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

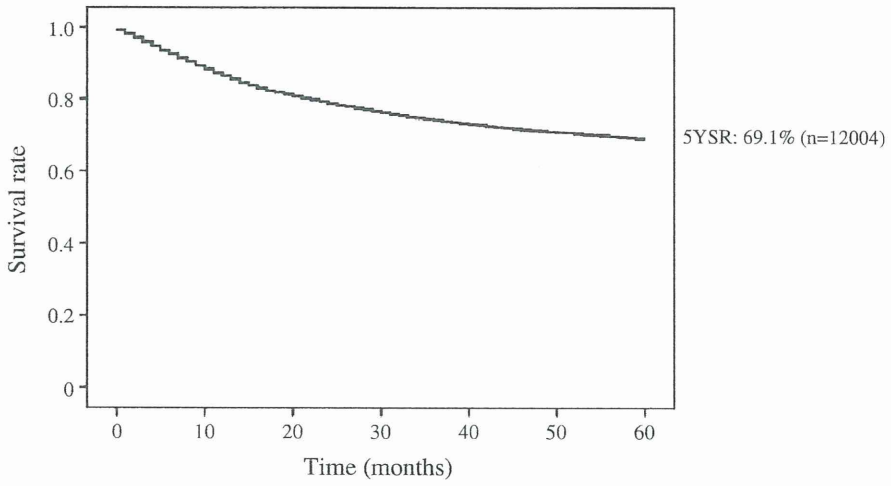

Fig. 3 Kaplan–Meier survival for all 12004 patients with primary gastric cancer. *5YSR* 5-year survival rate

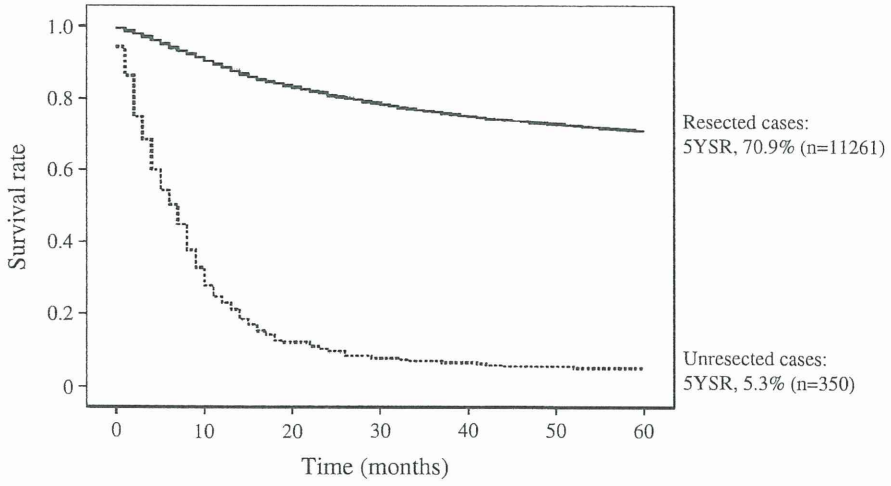

Fig. 4 Kaplan–Meier survival for resected cases and unresected cases

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,

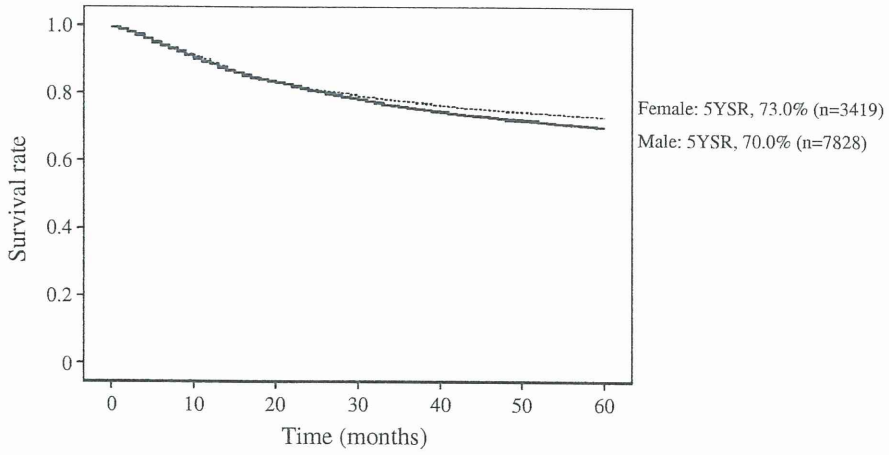

Fig. 5 Kaplan–Meier survival of the resected cases stratified by sex

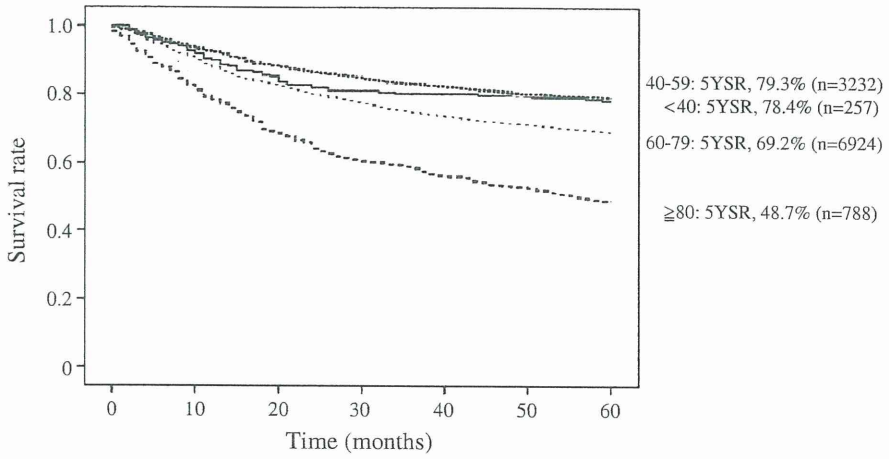

Fig. 6 Kaplan–Meier survival of the resected cases stratified by age

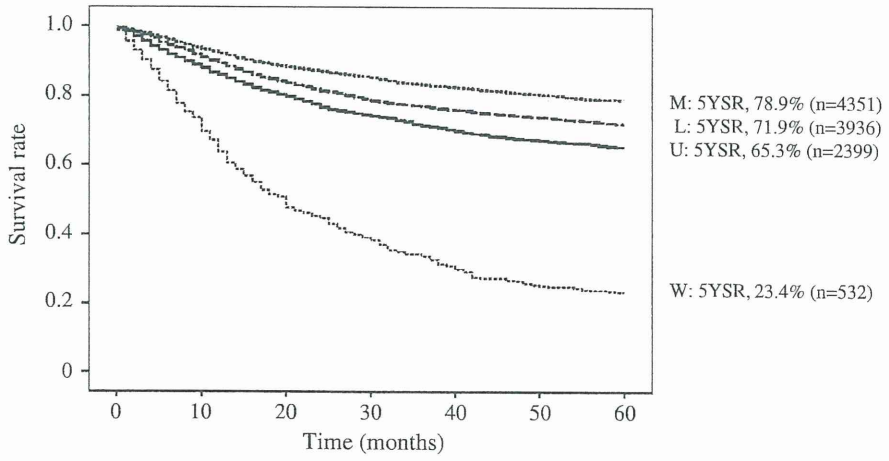

Fig. 7 Kaplan–Meier survival of the resected cases stratified by tumor location. *W* whole stomach, *M* middle third, *L* lower third, *U* upper third of stomach

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).

