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SPECIAL ARTICLE

Gastric cancer treatment in Japan: 2008 annual report of the JGCA nationwide registry

Yoh Isobe · Atsushi Nashimoto · Kohei Akazawa · Ichiro Oda · Kenichi Hayashi · Isao Miyashiro · Hitoshi Katai · Shunichi Tsujitani · Yasuhiro Kodera · Yasuyuki Seto · Michio Kaminishi

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Abstract The Japanese Gastric Cancer Association (JGCA) started a new nationwide gastric cancer registry in 2008. Approximately 50 data items, including surgical procedures, pathological diagnoses, and survival outcomes, for 12004 patients with primary gastric cancer treated in 2001 were collected retrospectively from 187 participating hospitals. Data were entered into the JGCA database according to the JGCA *Classification of gastric carcinoma, 13th edition* and the International Union Against Cancer (UICC) *TNM Classification of malignant tumors, 5th edition* by using an electronic data collecting system. Finally, data of 11261 patients with gastric resection were analyzed. The 5-year follow-up rate was 83.5%. The direct death rate was 0.6%. TNM 5-year survival rates (5YSRs)/JGCA 5YSRs were 91.8/91.9% for stage IA, 84.6/85.1% for stage IB, 70.5/73.1% for stage II, 46.6/51.0% for stage IIIA, 29.9/33.4% for stage IIIB, and 16.6/15.8% for stage IV. The proportion of patients more than 80 years old was 7.0%, and their 5YSR was 48.7%. Compared to the JGCA archived data, though the follow-up rate needs to be improved, these data suggest that the postoperative results of patients with primary gastric carcinoma have improved in those with advanced disease and in the aged population in Japan.

All the authors belong to the Registration Committee of the Japanese Gastric Cancer Association.

Y. Isobe (✉)
Department of Surgery, National Hospital Organization Tokyo Medical Center, 2-5-1 Higashigaoka, Meguro-ku, Tokyo 152-8902, Japan
e-mail: isobey@mb.infoweb.ne.jp

A. Nashimoto
Department of Surgery, Niigata Cancer Center Hospital, Niigata, Japan

K. Akazawa
Department of Medical Informatics, Niigata University Medical and Dental Hospital, Niigata, Japan

I. Oda
Endoscopy Division, National Cancer Center Hospital, Tokyo, Japan

K. Hayashi
Department of Surgery, Yamagata Prefectural Kahoku Hospital, Yamagata, Japan

I. Miyashiro
Department of Surgery, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan

H. Katai
Department of Surgery, National Cancer Center Hospital, Tokyo, Japan

S. Tsujitani
Department of Surgery and Science, Graduate School of Medical Science, Kyushu University, Fukuoka, Japan

Y. Kodera
Department of Surgery, Nagoya University School of Medicine, Nagoya, Japan

Y. Seto
Department of Gastrointestinal Surgery, Graduate School of Medicine, University of Tokyo, Tokyo, Japan

M. Kaminishi
Department of Surgery, Showa General Hospital, Tokyo, Japan

Keywords Gastric cancer · Registry · Survival rate · Japan

Introduction

From 1998, the Japanese Gastric Cancer Association (JGCA) began conducting a nationwide gastric cancer registration project by using electronic data collecting systems. Detailed survival analyses of 8851 patients with primary gastric cancer treated in 1991 were reported in 2006 [1]. However, this nationwide registry was suspended because of several issues such as the operation of the Act Concerning Protection of Personal Information, revision of the JGCA classification for gastric cancer, and rapid changes in the information technology (IT) environment at the member hospitals. After a period of 10 years in which the program was inactive, the registration committee of the JGCA started a new registration program to collect anonymized data simply, correctly, and quickly, in 2008 [2, 3]. Based on this program, we investigated the survival outcomes of patients with primary gastric cancer treated in 2001.

Subjects, materials, and methods

In the 2008 JGCA nationwide registration program, approximately 50 data items, including surgical procedures, pathological diagnoses, and prognoses, for patients with primary gastric carcinoma surgically treated in 2001 were collected retrospectively in 2008 by using custom-made software. This software could be downloaded from the JGCA website. The JGCA member hospitals could participate in this project voluntarily.

The registration data of this system are listed in Table 1. Definition and documentation of the items were based on the Japanese (JGCA) *Classification of gastric carcinoma, 13th edition* [4, 5] and the International Union Against Cancer (UICC) *TNM Classification of malignant tumors, 5th edition* [6]. These two classifications were not compatible with each other and items could not be converted automatically. The JGCA T-category was identical to the TNM classification. On the other hand, in the JGCA classification, peritoneal metastasis and liver metastasis were individually recorded as P- and H-categories, both of which could be translated into the M-category in the TNM classification. Intraoperative peritoneal washing cytology (CY) was an independent category in the JGCA classification. The JGCA N-category was defined by the anatomical extension of lymph node metastasis in association with the location of the primary tumor, while the TNM N-category was defined by number of metastatic regional lymph nodes. Items that are compatible in the JGCA classification and the TNM classification, and items that are not compatible are listed in Table 2 for convenience.

After the patients' data were entered with the data entry software, the patients' names and other personal information were removed from the exporting data set for privacy protection. A compact disk containing the linkable anonymous data was then mailed to the JGCA data center, located at Niigata University Medical and Dental Hospital. The accumulated data of the patients were reviewed and analyzed by the JGCA registration committee. One- to 5-year survival rates (5YSRs) were calculated for various subsets of prognostic factors by the Kaplan–Meier method. Deaths of any cause observed during 5 postoperative years were counted as events in the survival analysis. SPSS Ver. 15 software (SPSS, Chicago, IL, USA) was used for

Table 1 Registration data

Category	Item
Personal information	Name of hospital, serial no., case no., ID no.[a], age, sex
Follow-up	Date of follow-up, survival situation, causes of death
Surgery	Date of operation, approach, operative procedure, LN dissection (D), organs resected together with stomach, type of reconstruction
Pathology	Anatomical subsite, macroscopic type, size of tumor, histological type, depth of tumor invasion, ly, v, number of dissected LNs, number of metastatic LNs, N, PM/DM, CY
JGCA final diagnosis	Depth of tumor invasion, adjacent structure involved, fN, H, P, M, curability, stage
UICC TNM categories	T, N, M, stage

