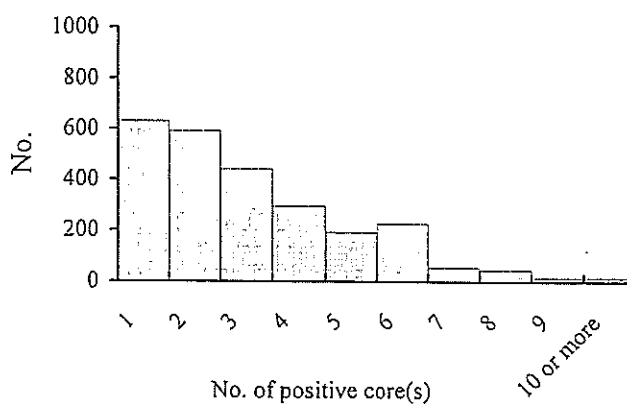


II.4. Number of cancer positive core(s) in systematic prostate biopsy

Core(s)	Number	%
1	631	25.03
2	592	23.48
3	443	17.57
4	296	11.74
5	192	7.62
6	226	8.97
7	55	2.18
8	46	1.83
9	16	0.64
10 or more	16	0.64
Total	2513	100

*uncertain: 158 patients.



II.5. Correlation between DRE findings and image findings

DRE	Image findings					Total
	Not visible	Confined	Extra-capsule	Invades	Uncertain	
Not palpable	678	409	37	22	28	1174
One lobe	111	510	111	31	23	786
Both lobe	29	204	88	25	16	362
Extra-capsule	5	31	159	15	5	215
SV invasion	1	2	11	25	1	40
Extra-prostate	0	2	0	3	0	5
Uncertain	12	51	10	7	9	89
Total	836	1209	416	128	82	2671

II.6. T stage distribution†

Stage	Number	%
T1c	721	26.99
T2a	794	29.73
T2b	528	19.77
T3a	426	15.95
T3b	202	7.56
Total	2671	100

†T stage followed by 1997 UICC's TNM classification.

II.7. Correlation between Gleason's score† and T stage

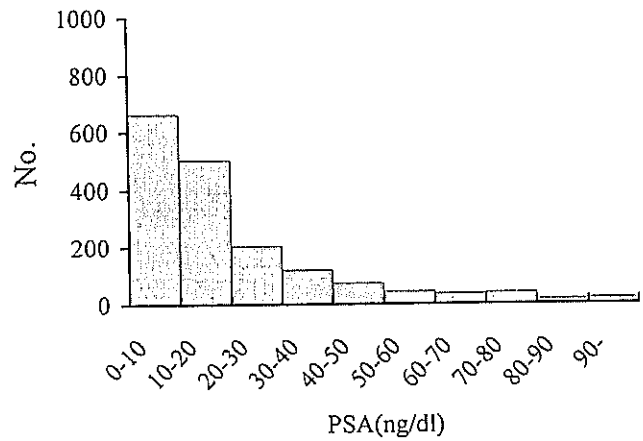
Gleason's score	T stage (1997 UICC)					Total
	T1c	T2a	T2b	T3a	T3b	
2	37	28	16	2	1	84
3	48	50	19	13	3	133
4	51	65	31	16	4	167
5	73	109	70	51	22	325
6	91	109	61	39	22	322
7	93	101	98	88	49	429
8	17	26	25	35	15	118
9	18	24	28	44	18	132
10	5	4	5	4	0	18
Total	433	516	353	292	134	1728

†The Gleason grade was not judged in 943 patients.

III. Correlation between PSA and clinicopathological factors in clinical T1c-T3N0M0 prostate cancer

III.1. PSA distribution†

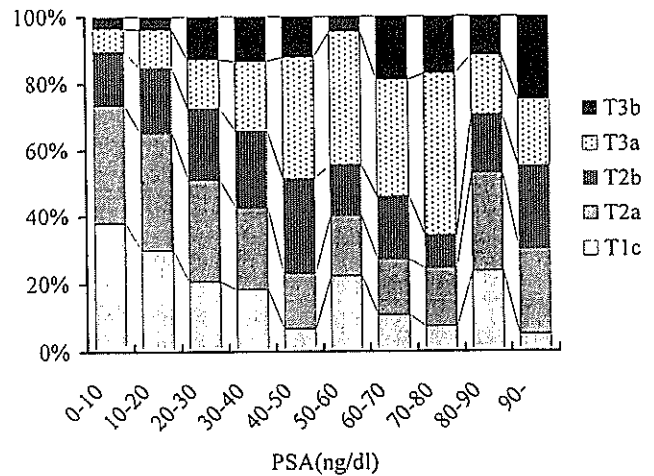
PSA(ng/dl)	Total	%
0-10	663	36.131
10-20	504	27.466
20-30	204	11.117
30-40	120	6.54
40-50	74	4.033
50-60	45	2.452
60-70	37	2.016
70-80	41	2.234
80-90	17	0.926
90>	20	1.09
1725	100	



†Cases were divided into groups of PSA value by 10 ng/mL as indicated. Methods of measurement was Tandem-R as the standard, and include all Tandem-R compatible kits, such as E test TOSOH, CHEMILUMI ACS-PSA, SHIFALITE PSA and LUMIPULSE PSA. Bars demonstrate the number of cases between equal and over the value on the left lower corner and below the value on the right lower corner of each bar. Cases with PSA equal and over 90 ng/mL were counted as a group. The numbers below each bar indicates the percentage of cases in each group among all registered cases.

III.2. Correlation between PSA and clinical T stage

PSA(ng/dl)	T stage					Total
	T1c	T2a	T2b	T3a	T3b	
0-10	251	236	107	46	23	663
10-20	150	178	99	58	19	504
20-30	42	62	44	30	26	204
30-40	22	29	28	25	16	120
40-50	5	12	21	27	9	74
50-60	10	8	7	18	2	45
60-70	4	6	7	13	7	37
70-80	3	7	4	20	7	41
80-90	4	5	3	3	2	17
90>	1	5	5	4	5	20
Total	492	548	325	244	116	1725



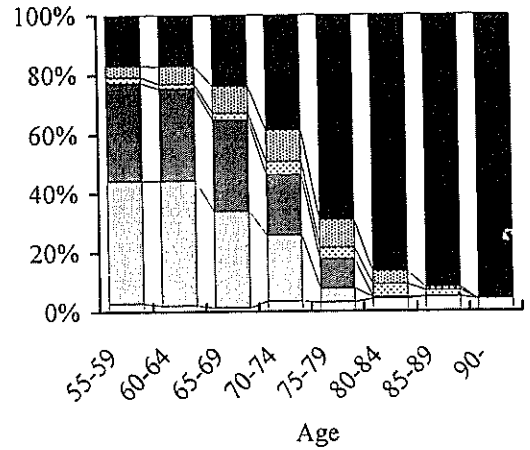
Cases were divided into groups of PSA value by 10 ng/mL as indicated. Bars demonstrate the percentage of each T stage among each PSA group. Cases with PSA equal and over 90 ng/mL were counted as a group.