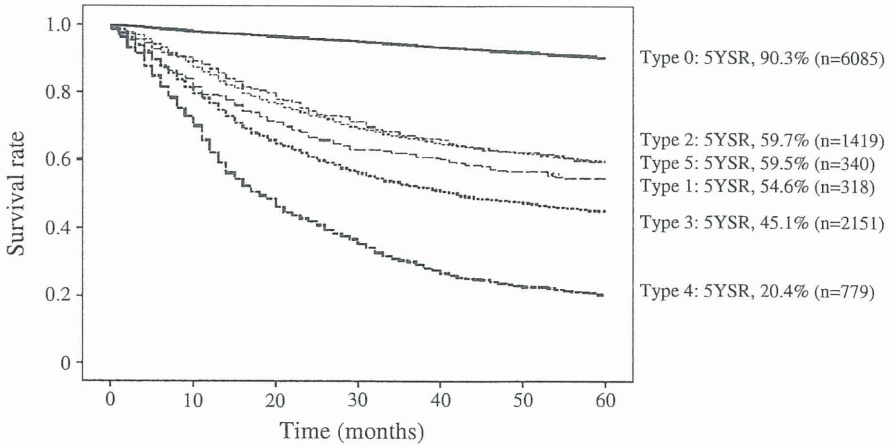

Fig. 8 Kaplan–Meier survival of the resected cases stratified by macroscopic type

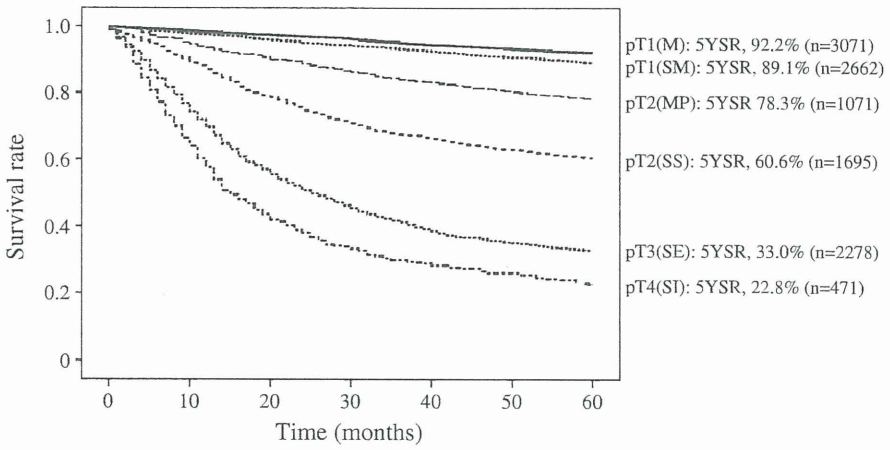

Fig. 9 Kaplan–Meier survival of the resected cases stratified by depth of tumor invasion. *M* mucosa or muscularis mucosa, *SM* submucosa, *MP* muscularis propria, *SS* subserosal, *SE* serosa, *SI* adjacent structures

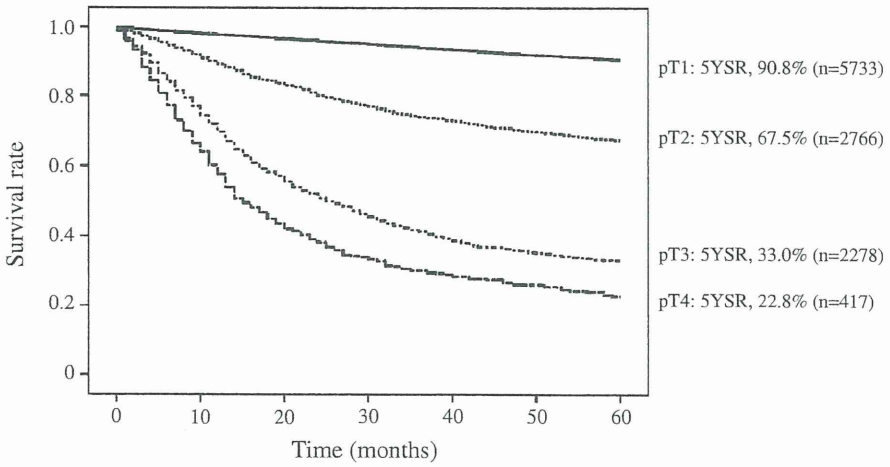

Fig. 10 Kaplan–Meier survival of the resected cases stratified by pT classification

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.

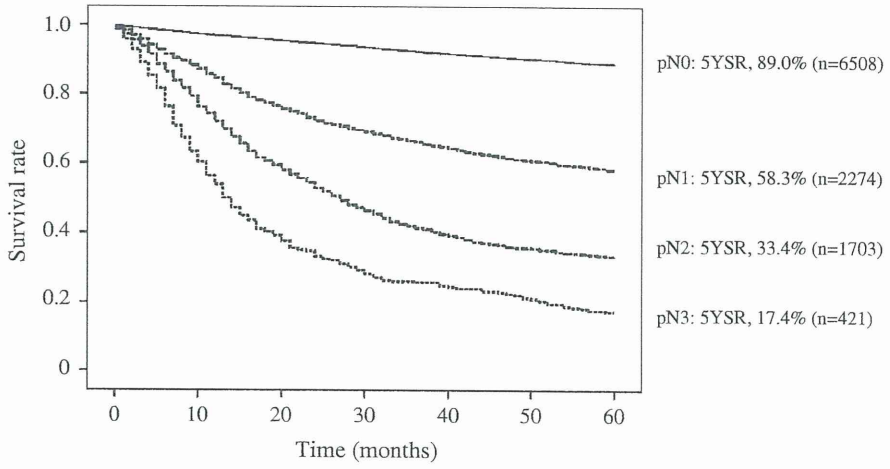

Fig. 11 Kaplan–Meier survival of the resected cases stratified by lymph node metastasis

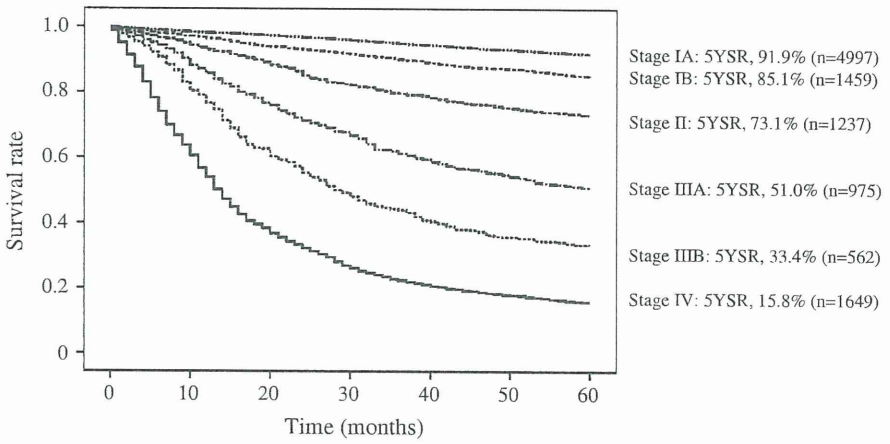

Fig. 12 Kaplan–Meier survival of the resected cases stratified by Japanese Gastric Cancer Association (JGCA) stage