LN lymph node, *ly* lymphatic invasion, *v* venous invasion, *N* extent of LN metastasis (JGCA), *PM/DM* involvement of proximal and distal margin, *CY* peritoneal cytology, *fN* extent of LN metastasis (final diagnosis), *H* liver metastasis, *P* peritoneal metastasis, *M* distant metastasis, *JGCA* Japanese Gastric Cancer Association, *UICC* International Union Against Cancer

[a] ID no. was not exported to the registration data set

Table 2 Compatibility to convert JGCA classification to TNM classification

Category	JGCA 13th ed.	TNM 5th ed.	Compatibility
T	1–4	0–4	Compatible
N	0	0	Identical
	1–3	1–3	Incompatible
M[a]	0	0	Compatible
	1	1	Compatible
H	0	None	
	1	M1	Compatible
P	0	None	
	1	M1	Compatible
CY	0	None	
	1	None	
Stage	IA	IA	Identical
	IB, II, IIIA, IIIB, IV	IB, II, IIIA, IIIB, IV	Incompatible
Lymphatic invasion	ly0	L0	Identical
	ly1–3	L1	Compatible
Venous invasion	v0	v0	Identical
	v1–3	v1	Compatible
	None	v2	
Histological typing	Differentiated type	G1–2	Compatible
	Undifferentiated type	G3–4	Compatible
Residual tumor	Resection A–C	R0–2	Incompatible

[a] JGCA M-category is defined as distant metastases other than peritoneal, liver, or cytological metastases

statistical analyses. This nationwide registration program was approved by the ethics committee of the JGCA.

Results

The data were collected from 187 participating hospitals across the country. The geographical distribution of the registered patients among Japan's 47 prefectures is illustrated in Fig. 1. More than 1000 patients per year were registered in the prefectures of Tokyo and Osaka; on the other hand, the number of registered patients was less than 100 in 15 prefectures. The hospital volumes in the participating hospitals are indicated in Fig. 2. The median hospital volume was 66 patients per year.

Data of 13067 patients who had undergone surgery in 2001 for primary gastric tumors were eventually accumulated. Of these, 88 patients with benign tumor or non-epithelial tumor were excluded from the analysis. Ninety-four patients who received endoscopic mucosal resection were also excluded. Data of 881 patients lacked essential items. Consequently, data of the remaining 12004 patients were used for the final analysis.

The results are shown in Tables 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, and 28; data in these Tables are for the total number of patients, survival rates by year, standard error of 5YSR, direct death within 30 postoperative days, numbers lost to follow-up within 5 years, 5-year survivors, and main causes of death (such as local and/or lymph node metastasis, peritoneal metastasis, liver metastasis, distant metastasis, recurrence at unknown site, other cancer and other

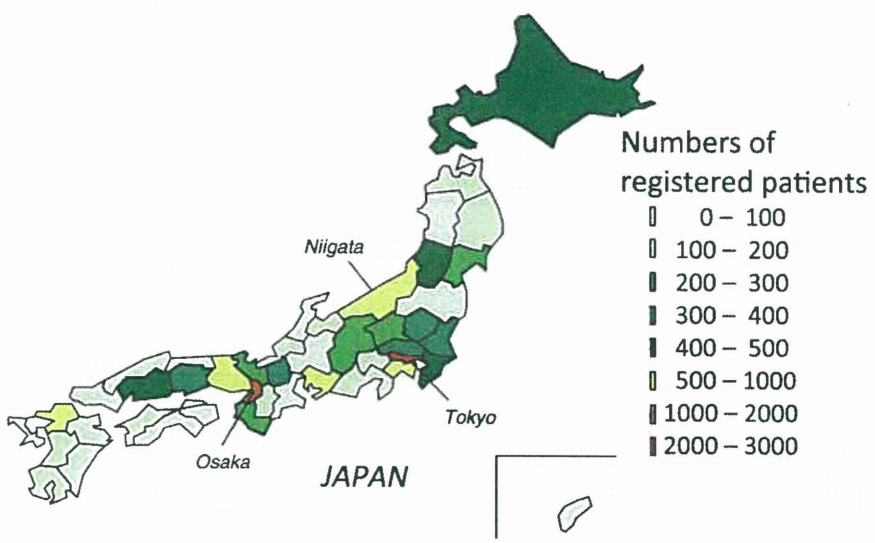

Fig. 1 Geographical distribution of the registered patients

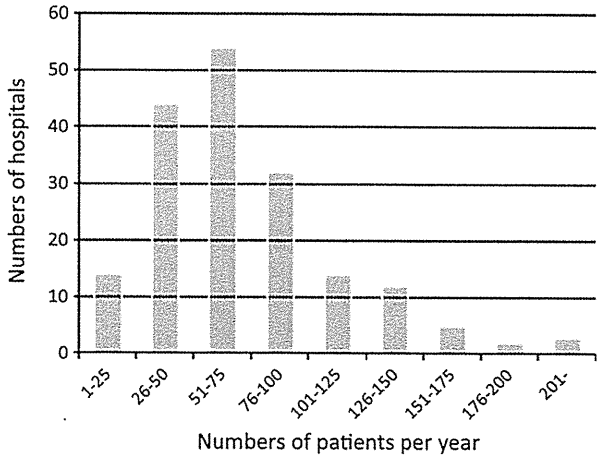

Fig. 2 Hospital volumes in the 187 participating hospitals

disease). Figures 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, and 14 show cumulative survival curves of patients stratified by essential categories.

The 5YSR in the 12004 patients with primary gastric cancer was 69.1% (Table 3; Fig. 3). Within 5 postoperative years, 1976 patients were lost to follow-up; the follow-up rate was 83.5%. Of the 12004 patients, 11261 underwent gastric resection; 350 were unresected; and in 393 the type of surgery was not specified. Accordingly, the resection rate was 97.0% (11261/11611). Sixty-three of the 11261 patients who had undergone gastrectomy died within 30 postoperative days; the direct death rate was 0.6% (Table 4; Fig. 4).

