staging system were rather complicated, the error checking system on the data entry screen did not work perfectly. In several categories, such as lymph node metastasis (N), the JGCA code could not convert to the TNM code automatically. A few "bugs" in the software were revealed just after we had analyzed thousands of data records. Therefore, the registration committee had to make great efforts to cleanse and validate the raw data sent to the data center from participating hospitals.

As compared with our archived data of 7935 patients treated in 1991 [1], though the proportions of each stage were similar, the direct death rate had significantly

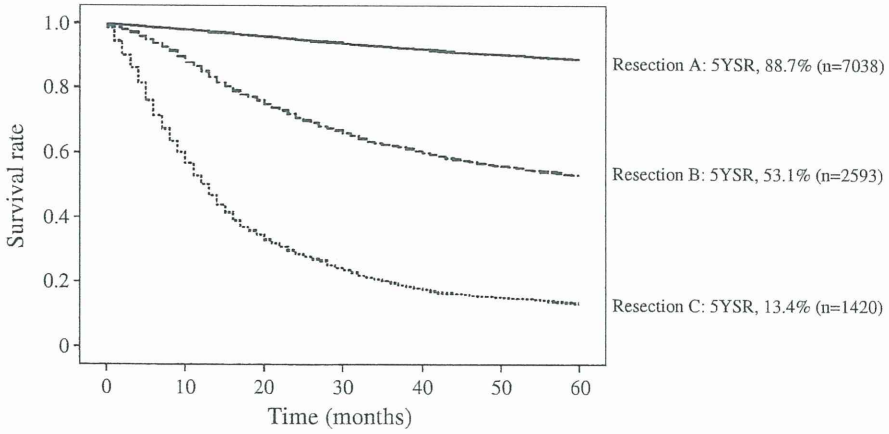

Fig. 14 Kaplan–Meier survival of the resected cases stratified by curative potential of gastric resection. *Resection A*, no residual disease with high probability of cure satisfying all of the following conditions: T1 or T2; N0 treated by D1, 2, 3 resection or N1 treated by D2, 3 resection; M0, P0, H0, CY0, and proximal and distal margins >10 mm; *Resection B*, no residual disease but not fulfilling criteria for "Resection A"; *Resection C*, definite residual disease

Table 29 Five-year follow-up rates stratified by TNM stage

	No. of patients	Lost to follow up	FUR (%)
Stage I	6290	1241	80.3
Stage II	1333	201	84.9
Stage III	1226	173	85.9
Stage IV	1638	157	90.4
Total	10487	1772	83.1

FUR 5-year follow-up rate

improved, dropping from 1.0 to 0.6% ($P < 0.001$); the proportion of patients aged more than 80 years old had increased, from 4.5 to 7.0% ($P < 0.001$); and the 5YSR of stage IV had improved, from 9.0 to 15.8% ($P < 0.05$). These data suggest that, in this decade, the treatment results may have improved in patients with advanced disease and in older patients.

However, these data were retrospectively collected, 7 years after surgery. We had legal difficulties in registering personal information, which was essential for long-term and prospective follow-up. The overall follow-up rate in our program was 83.5%, as already mentioned. A lower follow-up rate is generally considered to show misleading results of higher survival rates in patients with advanced disease. The Japanese Association of Clinical Cancer Centers (consisting of 25 cancer center hospitals) has reported that their follow-up rate was 98.5%, and the 5YSRs of 9980 patients who underwent surgery from 1997 to 2000 were 90.4% for TNM stage I, 67.8% for stage II, 43.3% for stage III, and 9.3% for stage IV [10]. On the other hand, our 5YSR in stage IV patients was 16.6% (Table 23). We might have overestimated our 5YSR in stage IV patients, but we found that the follow-up rate increased as the stage advanced; the follow-up rate of stage IV patients was 90.4% (Table 29). Of the 187 participating hospitals, 114 hospitals achieved high follow-up rates of 90% or more for stage IV patients. Therefore, the 5-year follow-up rates and 5YSRs in these 114 hospitals were calculated for reference. The mean follow-up rate for stage IV patients in these 114 selected hospitals was 97.7% and their 5YSR was 15.9% (Table 30). These data suggest that the lower follow-up rate in our program may not have serious effects on the 5YSRs. Although the correlation between follow-up rate and survival rate is complicated, we need to greatly improve our follow-up system to evaluate our survival rates more accurately.

Table 30 Follow-up rates and survival rates stratified by TNM stage in 187 participating hospitals and 114 selected hospitals

TNM stage	187 Participating hospitals			114 Selected hospitals		
	No. of patients	FUR (%)	5YSR (%)	No. of patients	FUR (%)	5YSR (%)
Stage IA	4795	80.2	91.8	3401	84.0	91.3
Stage IB	1495	80.6	84.6	1000	84.2	82.5
Stage II	1333	84.9	70.5	938	89.6	70.3
Stage IIIA	874	84.7	46.6	608	93.1	45.2
Stage IIIB	352	88.9	29.9	243	93.8	30.8
Stage IV	1638	90.4	16.6	1196	97.7	15.9

The 114 hospitals were selected on the criterion of achieving high follow-up rate of 90% or more for stage IV patients

This is the first nationwide report in which the JGCA refers to peritoneal washing cytology (CY). CY was conducted in 3481 (59.4%) of 5857 patients with T2, T3, or T4 cancer. The 5YSR of CY-positive (CY1) patients was 12.3% and their 5YSR was as poor as that of patients with peritoneal metastasis (P1; 12.4%). Although CY was not carried out commonly in 2001, it was regarded as a significant and independent prognostic factor.

The JGCA restarted a nationwide registration program after an inactive period of 10 years. The most urgent priority of this program was to report detailed 5YSRs in patients who had received a gastrectomy. Therefore, the structure of the database was required to be simple and the

number of registration items was kept to a minimum. We are now planning to register more items concerning remnant gastric cancer, chemotherapy, and endoscopic submucosal dissection by upgrading the data entry software. We will continue our efforts to collect qualified data annually.

Acknowledgments The JGCA Registration Committee appreciates very much the great effort of member hospitals in registering accurate and detailed data for this project. We also wish to thank Ms. Yoshimi Sugamura, Niigata University Medical and Dental Hospital, for her valuable assistance.

Appendix: Member hospitals

Data of gastric cancer patients in this report were collected from the surgical or gastrointestinal departments of the following 187 hospitals (in alphabetical order).