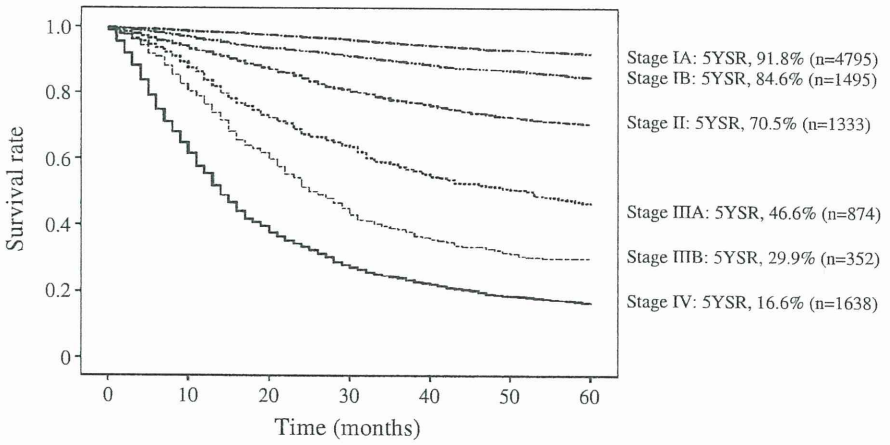

Fig. 13 Kaplan–Meier survival of the resected cases stratified by TNM stage

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

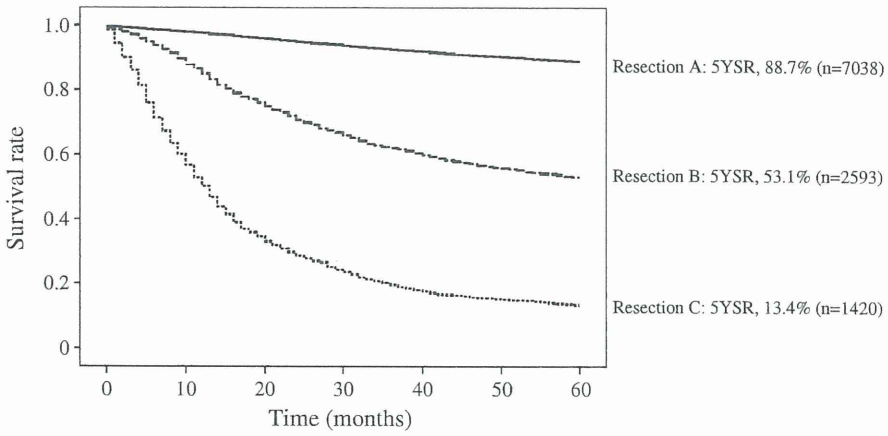

Fig. 14 Kaplan–Meier survival of the resected cases stratified by curative potential of gastric resection. *Resection A*, no residual disease with high probability of cure satisfying all of the following conditions: T1 or T2; N0 treated by D1, 2, 3 resection or N1 treated by D2, 3 resection; M0, P0, 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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Magnifying Narrowband Imaging Is More Accurate Than Conventional White-Light Imaging in Diagnosis of Gastric Mucosal Cancer

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BACKGROUND & AIMS: It is difficult to accurately diagnose patients with depressed gastric mucosal cancer based on conventional white-light imaging (C-WLI) endoscopy. We compared the real-time diagnostic yield of C-WLI for small, depressed gastric mucosal cancers with that of magnifying narrow-band imaging (M-NBI). **METHODS:** We performed a multicenter, prospective, randomized, controlled trial of patients with undiagnosed depressed lesions ≤10 mm in diameter identified by esophagogastroduodenoscopy. Patients were randomly assigned to groups that were analyzed by C-WLI (n = 176) or M-NBI (n = 177) immediately after detection; the C-WLI group received M-NBI after C-WLI. We compared the diagnostic accuracy, sensitivity, and specificity between C-WLI and M-NBI and assessed the diagnostic yield of M-NBI conducted in conjunction with C-WLI. **Results:** Overall, 40 gastric cancers (20 in each group) were identified. The median diagnostic values for M-NBI and C-WLI were as follows: accuracy, 90.4% and 64.8%; sensitivity, 60.0% and 40.0%; and specificity, 94.3% and 67.9%, respectively. The accuracy and specificity of M-NBI were greater than those of C-WLI ($P < .001$); the difference in sensitivity was not significant ($P = .34$). The combination of M-NBI with C-WLI significantly enhanced performance compared with C-WLI alone; accuracy increased from (median) 64.8% to 96.6% ($P < .001$), sensitivity increased from 40.0% to 95.0% ($P < .001$), and specificity increased from 67.9% to 96.8% ($P < .001$). **CONCLUSIONS: M-NBI, in conjunction with C-WLI, identifies small, depressed gastric mucosal cancers with 96.6% accuracy, 95.0% sensitivity, and 96.8% specificity. These values are better than for C-WLI or M-NBI alone.**

Keywords: Gastric Cancer; Early Detection; Benign; Malignant; Neoplasm; Biopsy.

Gastric cancer is the fourth most common malignancy and the second leading cause of death from cancer worldwide.[1] Early detection and curative treatment are the best strategies for improving patient survival. Esophagogastroduodenoscopy is the most sensitive method of early detection of gastric cancers. However, an accurate early diagnosis of gastric mucosal cancer is difficult with conventional white-light imaging (C-WLI) endoscopy; nevertheless, it remains the standard endoscopic examination modality worldwide.

Detection of mucosal cancers ≤20 mm in diameter is ideal, because they are curable using minimally invasive treatments such as endoscopic mucosal resection and endoscopic submucosal dissection.[2,3] Among the gastric mucosal cancers, the depressed type is the predominant morphology.[4–6] However, small depressed cancers (≤10 mm in diameter) are more difficult to distinguish from benign abnormalities (such as inflammation) compared with elevated cancers. Although chromoendoscopy using indigo carmine has contributed to an improvement in the diagnosis of gastric mucosal cancers,[7] there is no evidence of the superiority of chromoendoscopy over C-WLI. Therefore, C-WLI endoscopy remains the standard imaging modality for diagnosing gastric mucosal cancers.

Histologic evaluation of biopsy specimens from suspicious lesions is conventionally used to confirm a diagnosis. A highly accurate diagnosis without the need for a biopsy is the ultimate goal of endoscopists, because this would decrease the number of unnecessary biopsies, especially when confirming a negative biopsy of any suspicious cancerous lesion. This could reduce the risk of postbiopsy bleeding, costs associated with the procedure, and the workload on pathologists.

Magnifying narrow-band imaging (M-NBI), a recently developed advanced endoscopic imaging technology, was reported to be useful for the accurate diagnosis of gastric abnormalities such as cancers,[8–13] adenomas,[14] and intestinal metaplasia.[15] However, no randomized trials have been conducted to compare M-NBI with C-WLI. The present study was designed to assess and compare the real-time diagnostic yield of C-WLI for depressed gastric mucosal

Abbreviations used in this paper: CI, confidence interval; C-WLI, conventional white-light imaging; M-NBI, magnifying narrow-band imaging; NPV, negative predictive value; PPV, positive predictive value.

0016-5085/$36.00
doi:10.1053/j.gastro.2011.08.007

cancers with that of M-NBI when performed by skilled endoscopists.