The most frequent cause of death in patients who had received gastrectomy was peritoneal metastasis (n = 1040), followed, in descending order, by other diseases (n = 501), liver metastasis (n = 357), recurrence at an

Table 3 Survival outcomes of primary cancer

	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
Primary cancer	12004	86.4	78.7	74.1	71.1	69.1	0.4	95	1976	6588	309	1266	374	183	349	162	530	267

SE standard error, *5YSR* 5-year survival rate, *DD* direct death, *Lost to follow up* lost to follow-up within 5 years, *Alive* 5-year survivors, *L* local recurrence and/or lymph node metastasis, *P* peritoneal metastasis, *H* liver metastasis, *M* distant metastasis, *R* recurrence at unknown site, *OC* other cancer, *OD* other disease, *UK* unknown

Table 4 Survival outcomes of resected cases and unresected cases

	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
Resected cases	11261	88.6	80.9	76.2	73.0	70.9	0.4	63	1877	6354	267	1040	357	161	298	155	501	251
Unresected cases	350	23.0	9.8	7.1	5.6	5.3	1.3	20	40	14	32	176	12	13	43	0	10	10

Table 5 Survival outcomes by sex

	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
Male	7828	88.4	80.7	75.6	72.3	70.0	0.5	47	1314	4348	190	646	299	112	205	138	403	173
Female	3419	88.9	81.1	77.5	74.6	73.0	0.8	16	562	1997	76	392	58	49	93	17	97	78

Table 6 Survival outcomes by age

	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
<40	257	89.9	82.0	80.3	79.4	78.4	2.7	0	40	165	3	30	2	8	4	1	0	4
40–59	3232	92.5	86.6	83.1	80.6	79.3	0.7	12	516	2095	60	274	58	48	66	13	54	48
60–79	6924	87.9	80.1	74.9	71.6	69.2	0.6	37	1129	3818	186	651	259	91	182	135	322	151
≧80	788	78.5	64.3	58.6	53.1	48.7	2.0	14	178	256	18	84	35	13	29	6	123	46

Table 7 Survival outcomes by tumor location

	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
U	2399	86.0	76.7	71.3	67.5	65.3	1.0	13	370	1258	69	237	107	49	75	32	134	68
M	4351	92.2	87.1	83.3	80.8	78.9	0.6	23	760	2741	65	260	90	43	84	65	161	82
L	3936	89.4	81.4	77.1	74.2	71.9	0.7	21	685	2230	108	309	141	52	99	55	176	81
Whole	532	63.7	44.7	33.7	25.8	23.4	2.0	6	56	104	23	230	17	17	34	3	28	20

U upper third, *M* middle third, *L* lower third of stomach

Table 8 Survival outcomes by macroscopic type

	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
Type 0	6085	97.5	95.7	93.7	91.8	90.3	0.4	12	1143	4401	20	45	23	23	32	100	217	81
Type 1	318	79.1	66.7	61.7	56.5	54.6	2.9	4	49	136	12	18	28	7	14	7	36	11
Type 2	1419	84.8	73.0	66.5	62.5	59.7	1.4	11	220	669	58	127	126	29	59	10	81	40
Type 3	2151	76.5	60.8	52.4	47.8	45.1	1.1	21	306	760	119	425	152	62	124	25	112	66
Type 4	779	62.1	41.9	30.0	23.4	20.4	1.5	10	65	133	37	363	11	31	54	7	35	43
Type 5	340	86.8	74.3	67.4	62.6	59.5	2.8	4	48	166	13	49	16	7	15	4	15	7

Table 9 Survival outcomes by histological diagnosis

	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
pap	364	85.8	75.1	70.4	67.5	65.1	2.6	3	64	185	11	27	23	6	13	8	23	4
tub1	2752	95.2	91.1	87.9	85.3	83.5	0.7	5	519	1818	30	55	42	16	36	51	137	48
tub2	2997	89.2	81.4	76.3	73.1	70.6	0.9	20	537	1651	64	207	156	46	74	45	160	57
por1	1476	82.5	72.4	67.8	64.9	63.7	1.3	14	238	737	53	174	82	30	40	14	69	39
por2	1903	81.4	69.7	63.4	59.5	56.6	1.2	15	244	886	75	401	34	44	86	19	59	55
sig	1325	93.2	88.0	84.5	81.2	79.4	1.2	4	217	855	17	108	2	14	32	12	30	38
muc	231	81.5	68.8	60.4	53.7	51.2	3.4	1	24	100	9	54	5	1	10	3	19	6
Adenosquamous carcinoma	6	50.0	33.3	33.3	16.7	16.7	15.2	0	0	1	0	2	2	0	0	1	0	0
Squamous cell carcinoma	5	60.0	30.0	0.0	0.0	0.0	0.0	0	1	0	2	1	0	1	0	0	0	0
Miscellaneous carcinoma	45	65.2	53.1	48.1	45.6	45.6	7.7	0	4	18	2	8	7	2	2	0	1	1

Pap papillary adenocarcinoma, *tub1* tubular adenocarcinoma, well-differentiated type, *tub2* tubular adenocarcinoma, moderately differentiated type, *por1* poorly differentiated adenocarcinoma, solid type, *por2* poorly differentiated adenocarcinoma, non-solid type, *sig* signet-ring cell carcinoma, *muc* mucinous adenocarcinoma

Table 10 Survival outcomes by histological differentiation

	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
Differentiated type	6113	91.7	85.4	81.2	78.3	76.1	0.6	28	1120	3654	105	289	221	68	123	104	320	109
Undifferentiated type	4935	84.9	75.4	70.1	66.6	64.6	0.7	34	723	2578	154	737	123	89	168	48	177	138
Other type	144	81.6	75.3	71.9	68.4	68.4	4.1	1	29	74	6	12	11	4	2	1	3	2

Table 11 Survival outcomes by venous invasion (v)

	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
v0	6453	95.4	91.5	88.6	86.2	84.5	0.5	23	1228	4304	54	258	59	36	70	101	260	83
v1	2601	84.5	72.7	66.6	62.2	59.7	1.0	17	352	1276	103	365	115	53	112	29	127	69
v2	1347	75.7	59.8	50.4	45.8	42.6	1.4	17	168	463	71	271	95	44	74	16	84	61
v3	539	59.4	44.5	35.7	32.2	30.8	2.1	5	69	128	30	123	85	23	34	4	21	22

Table 12 Survival outcomes by lymphatic invasion (ly)

	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
ly0	4783	97.2	95.3	93.3	91.4	89.9	0.5	11	956	3389	10	48	23	11	35	80	177	54
ly1	2604	92.4	86.1	81.1	77.7	75.1	0.9	13	398	1606	51	187	84	36	37	40	115	50
ly2	2047	80.7	65.8	58.4	53.3	50.5	1.2	22	271	834	102	346	134	53	103	17	123	64
ly3	1481	65.2	45.4	36.3	31.6	29.4	1.3	16	194	334	95	438	110	57	110	13	77	53