Aichi Cancer Center Aichi Hospital, Aichi Cancer Center Hospital, Akashi Municipal Hospital, Aomori City Hospital, Asahikawa Medical University, Cancer Institute Hospital, Chiba Cancer Center, Chiba University Hospital, Dokkyo Medical University, Ebina General Hospital, Fuchu Hospital, Fujita Health University (Banbuntane Houtokukai Hospital), Fujita Health University Hospital, Fukui Red Cross Hospital, Fukui Saiseikai Hospital, Fukuoka University Chikushi Hospital, Fukuoka University Hospital, Fukushima Medical University Hospital, Gunma Prefectural Cancer Center, Gunma University Graduate School of Medicine (Department of General Surgical Science), Gunma University Graduate School of Medicine (Department of Thoracic Visceral Organ Surgery), Hachioji Digestive Disease Hospital, Hakodate Goryoukaku Hospital, Hakodate Municipal Hospital, Hamamatsu University School of Medicine, Hamanomachi Hospital, Health Insurance Naruto Hospital, Higashiosaka City General Hospital, Himeji Central Hospital, Hirakata City Hospital, Hiroshima City Hospital, Hiroshima Prefectural Hospital, Hiroshima University Hospital, Hitachi General Hospital, Hoshigaoka Koseinenkin Hospital, Hyogo Cancer Center, Hyogo Prefectural Nishinomiya Hospital, Ibaraki Prefectural Central Hospital, Ibaraki Seinan Medical Center Hospital, Ichinomiya Municipal Hospital, Imamura Hospital, Iwate Prefectural Central Hospital, Iwate Prefectural Isawa Hospital, Iwate Prefectural Kamaishi Hospital, JA Hiroshima Kouseiren Hiroshima General Hospital, Jichi Medical University Hospital, Jikei University School of Medicine (Aoto Hospital), Kagawa University Hospital, Kakogawa Municipal Hospital, Kanagawa Cancer Center, Kanazawa Medical University Hospital, Kawasaki Medical School Hospital, Kawasaki Municipal Hospital, Keio University School of Medicine, Keiyukai Sapporo Hospital, Kimitsu Chuo Hospital, Kinki Central Hospital, Kinki University School of Medicine (Nara Hospital), Kiryu Kosei General Hospital, Kitakyushu Municipal Medical Center, Kitasato Institutional Hospital, Kitasato University East Hospital, Kobe City Medical Center General Hospital, Kobe University Hospital, Koga General Hospital, Kokura Memorial Hospital, Kouchi Medical School Hospital, Kumamoto Regional Medical Center, Kumamoto University Hospital, Kurashiki Central Hospital, Kurobe City Hospital, Kushiro Rosai Hospital, Kyorin University Hospital, Kyoto Prefectural University of Medicine, Kyoto Prefectural Yosanoumi Hospital, Kyoto University Hospital, Kyushu University Hospital, Matsue City Hospital, Matsushita Memorial Hospital, Matsuyama Shimin Hospital, Minami Tohoku Hospital, Misawa City Hospital, Mitoyo General Hospital, Mitsui Memorial Hospital, Miyagi Cancer Center, Muroran General Hospital, Musashino Red Cross Hospital, Nagahama City Hospital, Nagano Municipal Hospital, Nagaoka Chuo General Hospital, Nagoya City University Hospital, Nagoya University Hospital, Nanpuh Hospital, Nara Medical University Hospital, Narita Red Cross Hospital, National Defense Medical College, National Kyushu Cancer Center, NHO Ciba Medical Center, NHO Ibusuki Hospital, NHO Kasumigaura Medical Center, NHO Kobe Medical Center, NHO Nagasaki Medical Center, NHO Osaka Medical Center, NHO Sendai Medical Center, NHO Shikoku Cancer Center, NHO Tokyo Medical Center, Niigata Cancer Center Hospital, Niigata Prefectural Shibata Hospital, Niigata University Medical and Dental Hospital, Nippon Medical School Chiba Hokusoh Hospital, Nippon Medical School Musashikosugi Hospital, Nippon Medical School, NTT West Osaka Hospital, Obihiro Tokushukai Hospital, Oita Red Cross Hospital, Oita University Hospital, Okayama Saiseikai General Hospital, Okayama University Hospital, Okitama Public General Hospital, Onomichi Municipal Hospital, Osaka City University Hospital, Osaka General Medical Center, Osaka Kouseinenkin Hospital, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka Red Cross Hospital, Otsu Municipal Hospital, Otsu Red Cross Hospital, Ryukyu University School of Medicine, Saga University Hospital, Sagamihara Kyodo Hospital, Saiseikai Fukuoka General Hospital, Saiseikai Maebashi Hospital, Saiseikai Niigata Daini Hospital, Saiseikai Noe Hospital, Saitama Medical Center, Saitama Red Cross Hospital, Saitama Social Insurance Hospital, Sakai Municipal Hospital, Saku Central Hospital, Sapporo Social Insurance General Hospital, Sayama Hospital, Seirei Hamamatsu General Hospital, Seirei Mikatahara General

Hospital, Self-defense Forces Central Hospital, Sendai Open Hospital, Sendai Red Cross Hospital, Shiga Medical Center for Adults, Shiga University of Medical Science, Showa General Hospital, Showa University Toyosu Hospital, Social Insurance Central General Hospital, Social Insurance Kinan Hospital, St. Luke's International Hospital, Suita Municipal Hospital, Surugadai Nihon University Hospital, Tochigi Cancer Center, Toho University Ohashi Medical Center, Tokushima Municipal Hospital, Tokushima University Hospital, Tokyo Dental College Ichikawa General Hospital, Tokyo Medical University, Tokyo Metropolitan Bokutoh Hospital, Tokyo Metropolitan Cancer and Infectious Disease Center Komagome Hospital, Tokyo Metropolitan Police Hospital, Tokyo Women's Medical University (Institute of Gastroenterology), Tokyo Women's Medical University Hospital (Department of Surgery 2), Tokyo Women's Medical University Medical Center East, Tonami General Hospital, Toranomon Hospital, Tottori University Hospital, Toyama University Hospital, Tsuchiura Kyodo General Hospital, Tsuruoka Municipal Shonai Hospital, University of Fukui Hospital, University of Miyazaki Hospital, University of Tokyo Hospital, University of Yamanashi Hospital, Wakayama Medical University, Yamagata Prefectural Central Hospital, Yamagata Prefectural Kahoku Hospital, Yamagata University Hospital, Yamaguchi Rousai Hospital, Yamanashi Prefectural Central Hospital, Yao Municipal Hospital, Yodogawa Christian Hospital, Yokohama City University Medical Center, Yuai Memorial Hospital.