Patients and Methods

Study Design and Participants

This randomized, controlled, open-label, multicenter trial was conducted at 9 centers in Japan. This study was conducted according to the Standards for the Reporting of Diagnostic Accuracy Studies (STARD) initiative[16] and the Declaration of Helsinki.

The frequency of synchronous or metachronous multiple gastric cancers was reported as 3 to 5 per 100 patient-years,[17–19] which is higher than the incidence of gastric cancer in the general population. In other words, patients with gastric cancer might constitute a cancer-enriched population, which may be a more suitable model for screening of potential gastric cancers than the general population. Therefore, we recruited patients aged 20 years or older with untreated gastric cancers and patients with a history of gastric cancer. Patients who had been treated with endoscopic mucosal resection or endoscopic submucosal dissection were included in the latter group, because their stomachs were preserved with minimum injury. We excluded patients who had been treated with surgical resection, because the stomach was either removed or was reduced in size. Other exclusion criteria were serious complications that could interfere with the examination protocol and the use of medication that might interfere with the collection of a biopsy specimen. Written informed consent was obtained, and the institutional review board of each participating hospital approved the study. The clinical trial number of this study was UMIN-CTR000001072.

To detect a target lesion, screening was performed using C-WLI endoscopy. Previously undetected lesions were considered ideal potential targets for evaluating the diagnostic yield without bias. Therefore, the target lesions for this study were "newly detected and undiagnosed" small, depressed gastric lesions ≤10 mm in diameter. We did not target lesions that had been analyzed histologically. Small, depressed lesions with apparent erosion or ulceration were also not evaluated, because it is difficult to visualize surface changes in these lesions. If the patient had multiple such lesions, only the first lesion detected was selected for examination. The diameter of each lesion was estimated by comparing it with the size of the biopsy forceps.

Randomization and Masking

When a target small, depressed lesion was detected by C-WLI screening, patients were immediately assigned randomly to undergo detailed examination using C-WLI or M-NBI at a 1:1 ratio. After the randomization, all endoscopists knew which imaging method would be used for the detailed examination when making a diagnosis of the target lesion. Randomization was performed promptly on-site using tables of random numbers stratified by hospital, and the results thereof were kept in sealed, numbered envelopes. The random allocation sequence was prepared at the data management center. Both the assignment result and the corresponding envelope number were recorded by the data management center. At each participating hospital, sealed envelopes were stored by a third party who was not involved in the study, and the envelopes were opened by an assistant physician in serial order only when randomization was performed. The assigned patient identification number, envelope number, and assignment result were recorded on-site and faxed to the data management center on the day of the examination.

Procedure and End Points

The study design and the protocol examination are outlined in Supplementary Figure 1 and Supplementary Materials and Methods. The diagnosis for the target lesion was made by one endoscopist according to predetermined diagnostic criteria for C-WLI and M-NBI without any consultation with other physicians, and an assistant physician immediately recorded the results using a case report form. For each modality, the interval between the start of the observation and the time at which an endoscopic diagnosis was made was measured using a stopwatch. For the C-WLI group, M-NBI examination was performed after completion of a diagnosis based on C-WLI. This procedure was used to evaluate the effect of using M-NBI in conjunction with C-WLI. After all records were compiled, at least one biopsy specimen was obtained from the target lesion.

The primary aim of the study was to compare the diagnostic accuracy between C-WLI and M-NBI. The secondary aim was to compare diagnostic sensitivity, specificity, and examination time between C-WLI and M-NBI and to evaluate the effects of an additional M-NBI study after the initial C-WLI in terms of diagnostic accuracy, sensitivity, specificity, and examination time. Histopathology diagnosis of obtained biopsy specimens was used as a gold standard for the diagnosis.

Endoscopy System

The NBI system is an innovative optical image-enhanced technology that involves a narrow-bandwidth NBI filter in the video endoscopy system. The central wavelengths of the NBI filters are 415 nm and 540 nm, and each has a bandwidth of 30 nm. Because 415-nm and 540-nm light are well absorbed by hemoglobin, the microvascular architecture of the mucosal surface can be visualized readily. Details of this system have been reported elsewhere.[20–22]

We used high-resolution magnifying endoscopy with a capability of 80-fold optical magnification (GIF-Q240Z, GIF-H260Z, and GIF-FQ260Z; Olympus Medical Systems, Tokyo, Japan) and a high-resolution liquid-crystal monitor (OEV191H; Olympus Medical Systems). We alternated between the 2 imaging modalities (C-WLI and M-NBI) by pushing a button on the endoscope (Evis Lucera Spectrum System; Olympus Medical Systems). We used a fixed structure enhancement setting and color tone for the video processor.

Participating Endoscopists

All examinations were performed by 31 endoscopic specialists accredited by the Japan Gastroenterological Endoscopy Society in 9 institutes. Before the onset of the study, all participating endoscopists were trained using images of small, depressed lesions to minimize diagnostic variation between them.

Diagnostic Criteria for C-WLI and M-NBI

Figure 1 shows a representative endoscopic image of a small, depressed gastric cancer and a small, depressed benign lesion. The diagnostic method based on endoscopic findings is outlined in Supplementary Materials and Methods.

The endoscopic diagnostic criteria for small, depressed gastric cancers using C-WLI were defined based on previous reports of C-WLI findings: an irregular margin and a spiny depressed area.[23] The observation of 2 findings (irregular margin and spiny