IV. Main initially planned treatment for fresh cases without concomitant malignancy patients in clinical T1c-T3N0M0 prostate cancer

IV.1. Age distribution and treatment

Age range	Treatment						Total
	W/W	RPP	RPP+Hx	Rx	Rx+Hx	Hx	
55-59	3	44	35	2	4	18	106
60-64	5	101	74	4	14	41	239
65-69	6	148	141	10	41	108	454
70-74	21	132	122	27	63	229	594
75-79	12	18	38	15	36	268	387
80-84	8	1	0	8	8	163	188
85-89	5	0	0	2	1	93	101
90>	1	0	0	0	0	24	23
Total	61	444	410	68	167	944	2094

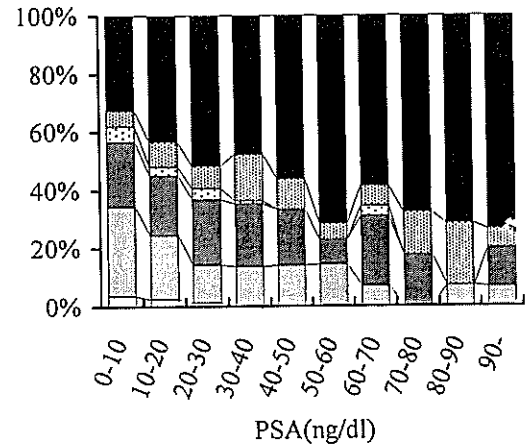
Clinical T1c-T3 cases were divided by age. Bars demonstrate the percentage of adopted treatment among each age group.



IV.2. PSA and treatment

PSA(ng/dl)	Treatment						Total
	W/W	RPP	RPP+Hx	Rx	Rx+Hx	Hx	
0-10	18	152	110	26	27	161	494
10-20	10	89	83	12	34	175	403
20-30	2	20	35	6	12	80	155
30-40	0	12	19	1	14	42	88
40-50	0	8	11	0	6	32	57
50-60	0	5	3	0	2	25	35
60-70	0	2	7	1	2	17	29
70-80	0	0	6	0	5	23	34
80-90	0	1	0	0	3	10	14
90>	0	1	2	0	1	11	15
Total	30	290	276	46	106	576	1324

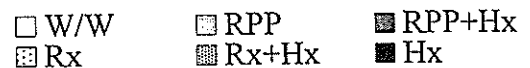
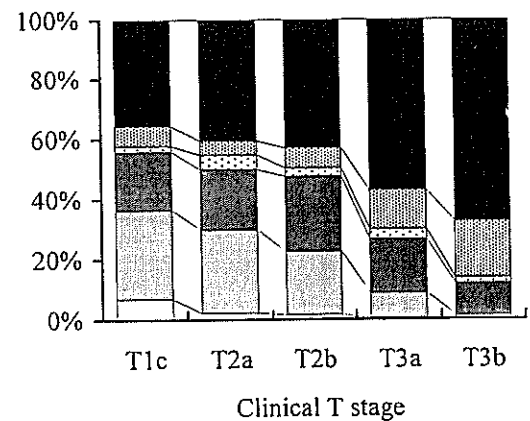
Clinical T1c-T3 cases were divided into groups of PSA value by 10 ng/mL as indicated. Bars demonstrate the percentage of adopted treatment among each PSA group. Cases with PSA equal and over 90 ng/mL were counted as a group.



IV.3. Main treatment and clinical T stage†

Initial treatment	T stage					Total
	T1c	T2a	T2b	T3a	T3b	
W/W	39	14	7	2	0	62
RPP	167	173	88	29	2	459
RPP+Hx	110	126	105	63	17	421
Rx	11	31	12	12	3	69
Rx+Hx	37	29	28	46	30	170
Hx	202	255	181	202	108	948
Total	566	628	421	354	160	2129

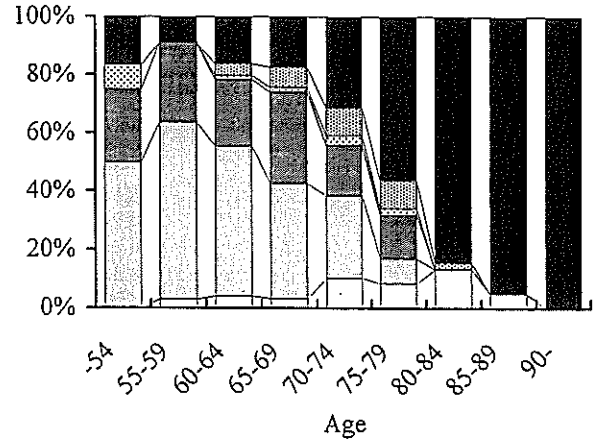
†Bars demonstrate the percentage of adopted treatment and each stage.



IV.4. T stage, age and initially planed treatment

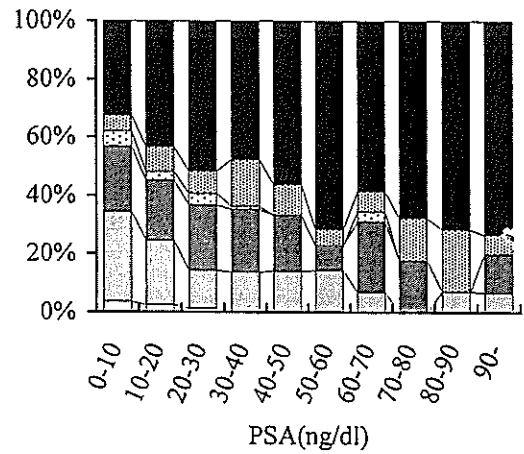
T1c

Age	W/W	RPP	RPP+Hx	Rx	Rx+Hx	Hx	Total
<54	0	6	3	1	0	2	12
55-59	1	20	9	0	0	3	33
60-64	3	38	17	1	3	12	74
65-69	4	50	40	2	9	22	127
70-74	16	44	27	5	15	49	156
75-79	8	8	14	2	9	53	94
80-84	6	0	0	0	1	38	45
85-89	1	0	0	0	0	19	20
90>	0	0	0	0	0	4	4
Total	39	166	110	11	37	202	565