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Clinical Study

Pilot Study on Clinical Effectiveness of Autofluorescence Imaging for Early Gastric Cancer Diagnosis by Less Experienced Endoscopists

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This study aimed to assess and compare effectiveness of Autofluorescence imaging (AFI) in diagnosis of early gastric cancer (EGC) between experienced and less experienced endoscopists. Fifty selected images (20 neoplastic lesions and 30 benign lesions/areas) of both white light endoscopy (WLE) and AFI were blindly reviewed by two groups; first consisted of five experienced endoscopists and second included five less experienced endoscopists. Sensitivity, specificity, and accuracy were 70%, 78%, and 75%, respectively, for AFI and 81%, 76%, and 78%, respectively, for WLE in the experienced group. In the less experienced group, sensitivity, specificity and accuracy were 80%, 81% and 80%, respectively, for AFI and 65%, 77%, and 72%, respectively, for WLE. Interobserver variability for the less experienced group was better with AFI than WLE. AFI improved sensitivity of endoscopic diagnosis of neoplastic lesions by less experienced endoscopists, and its use could beneficially enhance the clinical effectiveness of EGC screening.

1. Introduction

Gastric cancer incidence and mortality have declined dramatically over the past 70 years [1]. Despite these declines, gastric cancer is still the fourth most common cancer and the second leading cause of cancer-related deaths worldwide [2]. Development of esophagogastroduodenoscopy (EGD), a screening tool for early gastric cancer (EGC), in place of radiology [3] has allowed widespread availability of screening in high-risk countries such as Japan and Korea resulting in decreased mortality. In contrast, relatively few gastric cancers are discovered at an early stage in most Western countries [4].

We have witnessed firsthand significant advances in endoscopic treatment for early gastric cancer in recent years including development of endoscopic submucosal dissection (ESD) [5–7]. In order to fully benefit from the advantages of endoscopic treatment, however, it is important to detect gastric cancers at the earliest possible stage [8]. Most cases of EGC are slightly depressed or elevated lesions and red or pale in color, but some EGC are quite flat and almost isochromatic so there is very little contrast with the surrounding mucosa. Such subtle changes of EGC can make for a challenging endoscopic diagnosis. The difficulties involved in making an accurate diagnosis can be compounded by the inexperience of some endoscopists particularly in countries where the incidence of gastric cancer is low.

Following development of a fluorescence detection method for neoplastic lesions in 1957, autofluorescence imaging (AFI) has attracted considerable attention in the diagnosis of early cancerous lesions [9, 10]. AFI is a novel imaging method that produces computerized real-time pseudocolor images by detecting faint fluorescence

Table 1: Neoplastic lesion characteristics and AFI colors.

		Number of lesions	AFI color	
			Magenta	Green
Pathological type	Carcinoma (differentiated)	13	9	4
	Carcinoma (undifferentiated)	3	0	3
	Adenoma	4	4	0
Location	Upper third of stomach	2	1	1
	Middle third of stomach	9	6	3
	Lower Third of Stomach	9	6	3
Macroscopic type	Elevated	9	9	0
	Flat	2	2	0
	Depressed	9	2	7
WLE color	Reddish	9	4	5
	Isochromatic	8	8	0
	Pale	3	1	2

AFI: autofluorescence imaging; WLE: white light endoscopy.

emitted from endogenous fluorophores exposed to excitation light. Neoplastic lesions with an altered fluorescence can be distinguished from the enhanced surrounding normal pattern by variations in color.

Several published reports have examined the advantages of AFI for detection of colorectal cancer [11–14]. It may also be easier for less experienced endoscopists to detect gastric neoplastic lesions using AFI even when such lesions cannot be detected by conventional white light endoscopy (WLE) [15]. The aim of this pilot study was to assess and then compare the effectiveness of AFI in the diagnosis of gastric neoplastic lesions between experienced and less experienced endoscopists.

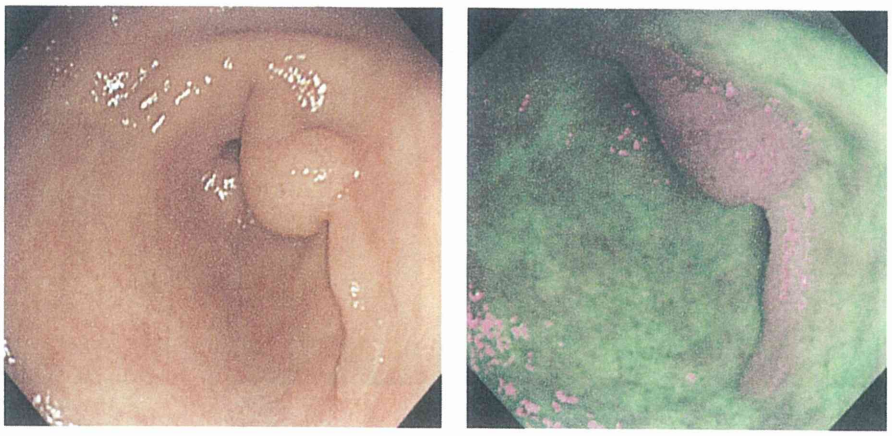
2. Methods

2.1. Study Design. During endoscopy using a prototype AFI system that included both WLE and AFI functions performed by one experienced endoscopist (C. Yokoi), pictures of neoplastic lesions and benign lesions/areas were taken from 44 patients with EGC after obtaining their informed consent who were referred to our hospital for treatment from August 2005 to March 2006. Pictures of 45 EGCs were collected along with 172 pictures of benign lesions/areas from these 44 patients. All neoplastic and benign lesions were assessed histopathologically from biopsy specimens. Pictures of poor quality were excluded, and 50 pictures were then selected at random by the study coordinator (K. Tada) for this pilot study including 20 pictures of neoplastic lesions (four adenomas and 16 EGCs) and 30 pictures of benign lesions/areas (four polyps, six ulcer scars, four atrophic changes, and 16 normal mucosal areas). The clinicopathological characteristics of the neoplastic lesions were classified based on the Japanese Classification of Gastric Carcinoma [16] while the descriptions of WLE and AFI colors were determined by the study coordinator (Table 1). All slightly elevated and flat lesions appeared magenta in a green field, and 7 of 9 slightly depressed lesions displayed green in a magenta field. The mean lesion size was 20 mm.