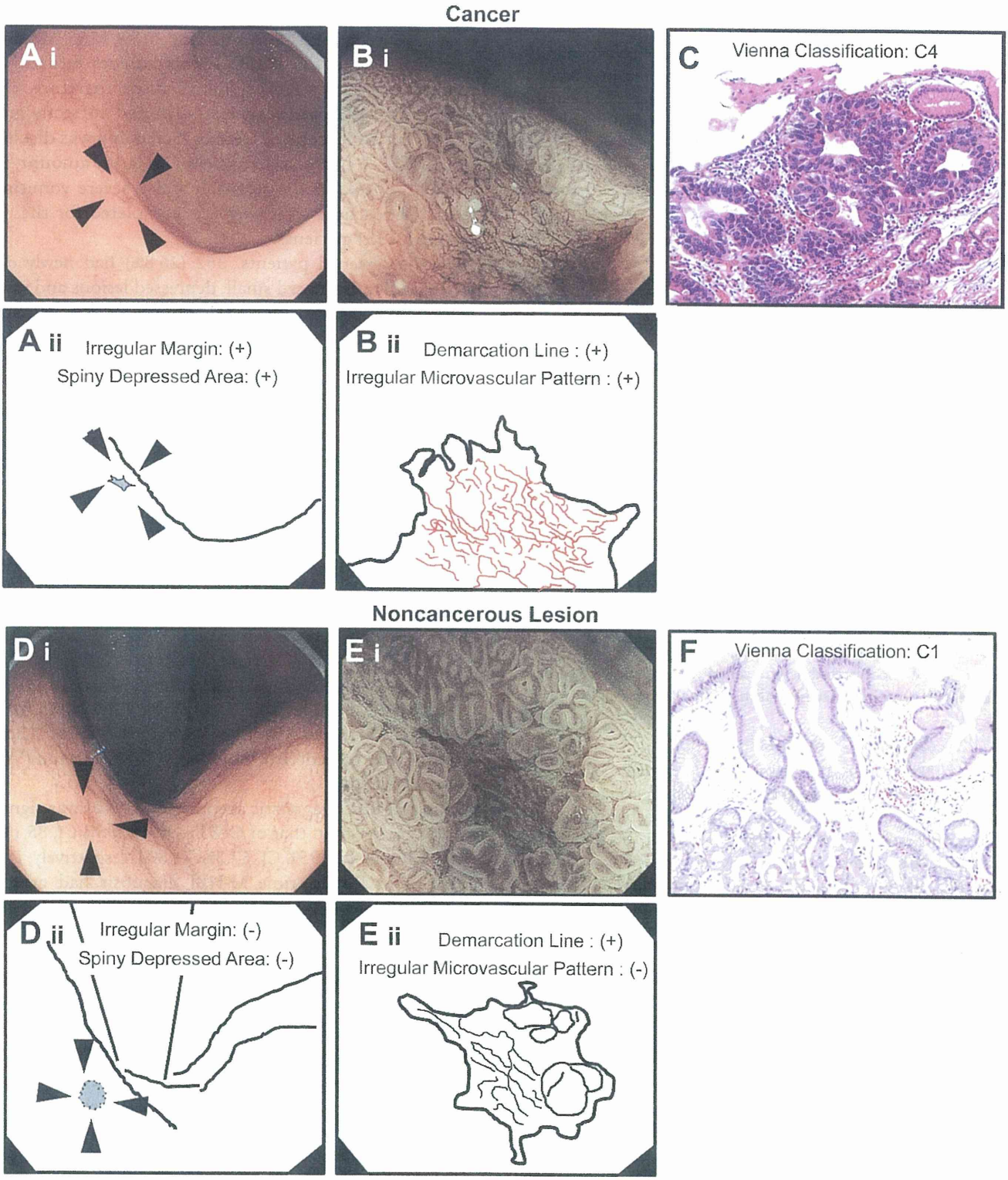

Figure 1. Representative endoscopic findings for gastric small, depressed lesions. *A–C* show a case of cancer, and *D–F* show a case of noncancerous lesions. *A* shows an endoscopic image obtained using C-WLI. A small, depressed lesion (*arrowheads*) is evident in the anterior wall of the lower part of the gastric body. This lesion was evaluated as having an irregular margin and a spiny depressed area. *B* shows an endoscopic image obtained using M-NBI, which enabled clear visualization of the demarcation line and an irregular microvascular pattern. *A′* and *B′* are schematic representations of the images shown in *A* and *B*, respectively. *C* shows a lesion that was histologically diagnosed as a differentiated adenocarcinoma, Vienna Classification C4. *D* shows an image obtained using C-WLI. A small reddish area (*arrowheads*) is evident in the anterior wall of the upper part of the gastric body. Because the depressed area was not "spiny" and because a definite margin was not apparent, this case was evaluated as not having a spiny depressed area or an irregular margin. *E* shows an image obtained using M-NBI, which enabled clear visualization of a demarcation line and the absence of an irregular microvascular pattern. *D′* and *E′* are schematic representations of the images shown in *D* and *E*, respectively. *F* shows a lesion that was histologically diagnosed as gastritis, Vienna Classification C1.

depressed area) in the target lesion was classified according to 3 categories: present, absent, or indeterminate.

The endoscopic diagnostic criteria for small, depressed gastric cancers using M-NBI were defined based on previous reports by Yao et al: a demarcation line between the depressed cancerous lesion and the surrounding noncancerous area and an irregular microvascular pattern inside the lesion.[24] Observations of 2 findings (demarcation line and irregular microvascular pattern) in the target lesion were also classified according to 3 categories: present, absent, or indeterminate.

Endoscopic diagnoses were determined according to the combined visibility of the 2 findings as follows (Supplementary Figure 2). (1) If both findings were present, the diagnosis was "cancer." (2) If either finding was indeterminate, the diagnosis was "inconclusive." (3) If either or both findings were absent, the diagnosis was "noncancerous."

For analyzing diagnostic accuracy, sensitivity, and specificity, lesions diagnosed as "inconclusive" were considered as endoscopic "noncancerous" lesions.

Pathology Diagnosis

The biopsy specimens were evaluated using H&E staining. The diagnostic pathology criteria were based on the revised Vienna classification.[25] C4 (mucosal high-grade neoplasia) or C5 (submucosal invasion by neoplasia) were diagnosed as cancer, and C1 (negative for neoplasia), C2 (indefinite for neoplasia), or C3 (mucosal low-grade neoplasia) were diagnosed as noncancerous lesions. In this study, we used a central system of consultation with a main expert pathologist. If an indeterminate lesion were to be encountered, it was scheduled to be reviewed by this consulting pathologist in making a final diagnosis.

Statistical Analysis

We assumed that the accuracy, sensitivity, and specificity of C-WLI and M-NBI compared with histologic diagnosis would be 60% and 85%, respectively. To set a probability for error of 0.05 and attain a power of 80% for testing the superiority of M-NBI, 108 patients including at least 43 cancerous lesions were needed. Next, we calculated how many patients would need to be screened. Because the frequency of small depressed lesions was reported to be 8.1% in the general population,[9] the required size of the screening sample was 1100 patients.

Statistical analysis was performed using SPSS software, version 17 (SPSS Inc, Chicago, IL). For diagnostic performance, accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) are presented as percentages with 95% confidence intervals (CIs). Continuous variables are expressed as medians and interquartile ranges. Analyses of the difference in diagnostic performance between C-WLI and M-NBI were conducted using the population whose diagnoses had been confirmed by pathology using Pearson's χ^2 test. Analyses of the effect of additional M-NBI after the initial C-WLI on diagnostic performance were conducted using the population whose diagnoses had been confirmed by pathology and McNemar testing. Analysis of the examination duration was conducted using the population who completed protocol examination and the Mann–Whitney nonparametric test for comparisons between C-WLI and M-NBI, as well as the Wilcoxon signed rank test for comparisons between C-WLI and C-WLI plus M-NBI. All probability values calculated in this analysis were 2 sided, and $P < .05$ was considered significant.

Results

Between June 2008 and May 2010, 1365 patients were enrolled in the study. Eight patients refused to participate and 4 were registered twice; therefore, the remaining 1353 patients were registered correctly and underwent endoscopic screening. Screening was discontinued for 2 patients because of a large amount of residual digesta in the stomach and a severe vomiting reflex. Endoscopic screening was completed for the remaining 1351 patients.

Of the screened patients, 362 (26.8%) had newly detected and undiagnosed small, depressed lesions and were randomly assigned to one of 2 groups: (1) 180 patients were examined using C-WLI followed by M-NBI, and (2) 182 patients were examined using M-NBI alone. Four patients in the C-WLI group (one patient's lesion was >10 mm in diameter, one was discontinued from the examination because of Mallory–Weiss syndrome, and 2 had a missed biopsy) and 5 patients in the M-NBI group (one was examined with an unpermitted endoscope and 4 missed biopsy) were excluded. Data for 176 patients in the C-WLI group and 177 patients in the M-NBI group were used for the final analysis (Figure 2). The demographic and lesion characteristics of the 2 groups were balanced. In both groups, 13% of patients had newly diagnosed gastric cancer (20 per group; Table 1).

Table 2 shows endoscopic diagnoses for all lesions. Inconclusive diagnoses were obtained for 3 lesions (1.7%) using M-NBI, for 6 lesions (3.4%) using C-WLI, and for 2 lesions (1.3%) using C-WLI followed by M-NBI. These lesions were considered endoscopic "noncancerous" lesions for analysis.