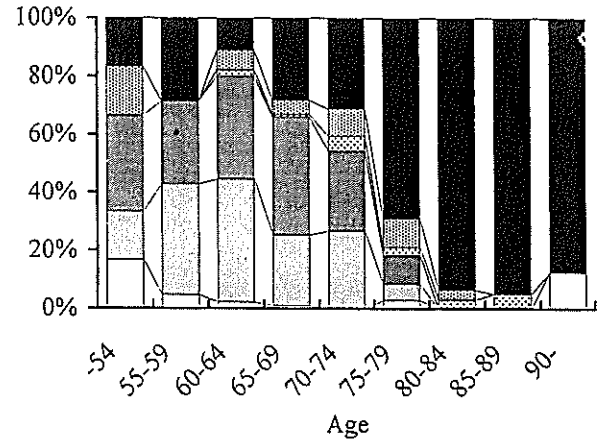
T2a

Age	W/W	RPP	RPP+Hx	Rx	Rx+Hx	Hx	Total
<54	0	6	3	0	0	0	9
55-59	1	13	13	2	2	4	35
60-64	1	37	18	2	0	4	62
65-69	0	63	36	3	10	25	137
70-74	5	49	44	11	13	70	192
75-79	1	5	11	9	3	82	111
80-84	2	0	0	3	1	41	47
85-89	4	0	0	1	0	27	32
90>	0	0	0	0	0	2	2
Total	14	173	125	31	29	255	627



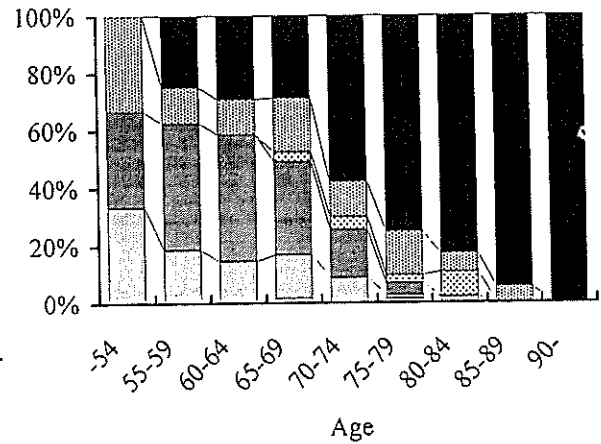
T2b

Age	W/W	RPP	RPP+Hx	Rx	Rx+Hx	Hx	Total
<54	1	1	2	0	1	1	6
55-59	1	8	6	0	0	6	21
60-64	1	19	16	1	3	5	45
65-69	1	25	42	1	5	29	103
70-74	0	31	32	6	11	36	116
75-79	2	4	7	2	7	49	71
80-84	0	0	0	1	1	29	31
85-89	0	0	0	1	0	19	20
90>	1	0	0	0	0	7	8
Total	7	88	105	12	28	181	421



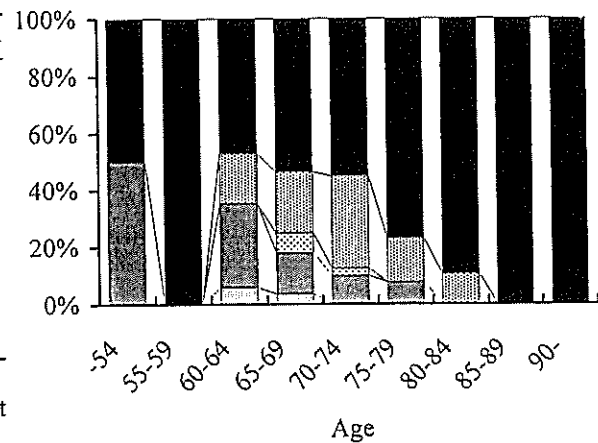
T3a

Age	W/W	RPP	RPP+Hx	Rx	Rx+Hx	Hx	Total
<54	0	1	1	0	1	0	3
55-59	0	3	7	0	2	4	16
60-64	0	6	18	0	5	12	41
65-69	1	9	19	2	11	17	59
70-74	0	8	15	4	11	52	90
75-79	1	1	3	2	11	54	72
80-84	0	1	0	4	3	38	46
85-89	0	0	0	0	1	17	18
90>	0	0	0	0	0	8	8
Total	2	29	63	12	45	202	353



T3b

age	W/W	RPP	RPP+Hx	Rx	Rx+Hx	Hx	Total
<54	0	0	1	0	0	1	2
55-59	0	0	0	0	0	1	1
60-64	0	1	5	0	3	8	17
65-69	0	1	4	2	6	15	28
70-74	0	0	4	1	13	22	40
75-79	0	0	3	0	6	30	39
80-84	0	0	0	0	2	17	19
85-89	0	0	0	0	0	11	11
90>	0	0	0	0	0	3	3
Total	0	2	17	3	30	108	160



Clinical T1c-T3b cases were divided by age.

Correlation between adopted treatment and each stage were plot the percentage of each groups

Abbreviations are follows: W/W; watchful waiting, RPP; retropubic radical prostatectomy, Hx: hormonal therapy, Rx; irradiation.

V.

Institutions that were registered

Institution	Number	Number of patients
University Hospital	31	1159
National Hospital	11	422
General Hospital	131	2984
Total	173	4565?

Thirty three patients in 4565 were deleted because of duplication, insufficient date, etc.