Table 13 Survival outcomes by depth of invasion

	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
pT1(M)	3071	98.1	96.9	95.0	93.5	92.2	0.5	5	606	2248	7	4	4	1	7	53	98	43
pT1(SM)	2662	97.5	95.0	93.1	90.9	89.1	0.6	6	500	1898	11	16	19	11	16	51	109	31
pT2(MP)	1071	93.4	88.7	84.0	80.9	78.3	1.3	3	183	675	13	23	31	19	22	17	68	20
pT2(SS)	1695	87.0	74.7	67.6	63.2	60.6	1.2	17	262	817	67	148	122	48	65	20	99	47
pT3(SE)	2278	69.7	50.9	41.3	35.8	33.0	1.0	26	264	601	132	712	140	72	148	10	102	97
pT4(SI)	417	57.7	38.1	30.0	26.0	22.8	2.2	5	45	77	36	134	39	8	40	4	24	10

p pathological finding, *M* mucosa or muscularis musoca, *SM* submucosa, *MP* muscularis propria, *SS* subserosal, *SE* serosa, *SI* adjacent structures

Table 14 Survival outcomes by pT classification

	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
pT1	5733	97.8	96.0	94.1	92.3	90.8	0.4	11	1106	4146	18	20	23	12	23	104	207	74
pT2	2766	89.5	80.1	74.0	70.1	67.5	0.9	20	445	1492	80	171	153	67	87	37	167	67
pT3	2278	69.7	50.9	41.3	35.8	33.0	1.0	26	264	601	132	712	140	72	148	10	102	97
pT4	417	57.7	38.1	30.0	26.0	22.8	2.2	5	45	77	36	134	39	8	40	4	24	10

Table 15 Survival outcomes by lymph node metastasis (pN)

	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
pN0	6508	97.0	94.7	92.5	90.6	89.0	0.4	22	1240	4616	18	95	38	16	44	109	248	84
pN1	2274	84.7	72.3	66.2	61.3	58.3	1.1	12	322	1074	78	309	139	46	99	23	118	66
pN2	1703	72.1	52.8	41.4	35.8	33.4	1.2	19	224	439	103	442	135	69	109	13	100	69
pN3	421	53.8	33.1	25.8	22.0	17.4	1.9	4	33	61	60	136	37	28	35	3	13	15

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

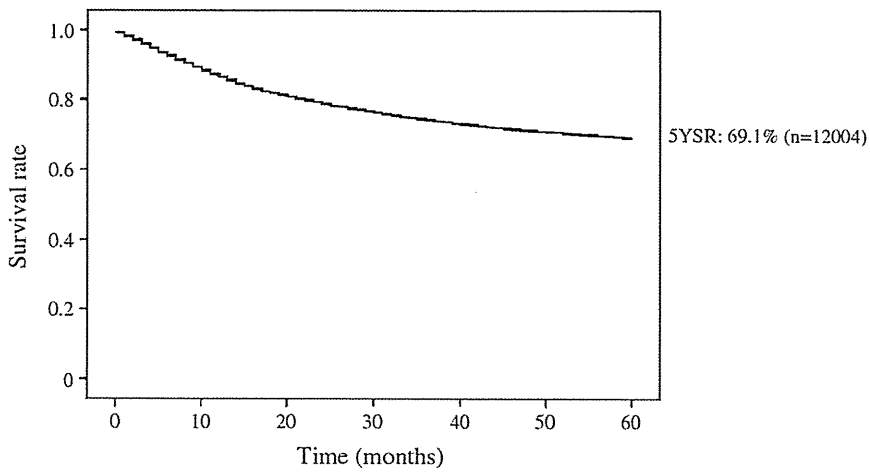

Fig. 3 Kaplan–Meier survival for all 12004 patients with primary gastric cancer. *5YSR* 5-year survival rate