The real-time diagnostic accuracy of M-NBI was significantly greater than that of C-WLI (90.4% [95% CI, 85.1%–94.3%] and 64.8% [95% CI, 57.2%–71.8%], respectively; $P <$ .001; Table 3). Real-time M-NBI diagnosis had greater specificity than C-WLI diagnosis (94.3% [95% CI, 89.4%–97.3%] and 67.9% [95% CI, 60.0%–75.2%], respectively; $P <$ .001; Table 3). The diagnostic sensitivities of M-NBI and C-WLI did not differ significantly (60.0% [95% CI, 36.1%–80.9%] and 40.0% [95% CI, 19.1%–63.9%], respectively; $P =$ .34; Table 3). M-NBI in conjunction with C-WLI significantly enhanced the diagnostic performance of the latter; accuracy increased from 64.8% (95% CI, 57.2%–71.8%) to 96.6% (95% CI, 93.5%–99.1%; $P <$ .001), sensitivity increased from 40.0% (95% CI, 19.1%–63.9%) to 95.0% (75.1%–99.9%; $P <$ .001), and specificity increased from 67.9% (95% CI, 60.0%–75.2%) to 96.8% (92.7%–99.0%; $P <$ .001; Table 3).

The median durations of the C-WLI and M-NBI procedures were 21 seconds (interquartile range, 12–40 seconds) and 55 seconds (interquartile range, 23–97 seconds), respectively, and this difference was highly significant ($P <$ .001). The median total duration of C-WLI followed by M-NBI (72 seconds [interquartile range, 40–144 seconds]) was significantly longer than that of

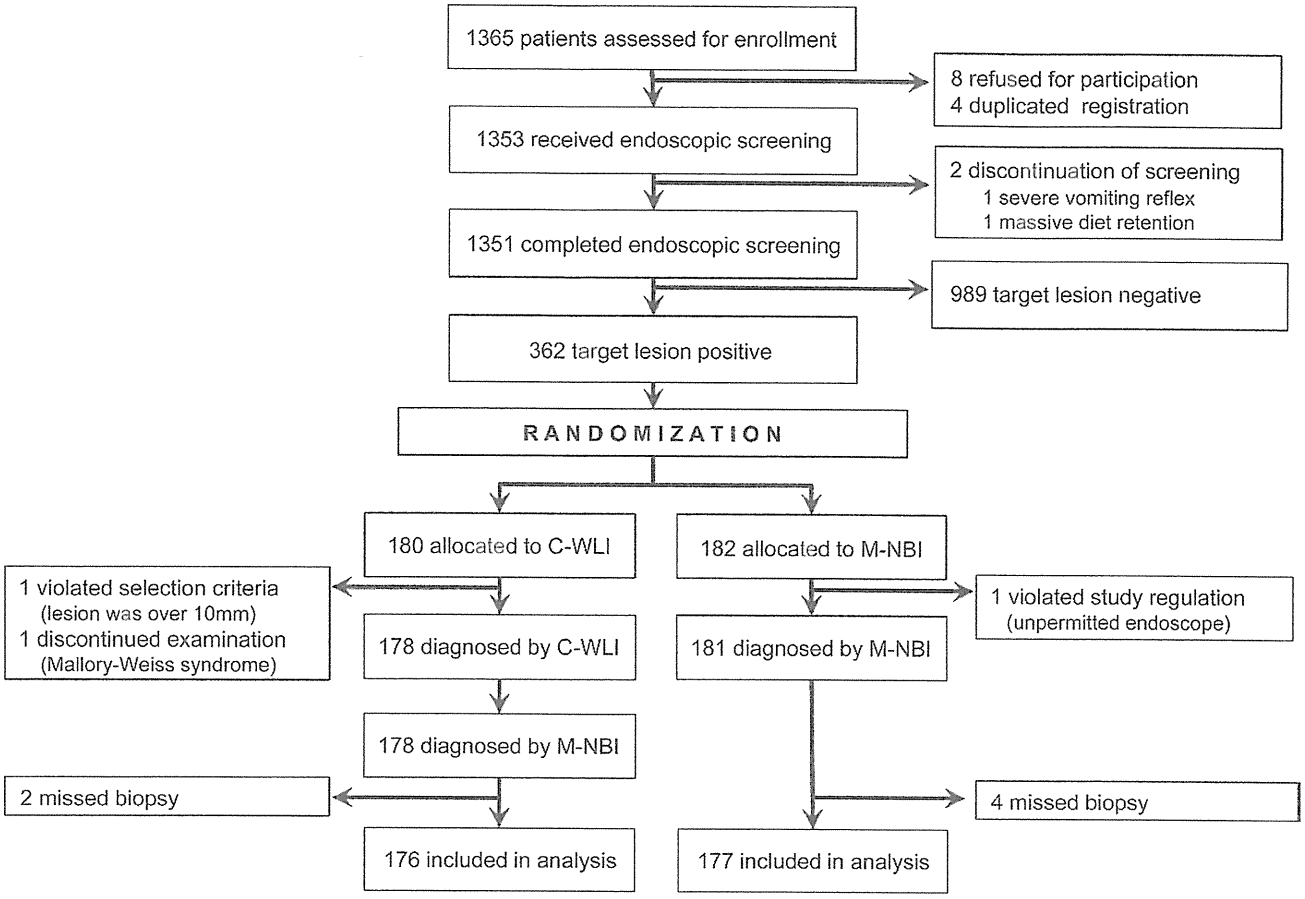

Figure 2. Patient enrollment, randomization, and examination.

C-WLI alone ($P < .001$). All patients tolerated the procedures well (Table 3).

Figure 3 shows the PPV and NPV data for each examination. M-NBI significantly improved the PPV compared with C-WLI alone to 57.1% (95% CI, 36.0%–78.3%) from 13.8% (95% CI, 2.9%–22.7%; $P = .001$). Furthermore, C-WLI followed by M-NBI dramatically improved the PPV from 13.8% (95% CI, 2.9%–22.7%) to 79.2% (95% CI, 62.9%–95.4%; $P < .001$). Similarly, the NPV of C-WLI of 89.8% (95% CI, 84.4%–95.3%) was improved by M-NBI to 94.9% (95% CI, 91.4%–98.3%; $P = .16$) and by C-WLI followed by M-NBI to 99.3% (95% CI, 98.1%–100%; $P < .001$).

Detailed C-WLI examination was discontinued during the procedure in one patient (1/362; 0.3%) because of bleeding associated with Mallory–Weiss syndrome. Although the bleeding stopped spontaneously without any endoscopic hemostatic treatment, a biopsy specimen was not obtained because the suspicious target lesion was missed. Two patients (2/362; 0.6%) were hospitalized on the day after examination because of bleeding from the biopsy site; although one patient needed a blood transfusion, both patients were discharged within a few days. None of the 3 patients experienced prolonged adverse effects. There were no serious adverse events directly related to the endoscopic observations.

Table 4 summarizes the clinical courses and pathologic diagnoses of 40 gastric cancers in 40 patients. Thirty-two patients were treated endoscopically (by endoscopic mucosal resection or endoscopic submucosal dissection). Five patients underwent surgical resection for synchronous advanced gastric cancers. The remaining 3 patients did not receive any treatment; 2 had other concomitant noncurable malignancies, and one refused treatment. Histologically, 39 lesions were of the intestinal type and one lesion was of the diffuse type. Regarding the depth of the 37 lesions that were removed, 35 were mucosal cancers, 2 of which were accompanied by submucosal invasion (0.3 mm and 0.8 mm). The depths of the 3 untreated lesions were estimated endoscopically as 2 mucosal cancers and one submucosal cancer.