We prepared 50 sets of AFI and WLE images for the same selected lesions and normal mucosa. Each image was assigned a random sequence number with the 50 AFI images displayed first followed by the 50 WLE images. A review of the images was performed individually by 10 endoscopists excluding the endoscopist who took the images and the study coordinator who were divided into two separate groups: five endoscopists with extensive experience in EGC from the National Cancer Center Hospital (NCCH) and five less experienced endoscopists working in a general hospital. Each of the endoscopists in the first group of reviewers had over 10 years of medical experience including more than three years at NCCH and had evaluated in excess of 700 EGCs annually. The endoscopists in the second group of reviewers each had less than five years of medical experience and had evaluated fewer than 30 cases of EGC per year. No information regarding any of the lesions was available to the reviewers. An answer sheet was given to each endoscopist with two options regarding each image: "neoplasm exists" or "no neoplasm."

2.2. Autofluorescence Imaging System. The prototype AFI system used in this study (XGIF-Q240FZ; Olympus Medical Systems Corp., Tokyo, Japan) was equipped with two charge-coupled devices (CCDs) at the tip of the endoscope that could easily be switched by pushing a single button on the scope handle: one for high-resolution white-light observation and the other for autofluorescence observation. The AFI system digitally creates real-time pseudocolor images from autofluorescence (excitation at 390–470 nm and detection at 500–630 nm) and green reflection (G′) at 540–560 nm. The system relies on a sequential method in order to provide clear image profiles and distinguish autofluorescence reduction of neoplastic lesions caused by hemoglobin absorption.

2.3. AFI Diagnostic Criteria for Neoplastic Lesions. A neoplastic lesion was defined for AFI purposes as an area that contrasts in color with the surrounding background such as



(a) (b)

FIGURE 1: Diagnostic criteria for autofluorescence imaging (AFI). We defined a lesion suspected of being neoplasia using AFI (AFI-positive) as an area that was clearly different from the surrounding mucosa in color. (a) WLE image of an EGC. (b) AFI-positive image displayed the same EGC as a magenta area with defined margins within the green-colored mucosa.

TABLE 2: Interobserver variability for detection of neoplastic lesions with AFI and WL.

κ	AFI (95% CI)	WLE (95% CI)
Experienced endoscopists	0.42 (0.33–0.51)	0.52 (0.43–0.61)
Less experienced endoscopists	0.52 (0.43–0.61)	0.29 (0.20–0.38)

AFI: autofluorescence imaging; WLE: white light endoscopy.

"a magenta area in a green field" or "a green area in a magenta field" (Figure 1).

AFI images are considerably different from those of conventional WLE, however, so endoscopists have to become familiar with such images in order to attain an appropriate level of diagnostic skill. All participating endoscopists in this study were briefed on how to evaluate AFI images and given an opportunity to review 10 sample pictures beforehand at a 30-minute training lecture.

2.4. Statistical Analysis. We compiled the answers for the five endoscopists in each group and then calculated sensitivity, specificity, and accuracy for both groups. Data were analyzed using the chi-square test, and value differences of $P < 0.05$ were considered statistically significant. Interobserver variability was determined for each group using Kappa (κ) statistics. All statistical analyses were performed using STATA version 10.0 (StataCorp, College Station, Tex, USA).

3. Results

Detection of neoplastic lesions by the experienced endoscopists using AFI and WLE, respectively, resulted in a sensitivity of 70% (95% CI 60–78%) and 81% (95% CI 72–88%), a specificity of 78% (95% CI 71–84%) and 76% (95% CI 69–82%), and an accuracy of 75% and 78%. Less experienced endoscopists had a sensitivity of 80% (95% CI 71–87%) and 65% (95% CI 55–74%), a specificity of 81% (95% CI 74–86%) and 77% (95% CI 70–83%), and an accuracy of 80% and 72%, respectively, using AFI and WLE for diagnosis. Sensitivity in the less experienced group of endoscopists using AFI (80%) was significantly higher than when using WLE (65%) ($P < 0.05$). And sensitivity in the less experienced group of endoscopists using AFI (80%) was comparable to the more experienced group of endoscopists using WLE (81%) (Figure 4).

Interobserver variability for detection of neoplastic lesions by the group of less experienced endoscopists was better for AFI than with WLE (experienced group: AFI [κ = 0.42 (95% CI 0.33–0.51)] and WLE [κ = 0.52 (95% CI 0.43–0.61)]; less experienced group: AFI [κ = 0.52 (95% CI 0.43–0.61)] and WLE [κ = 0.29 (95% CI 0.20–0.38)]). There was no statistically significant difference in the interobserver variability using AFI between the experienced and less experienced endoscopist groups. In contrast, there was a significant difference using WLE between the two groups with the experienced endoscopist group having significantly better interobserver variability (Table 2).

With regard to lesions diagnosed by the group of less experienced endoscopists, three of the 20 (15%) neoplastic lesions were diagnosed more often by WLE, and 11 (55%) were diagnosed more often by AFI. All three (100%) neoplasias diagnosed more often by WLE were slightly depressed lesions. (Figures 2(a), 2(b), and 2(c)). In contrast, eight of the 11 (73%) neoplasias diagnosed more often by AFI were flat lesions (Figures 3(a) and 3(b)).

4. Discussion

The effectiveness of AFI for diagnosing EGC by highly experienced endoscopists has been assessed in several studies, but