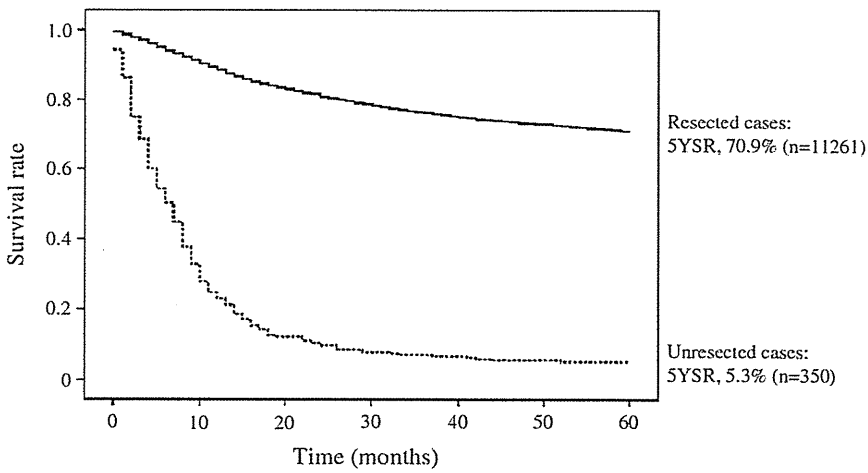

Fig. 4 Kaplan–Meier survival for resected cases and unresected cases

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,

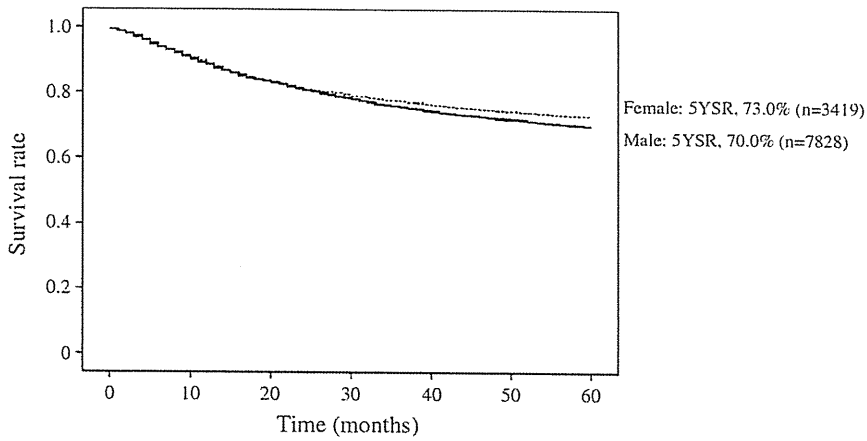

Fig. 5 Kaplan–Meier survival of the resected cases stratified by sex

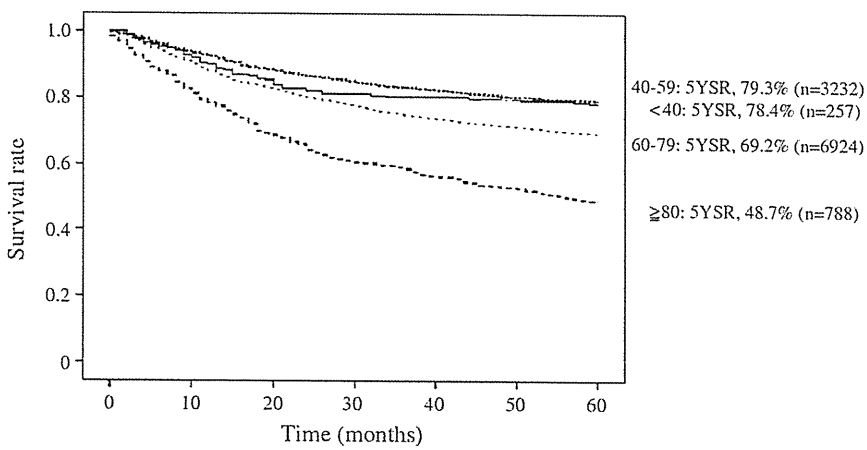

Fig. 6 Kaplan–Meier survival of the resected cases stratified by age

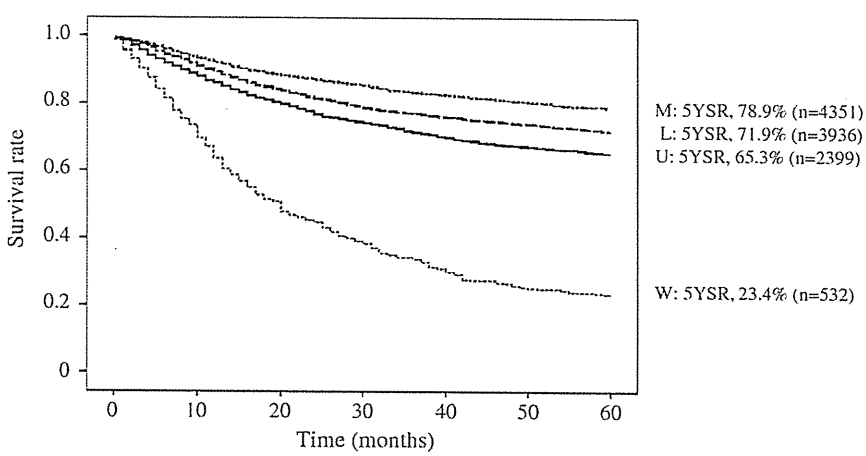

Fig. 7 Kaplan–Meier survival of the resected cases stratified by tumor location. *W* whole stomach, *M* middle third, *L* lower third, *U* upper third of stomach

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).

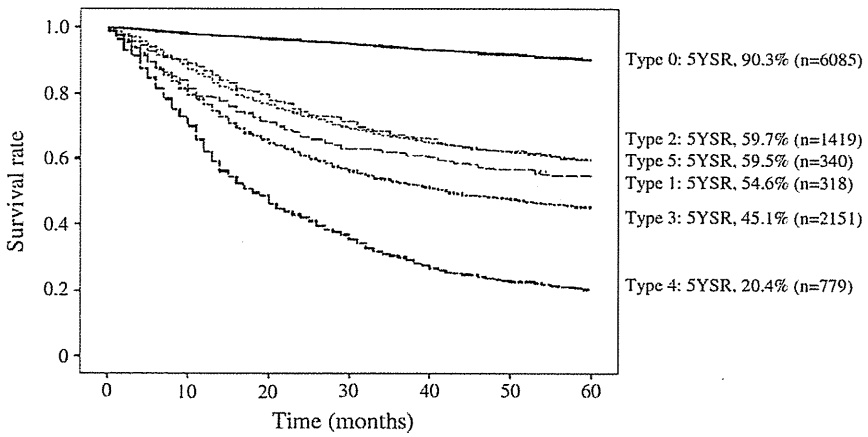

Fig. 8 Kaplan–Meier survival of the resected cases stratified by macroscopic type

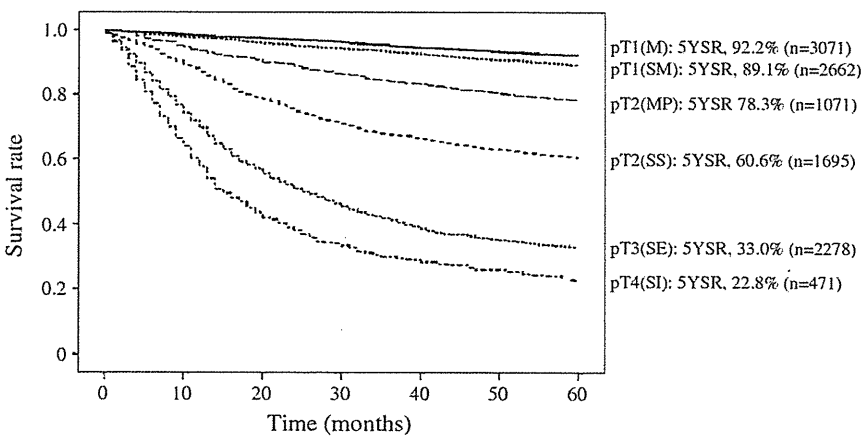

Fig. 9 Kaplan–Meier survival of the resected cases stratified by depth of tumor invasion. *M* mucosa or muscularis mucosa, *SM* submucosa, *MP* muscularis propria, *SS* subserosal, *SE* serosa, *SI* adjacent structures

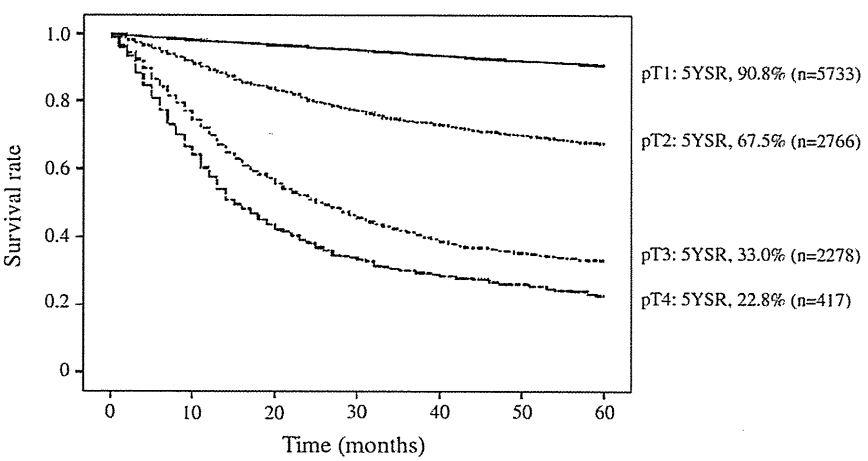

Fig. 10 Kaplan–Meier survival of the resected cases stratified by pT classification

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.