Discussion

In this multicenter randomized trial, we compared the diagnostic yield of C-WLI with that of M-NBI for small gastric cancers. The primary aim of this study was to compare directly the real-time diagnostic accuracy of 2 randomly assigned endoscopic modalities. One was the worldwide standard method of C-WLI; the other was M-NBI, which is the most advanced imaging method at present. This end point is the most impor-

Table 1. Baseline Characteristics of the Study Participants According to Treatment Group

	C-WLI (n = 176)	M-NBI (n = 177)	*P* value
Age (*y*)			
Median (range)	69 (45–93)	69 (37–87)	.56
Sex			
Male	138	140	.79
Female	38	37	
Endoscope			
GIF-Q240Z	71	65	.83
GIF-H260Z	104	109	
GIF-FQ260Z	1	3	
Size of lesion (*mm*)			
≤5	74	71	.75
>5	102	106	
Mean	5.6	5.6	.97
Location of lesion			
Upper third			
Anterior wall	4	2	.51
Lesser curvature	9	10	
Posterior	22	12	
Greater curvature	4	3	
Middle third			
Anterior wall	7	7	
Lesser curvature	13	25	
Posterior	12	11	
Greater curvature	8	6	
Lower third			
Anterior wall	18	23	
Lesser curvature	25	33	
Posterior	26	18	
Greater curvature	28	27	
Histopathology diagnosis			
Cancer	20	20	1.00
Noncancerous	156	157	

tant aspect of this study, because if C-WLI proves superior to M-NBI, such advanced methods are not needed in practice. However, if M-NBI is indeed better than C-WLI, it should be used more in daily practice. The secondary aim of this study was to evaluate the additional effect of performing M-NBI after C-WLI. This end point is also important, because in daily practice M-NBI is usually performed after C-WLI. Therefore, the results might reflect the practical diagnostic potential. To evaluate these aims, we used a strictly controlled randomized study. Furthermore, the endoscopic diagnosis in each method (C-WLI and M-NBI) was made on-site and independently to avoid any bias.

M-NBI, especially when used in conjunction with C-WLI, significantly enhanced real-time sensitivity, specificity, and accuracy of diagnosis; therefore, we concluded that M-NBI is an essential modality for diagnosing small gastric mucosal cancer. Although there are reports on the diagnostic yield of M-NBI for differential diagnosis of gastric lesions, some were performed at only one institute,[9,10,12,13] one was evaluated by several expert endoscopists using stored images and did not involve real-time assessment,[12] and one included gastric lesions with a definite diagnosis.[13] To overcome these limitations, our study targeted newly detected and undiagnosed gastric superficial lesions, which were evaluated on-site. For these reasons, the present results are the most reliable and could be a milestone in the field of endoscopic diagnosis of early gastric cancers.

Regarding accuracy and specificity, M-NBI alone yielded excellent results (90.4% and 94.3%, respectively), which were significantly better than those obtained with C-WLI. However, the sensitivities of M-NBI alone (60.0%) and C-WLI alone (40.0%) were lower than the estimated values: 85% for M-NBI and 60% for C-WLI. The low sensitivity of C-WLI might be acceptable considering the difficulty of diagnosing small gastric cancers in daily clinical practice. Although the reason for the low sensitivity of the M-NBI group is unknown, it might be associated with the examination protocol in this study; M-NBI observation was performed without evaluating a gross finding of lesions using C-WLI. In daily practice, magnifying examinations are usually performed after C-WLI. Actually, when performed after the C-WLI observation, M-NBI yielded excellent diagnostic performance in terms of accuracy, sensitivity, and specificity (all values were >95%). In addition, M-NBI and C-WLI followed by M-NBI significantly improved the PPV and NPV compared with C-WLI alone. This has enormous significance in clinical practice, because the examination with high PPV and high NPV might enable the clinician to make appropriate judgments as to which lesion needs pathology to confirm the diagnosis. When the lesion is suspected to be a neoplasm by C-WLI followed by M-NBI, taking a biopsy specimen is highly recommended to confirm the pathology. On the other hand, when the lesion is not suspected to be a neoplasm by M-NBI alone or by C-WLI followed by M-NBI, we could avoid a negative biopsy. These results have the potential to enable so-called "optic biopsy." Taken together, C-WLI followed by M-NBI might be the best

Table 2. Endoscopic Diagnoses for All Small Depressed Lesions

		Cancerous lesion (%)			Noncancerous lesion (%)		
Group	Method	Correct diagnosis	Incorrect diagnosis	Inconclusive diagnosis	Correct diagnosis	Incorrect diagnosis	Inconclusive diagnosis
M-NBI	M-NBI	12/20 (60.0)	7/20 (35.0)	1/20 (5.0)	146/157 (93.0)	9/157 (5.7)	2/157 (1.3)
C-WLI	C-WLI	8/20 (40.0)	12/20 (60.0)	0/20 (0)	100/156 (64.1)	50/156 (32.1)	6/156 (3.8)
	C-WLI+M-NBI	19/20 (95.0)	1/20 (5.0)	0/20 (0)	149/156 (95.5)	5/156 (3.2)	2/156 (1.3)

Table 3. Diagnostic Performance of C-WLI and M-NBI for Gastric Small Depressed Lesions

Group	Method	Accuracy (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Examination time (s), median (interquartile range)
M-NBI	M-NBI	90.4[a] (85.1–94.3)	60.0 (36.1–80.9)	94.3[a] (89.4–97.3)	55[a] (23–97)
C-WLI	C-WLI	64.8 (57.2–71.8)	40.0 (19.1–63.9)	67.9 (60.0–75.2)	21 (12–40)
	C-WLI + M-NBI	96.6[b] (93.5–99.1)	95.0[b] (75.1–99.9)	96.8[b] (92.7–99.0)	72[b] (40–144)

[a]$P < .001$ for M-NBI vs C-WLI; [b]$P < .001$ for C-WLI vs C-WLI + M-NBI.

approach for making accurate diagnoses of small gastric cancers.

The durations of the M-NBI and C-WLI followed by M-NBI examinations were 34 seconds and 51 seconds, respectively, significantly longer than that required for C-WLI alone. However, these durations are clinically acceptable, because we managed to make accurate diagnoses without having to insert a spraying catheter or use indigo carmine. The importance of simple methods and accurate diagnoses for clinical practice is indisputable. Thus, Li et al showed that confocal laser endomicroscopy can be used to identify gastric superficial cancers with high validity and reliability.[26] However, confocal laser endomicroscopy requires the intravenous administration of a contrast agent. In contrast, M-NBI can be used by simply pushing a button on the endoscope. In addition, evaluation of demarcation lines and irregular microvascular patterns is sufficient for diagnosis with M-NBI, whereas confocal laser endomicroscopy requires knowledge of histopathology procedures for diagnosis.

Major bleeding caused by an endoscopic biopsy is rarely reported.[27] However, in our study, 2 patients experienced bleeding from the biopsy site. The best way of avoiding such bleeding is to avoid unnecessary biopsies. M-NBI, especially when used in conjunction with C-WLI, could help to reduce the number of unnecessary biopsies.