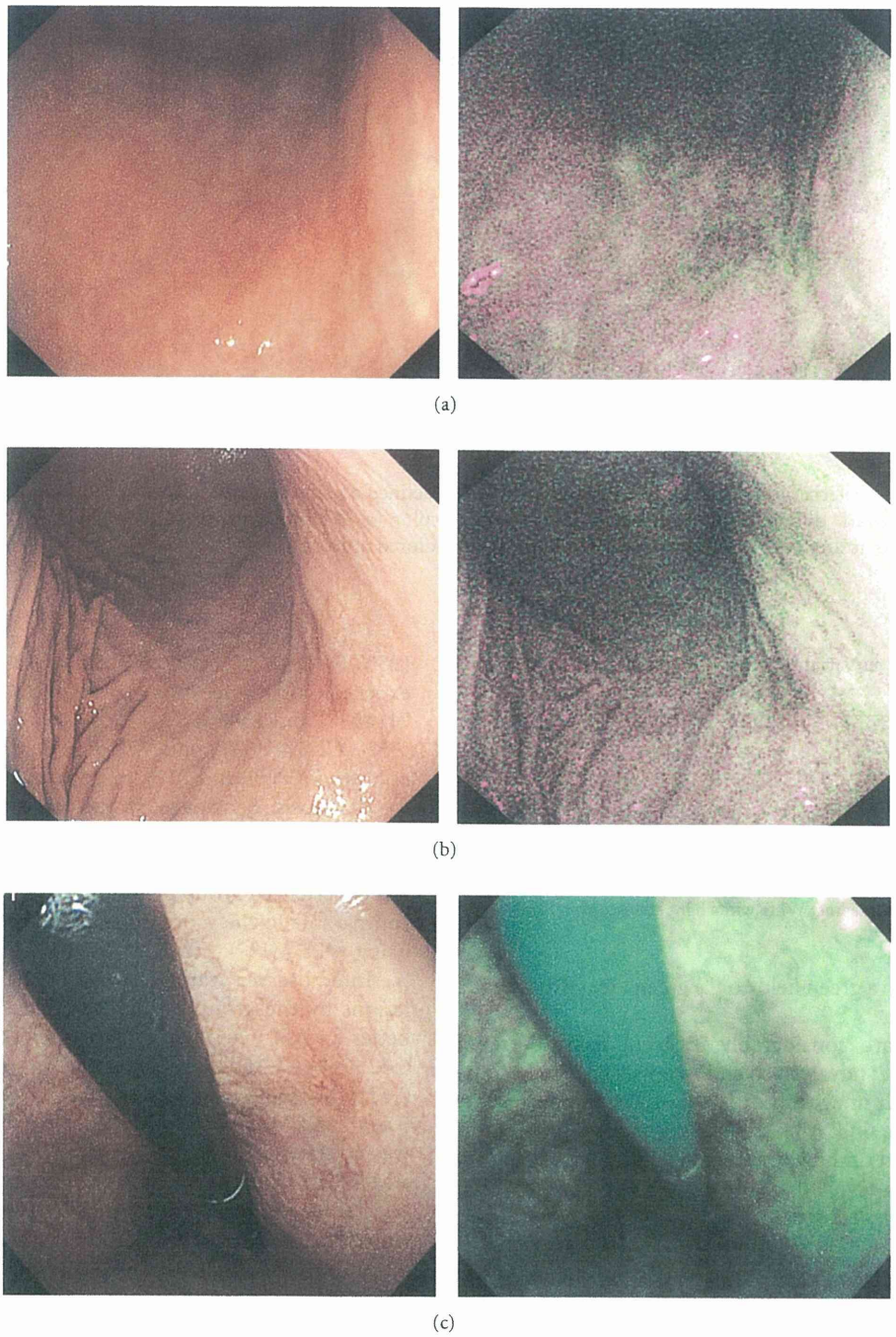
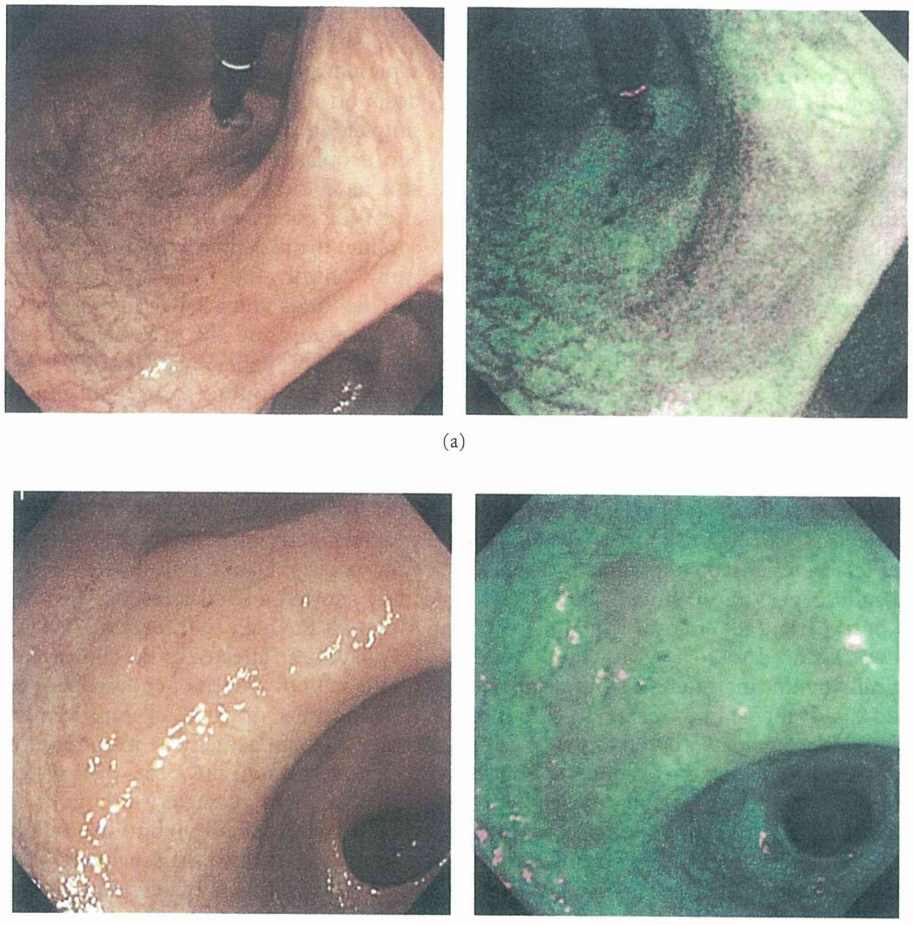


FIGURE 2: These three neoplastic lesions were diagnosed more easily using WLE. All three appeared reddish in color with a slightly depressed area.

there are no published reports evaluating less experienced endoscopists [15, 17].

AFI can differentiate tissue types based on variations in their fluorescence emissions. When tissue is exposed to short wavelength (390–470 nm) light, endogenous biological substances such as collagen, nicotinamide adenine dinucleotide, flavin, and porphyrins are excited leading to the emission of longer wavelength (500–630 nm) fluorescent light (autofluorescence) [18]. Neoplastic and nonneoplastic tissues have different autofluorescence characteristics including nuclear-cytoplasmic ratio, mucosal layer thickness, and volume of blood flow [19]. These characteristics may facilitate differentiating between the two. During endoscopy using the AFI mode, neoplastic lesions contrast with normal mucosal tissue (i.e., "a magenta area in a green field" or "a green area in a magenta field").