Institution	Number of patients	Institution	Number of patients
Hokkaido		Obama Community Hospital	2
Hokkaido University Graduate School of Medicine	29	Fukui General Hospital	4
Otaru Municipal Hospital	26	Yamanashi Prefecture	
Asahikawa City Hospital	17	Yamanashi Medical University	27
Bibai Rosai Hospital	10	Yamanashi Prefectural Central Hospital	27
Asahikawa Red Cross Hospital	20	Nagano Prefecture	
Kin-Ikyo Chuou Hospital	17	Shinshu University School of Medicine	43
Kushiro City General Hospital	20	Matsumoto National Hospital	51
Jinyukai Hospital	21	Ina Central Hospital	39
Hokkaido Hospital for Social Health Insurance	16	Nagano Red Cross Hospital	58
Muroran City General Hospital	40	Nagano Municipal Hospital	53
Aomori Prefecture		Gifu Prefecture	
Aomori Rosai Hospital	21	Gifu University School of Medicine	19
Iwate Prefecture		Gifu Municipal Hospital	27
Iwate Rousai Hospital	20	Kizawa Memorial Hospital	13
Miyagi Prefecture		Gifu Red Cross Hospital	10
Tohoku University Hospital	21	Shizuoka Prefecture	
Ishinomaki Red Cross Hospital	13	Hamamatsu Medical Center	36
Miyagi Cancer Center	59	Hamamatsu Red Cross Hospital	12
Fukushima Prefecture		Seirei Mikatahara General Hospital	68
Fukushima Medical University Hospital	24	Hamaoka Municipal Hospital	6
Fujita Public Hospital	29	Aichi Prefecture	
Ibaraki Prefecture		Fujita Health University	46
Institute of Clinical Medicine University of Tsukuba	31	TOYOTA Memorial Hospital	15
Kitaibaraki Municipal General Hospital	8	Josai Municipal Hospital, City of Nagoya	16
Hakujuji General Hospital	6	Meijo Hospital	13
Tochigi Prefecture		National Chubu Hospital	22
Rosai Hospital for Silicosis	12	Koyo Hospital	7
Gunma Prefecture		Tottori Prefecture	
Gunma University Hospital	52	Nozima Hospital	11
Gunma Cancer Center	21	Shimane Prefecture	
Tatebayashi Kousei Hospital	41	Masuda Red Cross Hospital	18
Motojima General Hospital	8	Okayama Prefecture	
Saitama Prefecture		Okayama University Graduate School of Medicine and Dentistry	39
National Defense Medical College	35	Kawasaki Medical School	71
Koshigaya Municipal Hospital	22	Okayama Central Hospital	40
Saiseikai Kanagawaken Hospital	36	Kurashiki Medical Center	49
Yokoham Rosai Hospital	55	Kawasaki Hospital	27
The International Goodwill Hospital	27	Kurashiki Central Hospital	68
Niigata Prefecture		Konko Hospital	11
Niigata Cancer Center Hospital	64	Hiroshima Prefecture	
Niigata City General Hospital	37	Kohsei General Hospital	5
Itoigawa General Hospital	5	Yamaguchi Prefecture	
Toyama Prefecture		Yamaguchi University School of Medicine	17
Toyama Medical and Pharmaceutical University	26	Tokushima Prefecture	
Toyama Prefectural Central Hospital	16	Tokushima Municipal Hospital	21
Toyama Red Cross Hospital	16	Tokushima Red Cross Hospital	30
Asahi General Hospital	3	Oe Kyodo Hospital	17
Kamiichi Welfare Hospital	8	Kagawa Prefecture	
Saiseikai Toyama Hospital	5	Kagawa Medical University	31
Ishikawa Prefecture		Kagawa Prefectural Central Hospital	51
Kaga Chuoh Hospital	9	Sanuki Municipal Hospital	12
Fukui Prefecture		Ehime Prefecture	
Fukui Prefectural Hospital	8	National Shikoku Cancer Center	57
		Matsuyama Shimin Hospital	28
		Saiseikai Imabari Hospital	24

Institution	Number of patients	Institution	Number of patients
Matsuyama Red Cross Hospital	37	Nagahama City Hospital	26
Shikoku Central Hospital	8	Kyoto	
Jyuzen General Hospital	17	Kyoto Second Red Cross Hospital	20
Kochi Prefecture		Kyoto Yawata Hospital	2
Hata Kenmin Hospital	13	Saiseikai Kyoto Hospital	29
Fukuoka Prefecture		Hukuchiyama City Hospital	9
Graduate School of Medical Sciences, Kyushu University	35	Osaka	
Kokura National Hospital	13	Wakakusa Hospital	5
Omuta City General Hospital	27	Kinki University School of Medicine	19
Hara Sanshin General Hospital	102	The Center for Cancer and Cardiovascular Diseases, Osaka	90
Yahata City Hospital	10	Osaka Police Hospital	39
Chikushi Hospital Fukuoka University	16	Osaka Kosei-Nenkin Hospital	27
Tagawa Municipal Hospital	4	Higashiosaka City General Hospital	22
Nippon Steel Yawata Memorial Hospital	6	Osaka Seamen's Insurance Hospital	10
Satte General Hospital	9	Osaka Red Cross Hospital	30
Saitama Municipal Hospital	27	Rinku General Medical Center	25
Kawaguchi Municipal Medical Center	29	Izumisano Municipal Hospital	
The Kitasato Institute Medical Center Hospital	22	Ohno Memorial Hospital	9
Saiseikai Kurihashi Hospital	25	Kanbara Hospital	3
Jichi Omiya Medical Center	29	Bellland General Hospital	32
Chiba Prefecture		Hyogo Prefecture	
Graduate School of Medicine, Chiba University	32	Kobe National Hospital	17
Matsudo Municipal Hospital	38	Nishiwaki Municipal Hospital	18
Kameda Medical Center	23	Hara Genitourinary Hospital	27
Yatsu Hoken Hospital	19	Ashiya Municipal Hospital	26
Juntendo University Urayasu Hospital	28	Shinsuma Hospital	4
Tokyo		Self Defense Forces Hanshin Hospital	1
Keio University School of Medicine	138	Takayama Clinic	18
Kidney Center, Tokyo Women's Medical University	79	Kakogawa Municipal Hospital	19
Showa University School of Medicine	45	Nara Prefecture	
International Medical Center of Japan	35	Nara National Hospital	6
National Tokyo Medical Center	83	Yamato Takada Municipal Hospital	14
National Cancer Center Hospital	101	Saiseikai Chuwa Hospital	15
Tokyo Metropolitan Ohkubo Hospital	9	Nara Social Insurance Hospital	10
Cancer Institute Hospital	94	Kokuho Central Hospital	9
Toranomon Hospital	100	Ikoma General Hospital	2
Minamitama Hospital	18	Wakayama Prefecture	
Inagi Municipal Hospital	14	Wakayama Rosai Hospital	17
Nagakubo Clinic	36	Hidaka General Hospital	7
Tokyo Medical University Hachioji Medical Center	17	Kinan General Hospital	2
Kosei General Hospital	22	Nagasaki Prefecture	
National Hospital Tokyo Disaster Medical Center	21	Nagasaki University School of Medicine	28
Kanagawa Prefecture		Isahaya Insurance General Hospital	22
Kitasato University	96	Oita Prefecture	
Yokohama City Kowan Hospital	9	Oita National Hospital	16
Yokosuka Kyosai Hospital	40	Nakatsu Daiichi Hospital	21
Kawasaki Municipal Kawasaki Hospital	14	Yamaga General Hospital	3
St. Marianna University School of Medicine Toyoko Hospital	22	Miyazaki Prefecture	
Mie Prefecture		Miyazaki Medical College	21
Faculty of Medicine, Mie University	16	Kenritu Nobeoka Hospital	16
Takeuchi Hospital	32	Kushima City National Health Insurance Hospital	5
Shiga Prefecture		Kagoshima Prefecture	
		Satsumagun Ishikai Hospital	10
		Okinawa Prefecture	
		Okinawa Prefectural Naha Hospital	9