Our study has some limitations. First, the number of cancerous lesions was small, and it was less than the required sample size. This might be associated with insufficient power to evaluate sensitivity adequately. Then, further large numbers of patients for screening are needed to evaluate the sensitivity for diagnosing small gastric mucosal cancers of each modality. Second, this study was open labeled because the endoscopists knew which imaging modality was in use. Thus, a blinded study was impossible. Third, there is no arm that includes a dye-based imaging method such as indigo carmine or acetic acid. Indigo carmine and acetic acid are useful, but these dyes are only used in a few countries and institutes, and the standard worldwide endoscopic method to diagnose early gastric cancer is still C-WLI without any dye use. In addition, if we added a chromoendoscopy arm in this study, the required sample size would need to be enlarged and the study design and statistical analyses would be excessively complex. For these reasons, we did not include the dye-based imaging method.

Early detection of small gastric cancers makes it possible to effect a cure using minimally invasive treatments such as endoscopic mucosal resection and endoscopic

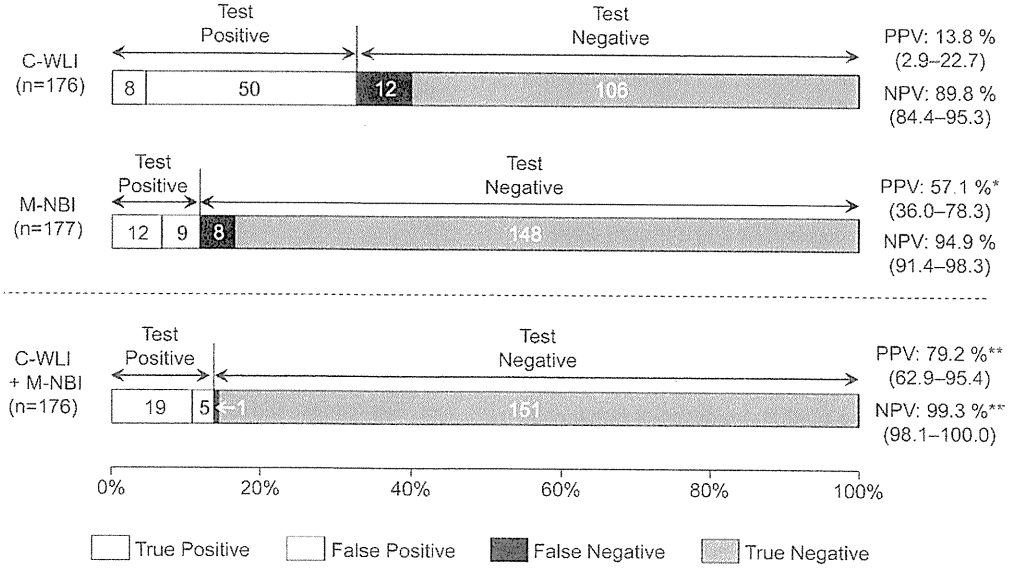

Figure 3. PPV and NPV in each examination. *The PPV for M-NBI was significantly higher than for C-WLI ($P = .001$). The NPV in M-NBI was higher than that of C-WLI; however, the difference was not significant ($P = .16$). **Both PPV and NPV were significantly enhanced by additional examination using M-NBI compared with C-WLI alone ($P < .001$).

Table 4. Clinical Course and Pathologic Diagnosis of Patients With Gastric Cancers

No. of patients	40
Treatment	
Endoscopic mucosal resection/endoscopic submucosal dissection	2/30
Surgery	5
No treatment	3
Histologic type	
Adenocarcinoma	40
Intestinal type	39
Diffuse type	1
Other diagnosis	0
Pathologic depth	
Mucosa	35
Submucosa	2
Muscularis propria	0
Unknown	3

submucosal dissection. In this study, all of the newly diagnosed small gastric cancers were good candidates for these procedures. Among the 37 cancers removed, 35 (95%) were mucosal. Early diagnosis using M-NBI and minimally invasive treatment is ideal for patients with gastric cancers, because it will improve their survival and quality of life. Although eradication of *Helicobacter pylori* is effective in reducing the incidence of gastric cancer,[17,28] endoscopic examination using M-NBI in conjunction with C-WLI should be indicated for high-incidence areas such as East Asia, South America, Eastern European countries, and Russia.[29]

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at doi: 10.1053/j.gastro.2011.08.007.

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Received May 28, 2011. Accepted August 11, 2011.

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Acknowledgments

Gastric NBI Study Investigators in Japan include the following: Noriya Uedo, Yoji Takeuchi (Osaka Medical Cancer for Cancer and Cardiovascular Diseases, Osaka); Hisashi Doyama, Yoshibumi Kaneko, Kenichi Takemura, Kazuhiro Miwa, Shinya Yamada (Ishikawa Prefectural Central Hospital, Ishikawa); Yutaka Saito, Ichiro Oda, Shigetaka Yoshinaga, Satoru Nonaka, Shusei Fukunaga (National Cancer Center Hospital, Tokyo); Manabu Muto, Yasumasa Ezoe, Shuko Morita, Takahiro Horimatsu (Kyoto University, Kyoto); Kenshi Yao, Takashi Nagahama, Hiroshi Tanabe, Takahiro Beppu, Yoichiro Ono, Masao Takeichi (Fukuoka University Chikushi Hospital, Fukuoka); Kazuhiro Kaneko, Tomonori Yano, Hiroaki Kon, Shinya Tsuruta (National Cancer Center Hospital East, Chiba); Yoshiro Kawahara, Toshio Uraoka, Seiji Kawano, Keisuke Hori (Okayama University Hospital, Okayama); Chizu Yokoi, Naoyoshi Nagata (National Center for Global Health and Medicine, Tokyo); Yasushi Sugiura (Kitano Hospital, Osaka); Hideki Ishikawa (Kyoto Prefectural University of Medicine, Kyoto); and Tomoko Aoyama (Medical Research Support, Osaka).

Conflicts of interest

The authors disclose no conflicts.

Funding

Supported by a part of grant-in-aid for cancer research from the Ministry of Health (H21-009), Labor, and Welfare of Japan.

Supplementary Materials and Methods

Study Flow

Written informed consent was obtained from all eligible patients. To detect a target lesion, endoscopic screening was performed using C-WLI. If no target lesion was detected, routine endoscopic examination was performed without study entry. When a target lesion was detected, patients were immediately assigned randomly to undergo detailed examination using C-WLI or M-NBI. For the C-WLI group, M-NBI examination was performed after completion of a diagnosis based on C-WLI. After all diagnoses were compiled, at least one biopsy specimen was obtained from the target lesion. The primary aim of this study was to compare directly the real-time diagnostic accuracy of 2 randomly assigned endoscopic modalities: C-WLI and M-NBI (*solid line box*). The secondary aim of this study was to evaluate the additional effect of performing M-NBI after C-WLI (*dashed line box*).

Diagnostic Method Based on Endoscopic Findings

Endoscopic diagnoses were made according to the combination of the endoscopic findings. In the case of C-WLI, an irregular margin and a spiny depressed area were used for the diagnostic findings. In the case of M-NBI, a demarcation line between the depressed cancerous lesion and the surrounding noncancerous area and an irregular microvascular pattern inside the lesion were used for the diagnosis. If both findings were present in each examination, the diagnosis of "cancer" was made. If either finding was indeterminate, the diagnosis was "inconclusive." If either or both findings were absent, the diagnosis was "noncancerous."