(a)

(b)

FIGURE 3: Here are two examples of neoplastic lesions diagnosed more easily using AFI. Each of them appeared as an isochromatic flat lesion using WLE.

		Sensitivity (%) (95% CI)		Specifcity (%) (95% CI)		Accuracy (%)
Experienced endoscopists	AFI	70 (60–78)	n.s.	78 (71–84)	n.s.	75
	WLE	81 (72–88)		76 (69–82)		78
Less experienced endoscopists	AFI	80 (71-87)	$P < 0.05$	81 (74–86)	n.s.	80
	WLE	65 (55–74)		77 (70–83)		72

AFI, autofuorescence imaging; WLE, white light endoscopy; n.s., no signifcant diference.

FIGURE 4: AFI and WLE image review results.

A number of studies have reported that AFI is effective for colorectal cancer screening, but this is still debatable while its suitability for gastric cancer screening remains somewhat more controversial [11–14, 20, 21]. Inflammatory and hyperplastic changes in the stomach can alter mucosal layer thickness and blood flow volume causing autofluorescence contrast variations with similar appearance to neoplastic lesions. Such difficulties are also reported in Barrett's esophagus [22]. False-positive results and low specificity, therefore, are more common in the stomach and Barrett's esophagus. Currently, AFI cannot distinguish precisely between gastric neoplastic lesions and inflammatory or hyperplastic changes. It is already known, however, that EGC is not easily detected by less experienced endoscopists. No detection, of course, means there is no treatment, so our primary objective in EGC screening should be higher sensitivity rather than diagnostic accuracy. False-positive lesion findings should be a secondary consideration to the actual sensitivity rate. AFI provides a simple dichromatic difference that may help less experienced endoscopists diagnose neoplastic lesions more easily. For this reason, we included less experienced endoscopists as well as highly experienced endoscopists in our study.

In the group of experienced endoscopists, the WLE sensitivity of 81% was reduced to 70% with AFI although there was no statistically significant difference indicating that AFI did not provide an advantage in terms of detection for that particular group. We postulate that sensitivity using WLE was already high in the experienced endoscopists group as variables such as surface irregularity, elasticity, thickness, hardness, converging folds, and background status were examined. The ability to interpret those changes using WLE improves with endoscopic experience. We believe that experienced endoscopists in this study attempted to interpret all characteristics of a lesion using AFI rather than just color contrast. Reliance on such variables, in fact, can mislead experienced endoscopists given AFI's low vision quality.

In contrast, AFI raised detection sensitivity from 65% to 80% and interobserver variability from 0.29 to 0.52 for less experienced endoscopists. Although the subtle mucosal changes of EGC make endoscopic diagnosis a challenge for less experienced endoscopists using WLE, our findings indicated that AFI might facilitate easier diagnosis of neoplastic lesions by such endoscopists. This was likely due to objective evidence of a definite difference in coloration between neoplastic lesions and the surrounding mucosa. AFI was particularly effective in the diagnosis of flat lesions. The overall sensitivity and interobserver agreement were unsatisfactory, however, for the differential diagnosis between neoplastic and benign lesions so we still need to perform a biopsy.

There are, however, a number of limitations to this pilot study. Firstly, we used still images taken by experienced endoscopists, and some of those lesions may not have been detected at all by less experienced endoscopists during real-time endoscopy. Quality of the AFI view depends on technical skill so less experienced endoscopists might not be able to reproduce the images used in this study. Our results, therefore, may not be reflected in actual examination, but the results of less experienced endoscopists were in fact better than experienced endoscopists using the same AFI pictures. In the future, effectiveness of AFI for screening of EGC should be assessed in a prospective study including experienced and less experienced endoscopists with diagnosis on a real-time basis. Secondly, in order to make it simpler, we included only two options "neoplasm exists" or "no neoplasm" for reviewers. It would have been better to also have them evaluate lesion characteristics such as AFI and WLE colors as well as macroscopic type. So we plan to conduct the real-time evaluations lesion features in the next study. Thirdly, there was no yardstick used in choosing the specific kinds and relative percentages of images presented in this study, and the percentage of neoplastic lesions was considerably higher than than that which would normally be the case in routine gastric screening. The actual choice of images could have had an effect on the results. For example, Kato et al. carried out a prospective study on the effectiveness of AFI for detecting EGC [17]. They reported sensitivity of 74% and specificity of 83% for WLE and sensitivity of 64% and specificity of 40% for AFI performed by experienced endoscopists. Data for the experienced endoscopists in our study showed a similar results regarding sensitivity of AFI. Although the high specificity of 78% with AFI in our study may have been affected by the choice of images, the sensitivity results in both groups of endoscopists were quite promising.

A number of practical improvements need to be made before AFI can actually be introduced into a clinical gastric screening setting (i.e., the AFI system video endoscope is too large in diameter with poor flexibility and lower overall image quality), but we believe that AFI has the potential to increase the sensitivity of endoscopic diagnosis of neoplastic lesions by less experienced endoscopists. This would be important not only in Japan but especially in those countries with a low incidence of gastric cancer. The AFI system is only being used on a limited basis in Japan and a few other countries at the present time, and greater availability and increased usage worldwide of this system should demonstrate its effectiveness and lead to wider acceptance.

The primary advantage of AFI is that it identifies suspicious lesions as areas evidencing color contrast almost instantaneously throughout the entire endoscopic field. Even if the false-positive rate using AFI is high, the examining endoscopists can use other modalities such as chromoendoscopy or NBI with magnification in addition to obtaining biopsies to verify their initial suspicion of EGC [23, 24]. This is provided, of course, that lesions are detected in the first place. AFI could then become an important technique for EGC screening by all endoscopists to diagnose suspected lesions.

This is the first study on the effectiveness of AFI by less experienced endoscopists. Although the results are encouraging, it should be noted that this was an uncontrolled pilot trial involving a relatively small number of lesions. Prospective randomized controlled trials involving a large number of subjects would be beneficial in the future to more fully evaluate the effectiveness of AFI in the diagnosis of EGC.

In conclusion, the use of AFI in this study increased sensitivity in the endoscopic diagnosis of gastric neoplastic

lesions by less experienced endoscopists. Such use may beneficially enhance the clinical impact of EGC screening by less experienced endoscopists, but this will need to be confirmed in a prospective study with diagnosis on a real-time basis.