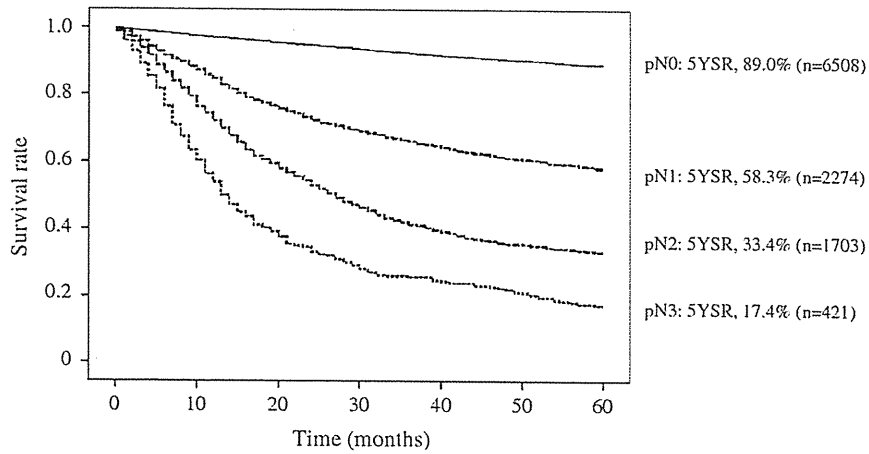

Fig. 11 Kaplan–Meier survival of the resected cases stratified by lymph node metastasis

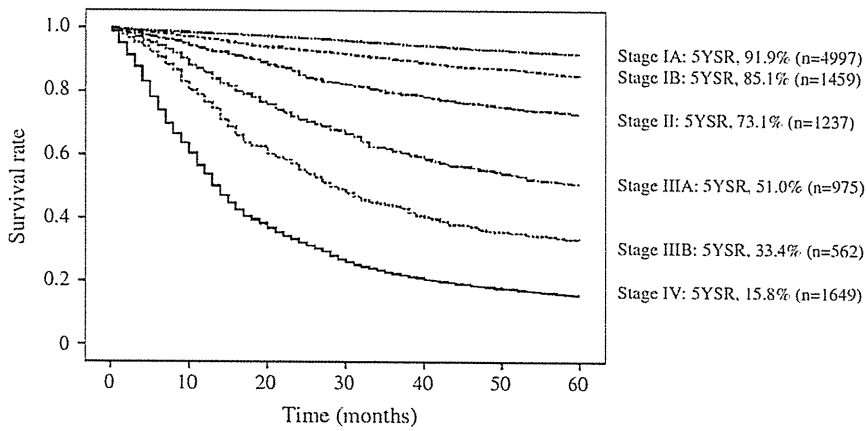

Fig. 12 Kaplan–Meier survival of the resected cases stratified by Japanese Gastric Cancer Association (JGCA) stage

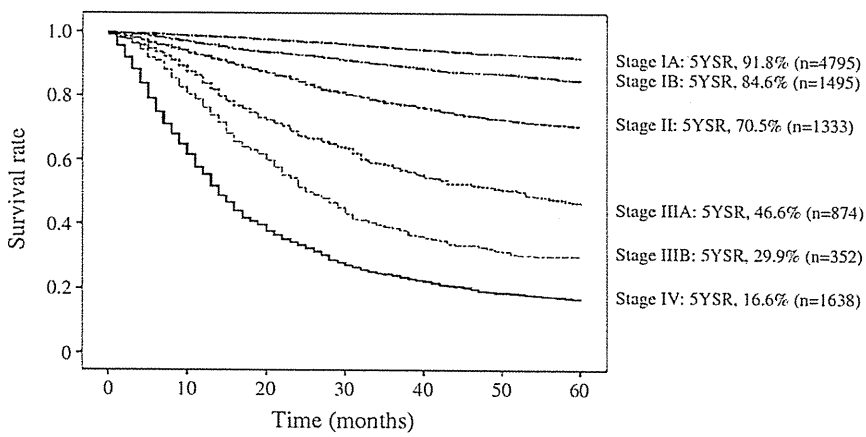

Fig. 13 Kaplan–Meier survival of the resected cases stratified by TNM stage

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

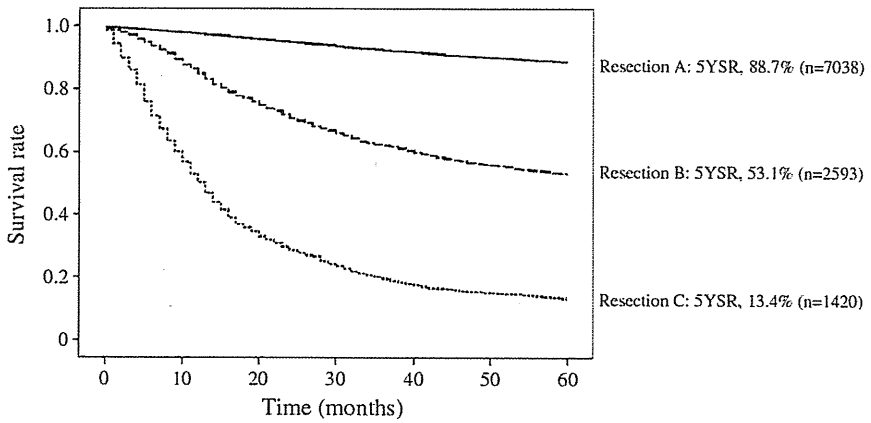

Fig. 14 Kaplan–Meier survival of the resected cases stratified by curative potential of gastric resection. *Resection A*, no residual disease with high probability of cure satisfying all of the following conditions: T1 or T2; N0 treated by D1, 2, 3 resection or N1 treated by D2, 3 resection; M0, P0, 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

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

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.