Focus on gastric cancer

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Epidemiology and incidence statistics

Gastric cancer is the second most common cancer in the world (Ferlay et al., 2001). It is unique in that its time trend and geographical distribution are very informative in estimating its risk factors. In the US, the crude mortality rate in Caucasian males was 33/100,000 in the early 20th century, and this declined to 5/100,000 in the late 20th century. The declining trend is worldwide, and the decline began earlier in developed countries. However, even among them, mortality is still high in Korea (43/100,000), Russia (35/100,000), Japan (31/100,000), and Portugal (22/100,000). The age-adjusted incidence reaches as high as 70/100,000 in Korean and Japanese males. The male to female ratio is consistently two to one in many geographical regions.

The decline took place following the popularization of refrigerators, which resulted in a decreased intake of salt and an increased intake of fruit and vegetables (Palli, 2000; Potter et al., 1997). The preventive effects of fruit and vegetables are consistently confirmed by many epidemiological studies. Most epidemiological studies have shown the promoting effect of salt and the preventive effect of vitamin C. The effects of salt were also shown by animal experiments. Some epidemiological studies suggest that consumption of grilled meat/fish increases the risk, and that the consumption of carotenoids and green tea reduce the risk. Epidemiological data linking *N*-nitrosamines to gastric cancers have so far been inconclusive, although their carcinogenicity at high doses is proven.

Infection by *Helicobacter pylori* is prevalent in areas with high incidences of gastric cancers, and increases the risk of gastric cancer. However, in some Asian countries, such as India and Thailand, incidences of gastric cancers are not high in spite of the high *H. pylori* infection rates, a phenomenon known as the "Asian Enigma" (Miwa et al., 2002). Possible explanations for this include host genetic factors, different virulence among strains of *H. pylori*, and dietary factors. Polymorphisms of proinflammatory cytokine genes have been shown to associate with risk of *H. pylori*-related gastric cancers (El-Omar et al., 2000).

Animal models

A rat model for gastric cancers induced by a chemical carcinogen, *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine, has been widely used for a variety of purposes, such as evaluation of various promoting and preventing factors and clarification of genes involved in genetic susceptibility (Yamashita et al., 2002). A model in which *H. pylori* could infect an animal was established using Mongolian gerbils, which contributed to clarification of the strong promoting effect of *H. pylori* (Shimizu et al., 1999).

In addition, there have been more than 10 lines of genetically modified mice that show hyperplasia of the gastric epithelium and/or intestinal metaplasia (Gut et al., 2002). These mouse models were created by targeting genes involved in ion trans-

port, signal transduction, transcriptional regulation, and cell adhesion. Development of gastric cancers was observed in mice lacking the pS2 trefoil protein, those lacking *Smad4/Dpc4*, those lacking the SHP2 binding site on the *Il-6* family corepressor gp130, and those lacking *RUNX3* (Judd et al., 2004; Lefebvre et al., 1996; Xu et al., 2000; Li et al., 2002).

Disease mechanism and molecular targets

Histological classification and gastric/intestinal phenotypes

Histological classification of gastric cancers is different between Japan and Western countries. Generally, "differentiated" and "undifferentiated" types in Japanese classification correspond to "intestinal" and "diffuse" types, respectively, in the Western classification established by Lauren. It has been considered that intestinal-type gastric cancers are associated with intestinal metaplasia, whereas diffuse-type gastric cancers are originated from gastric mucosa proper. Recent analysis of gastric and intestinal phenotypes in early gastric cancers has shown that cancer cells with gastric phenotypes were present in both intestinal and diffuse types of gastric cancer. Furthermore, phenotypic expression in gastric cancer cells was shown to be independent of phenotypic changes in the surrounding gastric mucosa (Tatematsu et al., 2003).

Gastric cancer predisposition

Germline mutations of *E-cadherin* were first found in a large family from New Zealand in which diffuse-type gastric cancers took place at an early age (Guilford et al., 1998). Although *E-cadherin* germline mutations are very rare, the finding provided to be useful information for clinicians to manage high-risk patients. Gastric cancers, mainly of the intestinal type, can be associated with hereditary nonpolyposis colorectal cancer (HNPCC) syndrome, most cases of which are caused by germline mutations of mismatch repair genes *hMLH1* or *hMSH2*, and are more prominently manifested in older generations of HNPCC patients. Patients with familial adenomatous polyposis, which is caused by germline mutations of *APC*, and Peutz-Jeghers syndrome also have increased risk for gastric cancer (Oberhuber and Stolte, 2000).

Molecular alterations in gastric cancer

Many genes have been analyzed in attempts to understand the molecular bases for human gastric cancers, but only a few with frequent alterations have been identified (Table 1). Oncogenic activations of β -*catenin* (17%–27% in intestinal type) and *K-ras* (0%–18% in both histological types) have been found in human gastric cancers (Lee et al., 2002; Park et al., 1999). In addition, amplifications of the *c-erbB2* and the *c-met* genes have each been found in approximately 10% of both histological types.

As for tumor-suppressor genes, *p53* mutations are repeatedly reported in gastric cancers of the diffuse type (0%–21%) and intestinal type (36%–43%) (Maesawa et al., 1995).

Table 1. Histology and genetic alterations of gastric cancers

	Diffuse type (%)	Intestinal type (%)
Oncogene activation		
β -catenin	0	17–27
K-ras	0–6	0–18
c-erbB2	12–13	12–13
Inactivation of tumor suppressor genes		
p53	0–21	36–43
APC	0–5	0
E-cadherin		
Mutation	33–50	0
Methylation	79	55
p16		
Mutation	0	0
Methylation	11*	50*
Microsatellite instability	5–32	23–41

*Incidences are overestimated due to analysis of CpG islands in exons.

Mutations of the *APC* tumor suppressor gene are found frequently in gastric adenomas, but only rarely in gastric cancers; this is clearly different from the similar frequencies of *APC* mutations in colorectal adenomas and carcinomas (Lee et al., 2002; Maesawa et al., 1995). Somatic mutations of *E-cadherin* are observed specifically in sporadic diffuse-type gastric cancers (33%–50%) (Becker et al., 1994). *RUNX3* was recently shown to be a tumor-suppressor gene of gastric cancers, although its mutations were rare (Li et al., 2002).