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GASTROENTEROLOGY

Conflicting clinical environment about the management of antithrombotic agents during the periendoscopic period in Japan

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anticoagulant, antiplatelet agent, bleeding, cerebrovascular and cardiovascular disease, complication, endoscopy.

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Abstract

Background and Aims: Although there are guidelines for the management of antithrombotic agents during the periendoscopic period, gaps between various guidelines create a confusing situation in daily clinical practice. The purpose of this study was to examine the current management of antithrombotic agents during the periendoscopic period in Japan.
Methods: This is a prospective cohort study in 12 high-volume endoscopy centers in Japan. A total of 970 outpatients receiving antithrombotic agents underwent endoscopies (705 esophagogastroduodenoscopies and 265 colonoscopies) with or without invasive procedures. Main outcome measures are adverse events in these patients.
Results: Need for cessation of antithrombotics before endoscopy was mostly determined by non-gastroenterologists (51%) who are unfamiliar with the Japan Gastroenterological Endoscopy Society (JGES) guideline, although cessation periods after endoscopy for most patients were determined by endoscopists (78%). Consequently, most patients underwent endoscopy without cessation (25%) or after a cessation period of 6–7 days (33%), indicating low permeation of the JGES guideline in Japan. Among 970 patients, two patients experienced major complications that may be related to thromboembolic events or gastrointestinal bleeding (95% confidence interval [CI]: 0–0.7%). One of these patients died due to sudden onset ventricular tachycardia. Invasive procedures, including 40 biopsies and two mucosal resections, were performed in 42 patients without cessation of antithrombotics, and no patients experienced major complications (95% CI: 0–8.4%).
Conclusions: This study revealed a conflicting clinical environment due to absence of a unified guideline in Japan. Further accumulation of data is mandatory to establish a unified guideline based upon solid evidence.

Introduction

There is solid evidence supporting the prophylactic use of antithrombotic agents for cerebrovascular and cardiovascular events.[1–5] However, these agents increase the risk of gastrointestinal bleeding.[6–9] On the other hand, discontinuation of these agents during the periendoscopic period can induce thromboembolic complications.[10] Therefore, endoscopists must make difficult decisions for patients with cerebrovascular and cardiovascular comorbidities during the periendoscopic period.

Although various societies have published guidelines regarding this dilemma, the permeation of these guidelines is low in Japan.[10–12] This is partly because of gaps between guidelines of Eastern and Western countries[13] and between those of Japanese societies, as shown in Table 1.

Table 1 Management of antithrombotic agents in various guidelines

	Low-risk procedure	High-risk procedure
American Society for Gastrointestinal Endoscopy *et al.*	Continue	Continue for aspirin and NSAIDs. Discontinue 7–10 days for clopidogrel and ticlopidine. Discontinue 3–5 days for warfarin.
The British Society of Gastroenterology *et al.*	Continue	Continue for aspirin. Discontinue 7 days for clopidogrel. Discontinue 5 days for warfarin and check of INR < 1.5.
Japan Gastroenterological Endoscopy Society	Discontinue 3 days for aspirin, 5 days for ticlopidine, 7 days for combination. Discontinue 3–4 days for warfarin. Check of INR < 1.5 before high-risk procedure. Discontinue 7 days for aspirin, 10–14 days for ticlopidine before extremely high-risk procedure.	
The Japanese Circulation Society	Discontinue 3 days for aspirin, 5 days for ticlopidine, 7 days for combination. Check of INR < 1.5 for discontinuation of warfarin.	Discontinue 7 days for aspirin, 10–14 days for ticlopidine, 3 days for cilostazol.

INR, international normalized ratio; NSAIDS, non-steroidal anti-inflammatory drugs;

The guideline of the Japan Gastroenterological Endoscopy Society (JGES) recommends cessation even for minimally invasive endoscopic procedures including biopsy, although most Western guidelines do not.[13–18] This discrepancy is based upon racial differences of bleeding risks and thromboembolic risks between Asians and Caucasians. However, there is insufficient evidence to support this racial difference.

Another reason for the low permeation in Japan is the difficulty of estimating thromboembolic risk for each patient's comorbidities. Thus, cessation is determined by the prescribing physicians of non-gastroenterological specialties who may be unfamiliar with the JGES guideline.[12] Meanwhile, most endoscopists sometimes perform endoscopy without cessation of antithrombotic therapy for patients with a high thromboembolic risk state based upon the premise of second endoscopy for biopsy if necessary. A second endoscopy eventually requires cessation for biopsy and only postpones difficult decisions. However, this clinical daily practice can delay a final diagnosis that is mandatory for initiating therapy.

To cope with these dilemmas, we performed a fact-finding study in a multi-center setting to clarify the present problems concerning management of antithrombotic agents during the periendoscopic period in Japan.

Methods

This study was conducted for two consecutive months between February 2010 and July 2010 at each institution after approval by the ethics committee of each institution. The following 12 institutes participated in this study: The University of Tokyo, Tokyo; Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka; National Center for Global Health and Medicine, Tokyo; National Cancer Center Hospital, Tokyo; St Luke's International Hospital, Tokyo; Niigata Prefectural Central Hospital, Niigata; Tokyo Medical University, Tokyo; Hitachi General Hospital, Hitachi; Tonan Hospital, Sapporo; Cancer Institute Hospital, Tokyo; Kobe University School of Medicine, Kobe; and Tokyo KoseiNenkin Hospital, Tokyo, Japan.

The method of investigation is approximately the same as our previous study in a single institute.[12] In brief, outpatients receiving anticoagulants or antiplatelet agents were enrolled to complete a questionnaire that was handed out before endoscopy. The patients returned the following questionnaires approximately 14 days after endoscopy.

- What anticoagulants or antiplatelet agents do you take?
- For what comorbidity were you prescribed each agent?
- What is the specialty of the physician who prescribed each agent?
- How long were you ordered to stop each agent before and after endoscopy?
- What is the specialty of the physician who determined your cessation period?
- Are you prescribed any antiulcer agents or other agents affecting the digestive organs?
- Have you experienced any additional symptoms before and during the two weeks after endoscopy?

To minimize the number of dropout patients, we called all patients who had not sent back or submitted responses by the deadline.