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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Present and Future Status of Gastric Cancer Surgery

Makoto Saka*, Shinji Morita, Takeo Fukagawa and Hitoshi Katai

Gastric Surgery Division, National Cancer Center Hospital, Tokyo, Japan

*For reprints and all correspondence: Makoto Saka, Gastric Surgery Division, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. E-mail: msaka@ncc.go.jp

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The type of surgery and the role of adjuvant therapies in the treatment of gastric cancer have changed in recent times. The treatment of gastric cancer with curative intent is moving away from standard D2 or more extensive surgery to a tailored approach depending on the stage of the disease. Data collected from extensive lymphadenectomy for all stages of gastric cancer have confirmed that some subsets of early gastric cancer are very low risk for nodal metastasis. This group of patients may benefit from resection by endoscopic or laparoscopic techniques and may also be suitable for function-preserving procedures. The extent of resection for gastric cancer has always excited debate. D2 gastrectomy was criticized for its higher mortality in the early European Phase III trials, but recent studies from Taiwan and Italy have shown that the procedure is safe when performed by experienced surgeons and has a survival benefit over D1 gastrectomy. The role of para-aortic lymph node dissection for nodes without apparent metastasis in advanced gastric cancer was assessed by a Phase III Japanese trial and showed no additional benefit over D2 resection. Radical gastric resections, involving resection of adjacent organs for direct tumor invasion result in higher rates of complications, and the role of multi-visceral resections has also been reevaluated. Effective adjuvant therapies for gastric cancer have been reported since the early part of 2000. Development of more effective adjuvant therapy combined with D2 resection should continue to improve survival in the future.

Key words: gastric cancer – surgery – function-preserving gastrectomy – laparoscopic gastrectomy – adjuvant therapy

INTRODUCTION

Chemotherapy helps to prolong survival in cases of advanced disease, but surgery is still the mainstay of curative treatment for gastric cancer. From uniform use of D2 or more extensive surgery, surgical treatment has evolved to become more tailor-made depending on the stage of the disease.

Extensive operations have been reevaluated for advanced gastric cancer and the role of effective adjuvant therapies in this setting has expanded. More radical operations than D2 for gastric cancer have often been carried out without clear evidence until clinical trials have failed to show the survival benefit of these procedures over D2. For early gastric cancer, less extensive resections and minimally invasive techniques have been developed, such as function-preserving procedures and laparoscopic surgery.

D2 LYMPHADENECTOMY

Total or subtotal gastrectomy with D2 lymphadenectomy is the gold standard surgical treatment for gastric cancer in eastern Asia. The procedure initially developed in Japan, has been safely performed and provided good survival outcomes for patients with gastric cancer regardless of disease stage (1,2). The use of this technique has been challenged by Western clinical trials since the 1990s.

Results of Early European Trials

Phase III trials on D2 dissection for curable gastric cancer were carried out by the Medical Research Council and the Dutch Gastric Cancer Group in the early 1990s (3,4). These trials failed to show a survival benefit for D2 over D1 dissection.

The British and Dutch trials demonstrated extremely high hospital mortality after D2, reaching 10 and 13%, respectively. In the British trial, the survival curve of D2 was never better than that of D1 until the end of the trial. In the Dutch trial, the survival curve of D2 caught up with that of D1 after 4 years and remained superior, but the difference between D1 and D2 survival never reached statistical significance.

Discussion of the Early Trials

The lack of surgical training in the technique of D2 gastrectomy and sub-optimal quality control may explain the inferior outcomes of D2 versus D1 gastrectomy in these early trials. Both trials were carried out without pre-trial training or preliminary studies to confirm the safety of the procedure, and were concluded before many surgeons would have reached the plateau of their learning curve. The 80 hospitals contributing data to the Dutch trial were all relatively low volume units, with most performing only a few gastric resections per year. With such limited experience, it is almost impossible to maintain the quality of the technique and gain adequate experience in managing major complications such as anastomotic leakage, pancreatic fistula or intra-abdominal abscess, all of which can lead to an increase in morbidity and mortality.

Routine resection of the tail of the pancreas in total gastrectomy has been credited with disappointing results. Detailed analysis of the Dutch and British studies showed that splenectomy and distal pancreatectomy were more significant causes of morbidity and mortality than D2 itself (5). In the D2 arm of these trials, splenectomy and distal pancreatectomy were mandatory during total gastrectomy. Resection of the distal pancreas and spleen is no longer deemed a necessary component of modern D2.

Fifteen-year follow-up results of the Dutch trial were recently reported in 2010 (6). The authors reported that D2 was associated with lower loco-regional recurrence and gastric cancer-related death rates than D1. They concluded that D2 is the recommended surgical approach for patients with resectable gastric cancer.

Recent Trials on D2 Dissection

The Italian Gastric Cancer Study Group (IGCSG) started a prospective one-arm Phase II study in 1994 to confirm the safety and efficacy in increasing survival, using the D2 gastrectomy (7). Following concerns about the high mortality observed in the Dutch and British trials, with total gastrectomy, they utilized the pancreas-preserving procedure according to the Maruyama technique instead of employing routine distal pancreatectomy (8). Furthermore, they implemented a strict quality control component consisting of pre-trial surgical training at a specialized center in Japan and intra-operative supervision by experienced surgeons. As a result, the Italian trial, including nine hospitals with a total of 191 patients, demonstrated 3% mortality. The survival results of this Phase II study were much better than that of the D2 arms in the Dutch and British trials (9).

Following the favorable results of the Phase II trial, the IGCSG conducted a Phase III trial comparing D1 ($n = 133$) with D2 ($n = 134$), including five specialized hospitals with a total of 267 patients. The post-operative 30-day mortality was 3% for D1 and 2.2% for D2 (10). The safety of D2 performed by experienced surgeons at specialized centers was confirmed in the Phase III study. The survival data from this study is eagerly awaited.

The results of a Phase III trial from Taiwan, comparing D1 ($n = 110$) with D3 ($n = 111$), were reported in 2006 (11). Their D3, according to the old Japanese Classification, in addition to D2, included lymph nodes within the hepatoduodenal ligament, on the superior mesenteric vein, behind the common hepatic artery and on the posterior pancreatic surface but not the para-aortic lymph nodes. This trial was conducted by three experienced surgeons at a single institution and showed statistically significant improvement in survival of D3 compared with D1, demonstrating 5-year survival rates of 59.5 and 53.6%, respectively ($P = 0.04$). This is the first Phase III trial in the world showing survival benefit of radical lymphadenectomy compared with the limited lymphadenectomy. However, this study cannot be considered as solid evidence for the superiority of D3 over D1 because of the rather small sample size and modest survival benefit.