Microsatellite instability (MSI) is observed in 5%–10% of diffuse-type gastric cancers and in 15%–40% of intestinal-type gastric cancers. The major mechanism for the MSI in gastric cancer is inactivation of the mismatch repair gene *hMLH1* resulting from hypermethylation of its promoter (Fang et al., 2003). Similarly, mutation of the *p16* gene is infrequent, but hypermethylation of *p16* is common (25%–42% overall) in gastric cancer, with the intestinal type having higher incidence (Ding et al., 2003; Oue et al., 2002).

Factors that induce molecular alterations

Although *hMLH1* and *p16* can be inactivated in gastric cancers by mutations or by promoter hypermethylation, inactivation by methylation is much more frequent than mutation in sporadic gastric cancers. The second hit in *E-cadherin* germline mutation carriers is also generally due to methylation (Machado et al., 2001). A genome-wide scan for aberrant methylations revealed silencing of nine genes in gastric cancers (Kaneda et al., 2002). Even in noncancerous gastric mucosae (Waki et al., 2002), aberrant methylation can be present. These findings suggest that aberrant methylation is deeply involved in gastric carcinogenesis, and aberrant methylation seems to be useful as a new target for diagnostics and prevention of gastric cancers.

The presence of Epstein-Barr virus (EBV) is observed in 7%–20% of gastric cancers, being slightly more frequent in diffuse-type gastric cancers. EBV is clonal in cancer tissue, and is maintained as a plasmid. EBV has been shown to extend cell generations of gastric epithelial cells in in vitro cell culture, but it cannot immortalize them (Takada, 2000). Recently, EBV-associated gastric cancers were shown to be more frequently associated with promoter methylation of *p16* (Kang et al., 2002).

There has been discussion about whether intestinal metaplasia (IM) is a precancerous lesion for gastric cancers. Although gastric cancers are frequently accompanied by IM, no molecular alterations that cause both IM and gastric cancers

have been identified. It is thus more likely that factors that induce molecular alterations for IM, such as *H. pylori* infection (Uemura et al., 2001), also induce molecular alterations for gastric cancers.

Diagnosis of gastric cancers

Most patients with gastric cancer are diagnosed when they undergo endoscopy and biopsy after exhibiting symptoms. In Japan, about 25% of patients are diagnosed by mass screening or a personal health check (Japanese National Gastric Cancer Registry). In high-risk areas of this disease, the most important issue is the education of general practitioners and the public to make them aware of the risk of this cancer. Early diagnosis used to be made by a barium meal study, especially in mass screening in Japan (Oshima, 1997). Endoscopy is being used more and more for secondary prevention in combination with a serum test of pepsinogen subtypes. However, there is a consensus that the efficacy of mass screening itself should be reevaluated (Tsubono and Hisamichi, 2000).

At an early phase of development, a well-differentiated carcinoma (WDC) replaces the mucosa of atrophic gastritis or IM without showing any invasion. As tumors progress, they start to invade the lamina propria mucosae or the muscularis mucosae, then the submucosal layer. As these invasive parts are often missed by biopsy, the lesions are often diagnosed as dysplasia. Thus, many lesions initially diagnosed as severe dysplasia turned out to be an invasive cancer, sometimes invading even the muscularis propria, after histological evaluation of resected materials (Fertitta et al., 1993).

Diagnostic criteria for early gastric cancers and endoscopic mucosal resection

Diagnostic criteria of WDC differs to some extent between the West and the East (Schlemper et al., 1997). In Western countries, the diagnosis of adenocarcinoma is made only when pathologists can recognize the evidence of invasion, while the term cancer is used in the East when cellular or structural atypia is evident, even without evidence of invasion. WHO classification now clearly states that the lesions called severe dysplasia/adenoma in the West are the same as noninvasive mucosal carcinoma in the East, and this is a result of pathologists' mutual communication and cooperation (Fenoglio-Preiser et al., 1997). The Western policy runs the risk of overlooking true cancers, but the Eastern policy may induce overtreatment. However, as the result of the development of the technique of endoscopic mucosal resection (EMR), the majority of such lesions are now treated endoscopically in Japan (Ono et al., 2001). Thus, paradoxically, "severe dysplasia" is often treated by surgery in the West, and "noninvasive mucosal carcinoma" is treated by EMR. This treatment can be applied exclusively to mucosal cancer, for which endoscopic ultrasound (EUS) is sometimes helpful. Because the histology of the entire specimen resected using EMR can be examined in detail, additional surgery can be applied without much delay if a patient's tumor is found to have submucosal invasion. Because of these potential advantages, distribution of the EMR technique to the West is urgently needed.

Metastases and their diagnosis

Gastric cancer remains a localized disease for a long time and metastasizes slowly. Table 2 shows the incidence of metastasis to lymph nodes, the liver, and the peritoneum according to tumor depth. Metastasis to sites other than these three sites is rare. Systemic metastasis seldom occurs until the late phase of

Table 2. Incidence of metastasis and five-year survival rates by tumor size and depth

Depth	Number of cases	Incidence (%)			Five-year survival rate (%)
		LN metastasis	Liver metastasis	Peritoneal metastasis	
pT1	M	1063	3.3	0.0	93.3
	SM	881	17.4	0.1	88.9
pT2	MP	436	46.4	1.1	81.3
	SS	325	63.7	3.4	65.8
pT3	SE	1232	78.9	6.3	35.5
pT4	SI	724	89.8	15.5	10.1
Overall		4683	47.8	4.5	60.3

Patients operated on between 1972–1991 at National Cancer Center Hospital, including exploratory laparotomy. pT1: pathologically confirmed tumor invasion of mucosa and/or muscularis mucosa (M) or submucosa (SM). pT2: pathologically confirmed tumor invasion of muscularis propria (MP) or subserosa (SS). pT3: pathologically confirmed tumor penetration of serosa (SE). pT4: pathologically confirmed tumor invasion of adjacent structures (SI).

local invasion (T3/4). By deeper invasion, nodal metastasis occurs more massively and to more distant areas. Nearly 20% of T2 tumors have metastasis at the second tier nodes. Systemic and local recurrences of T1/T2 lesions are rare when treated by proper lymph node dissection, while local recurrence is frequent after limited surgery (Sasako, 2003).

Conventional CT scanning is useful in detecting enlarged nodes, which are often irresectable. However, 25% of metastatic nodes are 5 mm or less and undetectable by any imaging diagnostic tool, including MRI, PET scan, or EUS (Noda et al., 1998).