We defined the following as antiplatelet agents: cyclooxygenase inhibitors (e.g. aspirin), phosphodiesterase inhibitors (e.g. cilostazol), purinergic receptor antagonists (e.g. ticlopidine), serotonin receptor antagonists (e.g. sarpogrelate), eicosapentaenoic acid preparations (e.g. icosapentate), and prostaglandin preparations. We investigated esophagogastroduodenoscopy (EGD) and colonoscopy (CS) with and without invasive procedures. Invasive procedures were defined as biopsy or resection including polypectomy and endoscopic mucosal resection (EMR) because subjects were limited to outpatients. Major complications were defined as symptomatic events requiring additional medical treatment.

Endoscopy was ordered by more than 100 physicians with various specialties during the study period. All patients received explanations of the risks and benefits of these endoscopies and were provided written informed consent by the physicians in charge. Furthermore, written informed consent for this study was obtained with questionnaires. By summarizing responses to questionnaires, we analyzed the actual current practice concerning management of antithrombotic agents during the periendoscopic period and estimated safety of the current practice in a prospective manner.

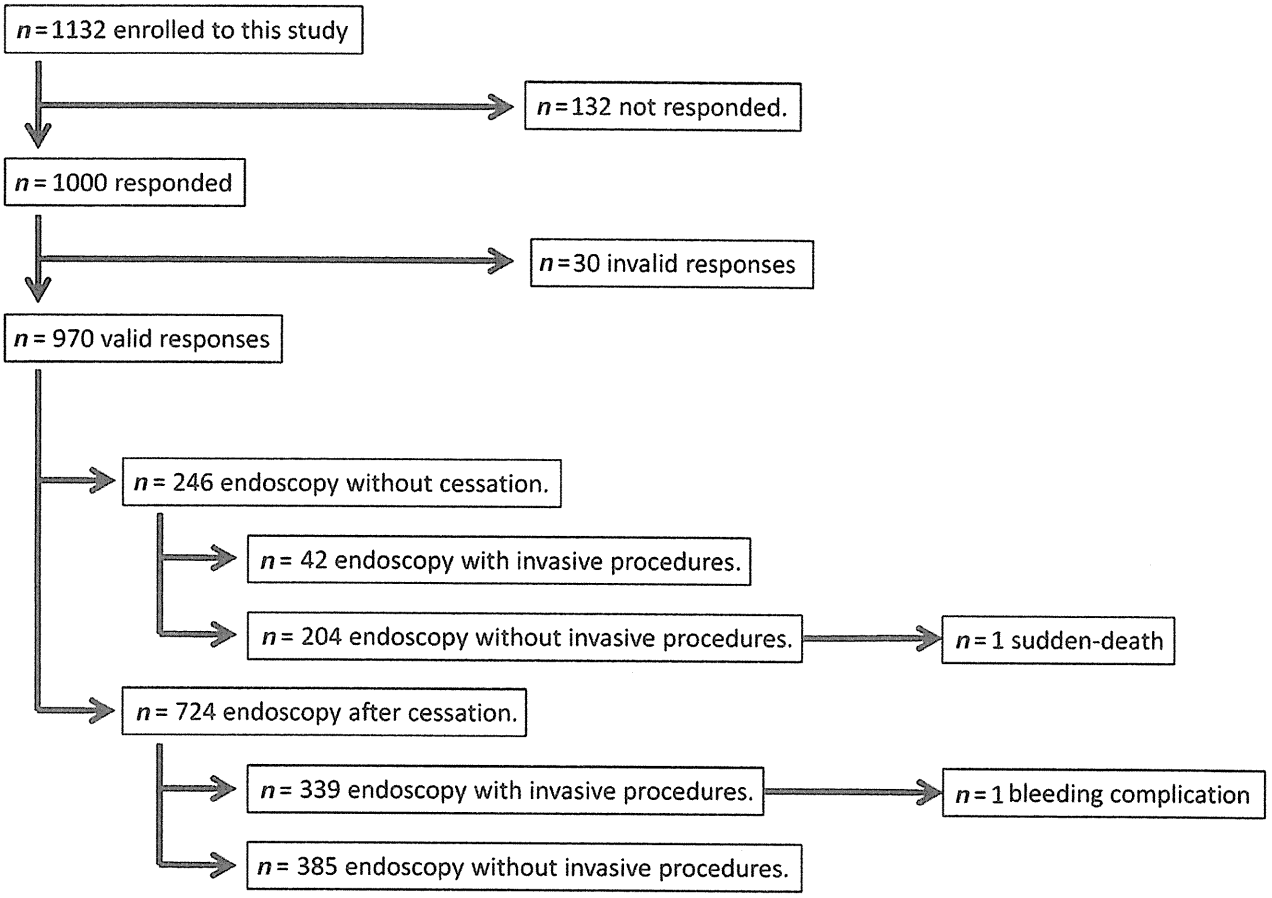

Figure 1 Flow diagram of the study (*n*, patients).

Statistical analyses were conducted using the χ^2 test with Yates' modification and Student's *t*-tests. $P < 0.05$ was considered significant.

Results

In total, 1132 patients were enrolled to this study. One thousand patients (88%) submitted responses to questionnaires. Among 1000 responses, 970 valid responses (86%) were analyzed as shown in Figure 1. Characteristics of 970 patients are summarized in Table 2. EGD and CS were performed in 705 patients (72.7%) and 265 patients (27.3%), respectively. Biopsy and resection were performed in 308 patients (31.7%) and 73 patients (7.6%), respectively. Differences of patients who underwent endoscopy with and without cessation are summarized in Table 3. The ratio of patients who underwent invasive procedures was lower in patients without cessation than in patients with cessation. Additionally, patients receiving multi-agents have a tendency to undergo no invasive procedures without cessation.

Proportion of prescribed agents

Among 970 patients, 804 patients (82.9%) were on a single agent, and 166 patients (17.1%) were on more than two agents. One

Table 2 Characteristics of 970 patients who sent back valid responses

	n	%
Age (years)	71.4 ± 8.1	
Gender (M : F)	715:255	
Number of agents		
Single-agent	804	82.9
Multi-agents	166	17.1
Two agents	141	14.5
Three agents	14	1.4
More than four agents	11	1.1
Modality		
Esophagogastroduodenoscopy	705	72.7
Colonoscopy	265	27.3
Endoscopic procedures		
Non-invasive procedures	589	60.7
Biopsy	308	31.7
Mucosal resection	73	7.6
Prophylactic antacid agent		
None	491	50.6
Proton pump inhibitor	235	24.2
H2 receptor antagonist	114	11.8
Others	130	13.4