Is Splenectomy Essential to D2 Total Gastrectomy?

Retrospective Japanese studies revealed that 20–30% of patients with advanced gastric cancer in the proximal stomach had nodal metastasis in the splenic hilum (12) and therefore pancreas-preserving splenectomy is part of the standard D2 total gastrectomy (8). After the British and Dutch trials on D2 showed that splenectomy was an important risk factor for post-operative morbidity and mortality, the Japan Clinical Oncology Group (JCOG) conducted a Phase III trial to evaluate the role of splenectomy in total gastrectomy (13). A total of 505 patients with advanced gastric cancer in the upper third of the stomach, without involvement of the greater curvature were randomly assigned to total gastrectomy with ($n = 254$) or without splenectomy ($n = 251$). Recruitment has been completed and final results are awaited. The trial is powered to evaluate the impact on overall survival. If the survival is approximately equivalent, splenic preservation will be the preferred treatment for patients with such tumors.

ADJUVANT THERAPY

A Phase III study comparing surgery alone to surgery plus post-operative adjuvant chemoradiotherapy (CRT), the INT0116/SWOG9008, showed a large survival benefit of the latter (14). The CRT arm included curative surgery and radiation therapy of 45 Gy with combination chemotherapy using fluorouracil and leucovorin. A total of 556 patients were randomly assigned to surgery alone ($n = 275$) or surgery plus CRT ($n = 281$).The median survival time of surgery alone and surgery plus CRT was 27 and 36 months, respectively ($P = 0.005$). In this trial, 90% of the patients underwent less extensive D0 or D1 surgery while only 10% underwent D2. Although the extent of lymphadenectomy failed to significantly correlate with survival due to the small patient population of D2, detailed analysis showed that inadequate surgery negatively affected survival (15). Sasako et al. (16) noted that the patient population in the CRT arm of this trial was quite similar to the population in a Japanese clinical trial comparing surgery alone to surgery plus adjuvant chemotherapy (17). Most of the prognostic factors, i.e. histological type, tumor location, age, tumor size, and, tumor depth were reasonably comparable between the groups. Nevertheless, the 5-year overall survival of the CRT arm of the INT0116 and the surgery alone arm of the Japanese trial were 42 and 61%, respectively. Sasako et al. strongly suggested that D2 surgery alone might produce better survival than D0/D1 surgery followed by CRT and that the effect of adjuvant CRT may not be so significant if D2 gastrectomy was performed as the standard operation.

The MAGIC trial, a Phase III trial comparing surgery alone to surgery plus peri-operative adjuvant chemotherapy, is the first study demonstrating a clear benefit of neoadjuvant chemotherapy (combined with post-operative chemotherapy) over surgery alone (18). The chemotherapy protocol consisted of three pre-operative and three post-operative cycles of intravenous epirubicin, cisplatin and fluorouracil. A total of 503 patients were randomly assigned to surgery alone ($n = 253$) or surgery plus peri-operative chemotherapy ($n = 250$). The 5-year survival rate of surgery alone and peri-operative chemotherapy group were 23 and 36%, respectively ($P = 0.009$). There was no hazard ratio analysis for the extent of surgery and therefore the benefit of peri-operative adjuvant chemotherapy in addition to D2 surgery remains unclear.

The results of the Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC trial) comparing surgery alone to surgery plus adjuvant S-1 was reported in 2007 (19). Administration of S-1 was started within 6 weeks after curative D2 surgery and continued for 1 year. Patients treated with adjuvant S-1 ($n = 529$) demonstrated a significantly better 3-year survival than those who underwent surgery alone ($n = 530$) (80.5 versus 70.1%, $P = 0.003$). In Japan, adjuvant S-1 therapy has become the standard treatment of choice for Stages II and III gastric cancer patients after curative D2.

MORE EXTENSIVE SURGERY THAN D2

More extensive surgery than D2 was often carried out in the 1980s and the early 1990s, without any high-level evidence favoring these more extensive procedures. Japanese clinical trials of para-aortic lymph node dissection (PAND) for advanced tumor without apparent metastasis to the nodes and left thoraco-abdominal approach (LTA) for cardiac tumors have shown no survival benefit for patients who underwent such extensive procedures (20,21).

Para-aortic Lymph Node Dissection

In advanced gastric cancer, the incidence of microscopic metastases in the para-aortic lymph nodes had been reported from 10 to 30% (22–24). Because the 5-year overall survival rate of patients with para-aortic nodal metastases could be as high as 20% after systematic dissection, PAND had been performed in Japan since the 1980s (25). JCOG conducted a Phase III trial at 24 hospitals in Japan comparing D2 alone ($n = 263$) to D2 plus PAND ($n = 260$) in the late 1990s (JCOG9501) (20). The 5-year overall survival rate was 69.2% for D2 alone and 70.3% for D2 plus PAND. The median operation time was 63 min longer and the median blood loss was 230 ml greater in the group assigned to D2 plus PAND. Treatment with D2 plus PAND did not significantly improve the survival rate in curable gastric cancer when compared with D2. The results may have been disappointing due to the low incidence of para-aortic node metastasis (8%) in this patient population. However, PAND is no longer routinely applied in patients without apparent para-aortic nodal metastases.

Along with para-aortic node metastasis, bulky nodal metastases surrounding the celiac artery and its branches usually suggest poor prognosis. A Phase II trial was carried out by JCOG to evaluate the efficacy and safety of pre-operative chemotherapy followed by D2 plus PAND for locally advanced gastric cancer with bulky celiac nodes and/or para-aortic node metastasis (JCOG0001) (26). The neoadjuvant chemotherapy consisted of irinotecan and cisplatin. This trial was terminated after 55 patients were enrolled because of three treatment-related deaths. The survival outcomes in these patients were promising, with the median survival time of 14.6 months and the 3-year survival rate of 27%.

Following the reasonable results of JCOG0001, JCOG conducted a Phase II trial of pre-operative S-1 plus cisplatin followed by D2 plus PAND for the same patient population as JCOG0001 (JCOG0405) (27). S-1 plus cisplatin is the Japanese standard chemotherapy regimen for unresectable or recurrent gastric cancer. Of 53 enrolled patients, 51 patients were eligible and resection rate and R0 rate were 92 and 82%, respectively. No treatment-related death was observed. Improvement in survival outcome is highly anticipated. The PAND procedure in this scenario is evaluated in combination with neoadjuvant chemotherapy for patients with apparent para-aortic node metastasis.