Treatment of gastric cancers and its recent advances

Tumors without distant metastasis are potentially curable, and treatment comprises resection of the primary tumor and control of lymph node metastasis. For differentiated-type T1 mucosal cancers, EMR is often successful, as metastasis does not generally occur (Gotoda et al., 2000). The Japanese Gastric Cancer Treatment Guideline indicates the criteria for EMR as follows: mucosal cancer of intestinal type, no ulcer nor ulcer scar in the lesion, and size smaller than 21 mm (Nakajima, 2002). For more advanced lesions, gastrectomy of over 2/3 of the stomach with proper lymph node dissection is regarded as standard treatment even in the West (Sasako, 2003; Allum et al., 2002; NCCN Guideline [http://www.nccn.com/physician_gls/f_guidelines.html]), in spite of the negative results of two large randomized trials (Bonenkamp et al., 1999; Cuschieri et al., 1999).

Tumors with distant metastasis are mostly incurable at present, with the rare exceptions of those with solitary liver metastasis or peritoneal nodules. For these advanced or recurrent tumors, chemotherapy shows a modest effect, and cure by medical treatment is rare, even in combination with radiotherapy. Combination chemotherapy using 5-fluorouracil with other agents remains the most popular regimen.

Chemoradiotherapy and D2 surgery

Recently, chemoradiotherapy (CRT) after a potentially curative operation was shown to improve the results of surgery without lymph node dissection (MacDonald et al., 2001). As adjuvant chemotherapy has not proven its efficacy over surgery alone, these results strongly suggest the efficacy of radiotherapy to achieve good local control. However, the results achieved by limited surgery followed by CRT are still worse than those of extended surgery, so-called D2 nodal dissection. Currently, questions regarding whether CRT in combination with limited surgery can replace D2 surgery and whether CRT can improve the results of D2 surgery alone remain to be answered. The for-

mer should be evaluated in the Western specialized centers, where D2 surgery can be carried out safely with sufficient quality. If this proves the efficacy of CRT, both questions should be investigated in Japan. Meta-analysis evaluating the effect of adjuvant chemotherapy without irradiation after curative surgery for gastric cancer suggested strongly the effect of the treatment. As none of the large sized trials has proven the effect of adjuvant chemotherapy, it is urgent to establish standard adjuvant treatment. At the moment, a large randomized trial is going on using TS-1, which showed the highest response rate as a single agent in the past. In Western countries, neoadjuvant chemotherapy for advanced gastric cancer is now being tested in a few large phase III trials. Neoadjuvant CRT is just now under investigation as a phase II trial in some American institutions.

New chemotherapeutic agent

Some new chemotherapeutic agents, such as Irinotecan, TS-1, and Docetaxel, show promise as being more effective than conventional drugs. A combination chemotherapy including TS-1 has shown a response rate of over 70% (Koizumi et al., 2003). Further studies may change the chemotherapy for gastric cancer.

Future challenges

Severe dysplasia/noninvasive mucosal carcinoma could contain different entities that have different abilities to invade the lamina propria mucosae. However, key molecular alterations that determine this progression are unknown. The presence of lymph node or distant metastasis is a very important factor in deciding a treatment strategy, but accurate diagnosis is still difficult. Clarification of molecular alterations that are closely linked with these characteristics will be beneficial to decide on a treatment strategy for individual cases. Popular use of EMR raises a new question, whether or not a secondary cancer will arise from the remnant stomach, and prediction of risk for developing gastric cancer is becoming more important. Recent genomic approaches demonstrate great potential for addressing these issues (Hasegawa et al., 2002). The more important and appropriate questions we ask, the more useful these new approaches will be.

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Extended Lymph Node Dissection for Gastric Cancer: Who May Benefit? Final Results of the Randomized Dutch Gastric Cancer Group Trial

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A B S T R A C T

Purpose

The extent of lymph node dissection appropriate for gastric cancer is still under debate. We have conducted a randomized trial to compare the results of a limited (D1) and extended (D2) lymph node dissection in terms of morbidity, mortality, long-term survival and cumulative risk of relapse. We have reviewed the results of our trial after follow-up of more than 10 years.

Patients and Methods

Between August 1989 and June 1993, 1,078 patients with gastric adenocarcinoma were randomly assigned to undergo a D1 or D2 lymph node dissection. Data were collected prospectively, and patients were followed for more than 10 years.

Results

A total of 711 patients (380 in the D1 group and 331 in the D2 group) were treated with curative intent. Morbidity (25% v 43%; $P < .001$) and mortality (4% v 10%; $P = .004$) were significantly higher in the D2 dissection group. After 11 years there is no overall difference in survival (30% v 35%; $P = .53$). Of all subgroups analyzed, only patients with N2 disease may benefit of a D2 dissection. The relative risk ratio for morbidity and mortality is significantly higher than one for D2 dissections, splenectomy, pancreatectomy, and age older than 70 years.

Conclusion

Overall, extended lymph node dissection as defined in this study generated no long-term survival benefit. The associated higher postoperative mortality offsets its long-term effect in survival. For patients with N2 disease an extended lymph node dissection may offer cure, but it remains difficult to identify patients who have N2 disease. Morbidity and mortality are greatly influenced by the extent of lymph node dissection, pancreatectomy, splenectomy and age. Extended lymph node dissections may be of benefit if morbidity and mortality can be avoided.

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INTRODUCTION

Gastric cancer is a common malignancy worldwide. Even in a low-incidence country like the Netherlands, it is ranked fifth with respect to incidence. Despite declining incidence, mortality of gastric cancer remains high. Surgery is the only possible curative treatment, and results of gastrectomy have improved throughout the years with respect to survival, morbidity, and postoperative mortality.^{1,2}

It is not clear, however, if extended lymph node dissection contributes to this

improvement. Despite promising results in nonrandomized studies, improved survival has never been demonstrated in randomized trials.³⁻⁶ In all these randomized trials, postoperative morbidity and mortality were significantly higher in the extended (D2) dissection group. Within the Dutch Gastric Cancer Trial (DGCT), the number of early gastric cancers was surprisingly high, and it has been argued that any beneficial effect of extended lymph node dissection, which would be expected in more advanced disease, might have been attenuated. We have

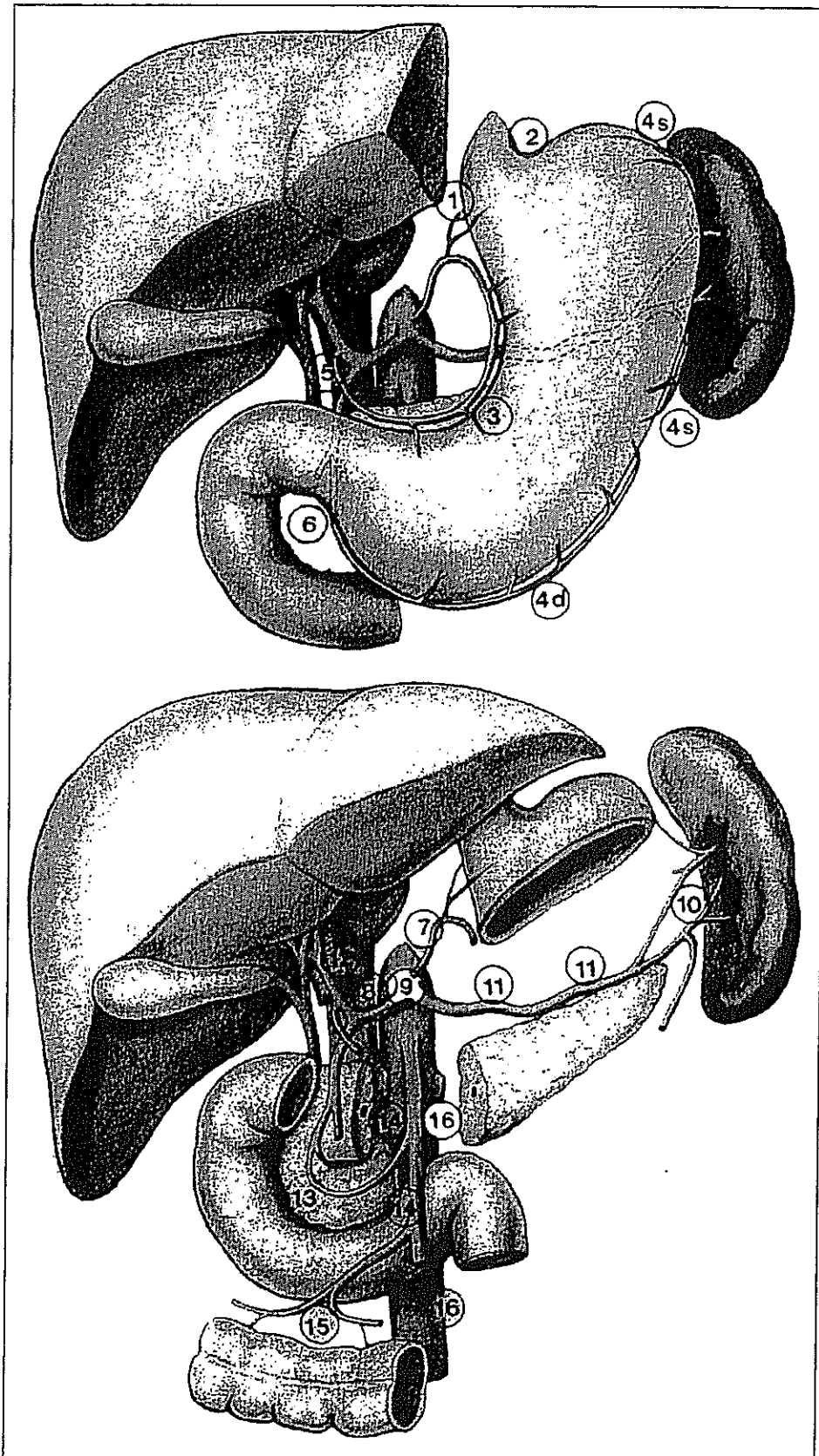


Fig 1. Lymph node stations surrounding the stomach. 1, right cardiac nodes; 2, left cardiac nodes; 3, nodes along the lesser curvature; 4, nodes along the greater curvature; 5, suprapyloric nodes; 6, infrapyloric nodes; 7, nodes along the left gastric artery; 8, nodes along the common hepatic artery; 9, nodes around the celiac axis; 10, nodes at the splenic hilus; 11, nodes along the splenic artery; 12, nodes in the hepatoduodenale ligament; 13, nodes at the posterior aspect of the pancreas head; 14, nodes at the root of the mesentery; 15, nodes in the mesocolon of the transverse colon; 16, para-aortic nodes.

D2 Dissection Beneficial for Some Patients

Table 1. Characteristics of 711 Patients and Tumors After Resection With Curative Intent* and Status at Last Follow-Up

Characteristic	Dissection Group			
	D1 (n = 380)		D2 (n = 331)	
	No. of Patients	%	No. of Patients	%
Median age, years	67		65	
Sex				
Male	215		187	
Female	165		144	
Median No. of lymph nodes investigated	17		30	
Status after resection				
Location of tumor				
More than two thirds of stomach	25	7	24	7
Upper third (C)	39	10	34	10
Middle third (M)	108	28	92	28
Distal third (A)	207	54	180	54
Unknown	1	< 1	1	< 1
Pathologic stage of disease				
T0	2	< 1	3	< 1
T1	98	26	85	26
T2	181	48	152	46
T3	94	25	82	25
T4	3	< 1	9	2
Tx	2	< 1	0	0
Lymph node involvement	205	54	185	56
R0 resection	339	89	293	89
Type of gastrectomy				
Total	115	30	128	38
Partial	265	70	205	62
Resection of spleen	41	11	124	37
Resection of tail of pancreas	10	3	98	30
Status at last follow-up				
Alive				
Without recurrence	112	98	116	99
With recurrence	2	2	1	1
Dead				
Hospital death	15	4	32	10
Without recurrence†	82	31	86	40
With recurrence				
Locoregional	56	21	40	19
Locoregional and distant	98	37	55	26
Distant	30	11	33	15

NOTE. Some data have previously been reported.⁶
 Abbreviations. D1, limited lymph node dissection group; D2, extended lymph node dissection group.
 *Because of rounding, percentages may not total 100.
 †These numbers include hospital deaths.

therefore reviewed the results of our randomized limited lymph node dissection (D1) versus extended lymph node dissection (D2) trial after follow-up of more than 10 years and focused on subgroups and prognostic factors.

PATIENTS AND METHODS

Patients with gastric adenocarcinoma were enrolled in the DGCT between August 1989 and July 1993. Eligible patients were randomly assigned for D1 (conventional) or D2 (extended) lymph node dissection if at laparotomy, no signs of distant lymph node, hepatic or peritoneal metastases were found. In case of metastases,

palliative surgery without formal lymph node dissection was done. The trial protocol has previously been published.⁷

D1 and D2 dissection were defined according to the guidelines of the Japanese Research Society for the Study of Gastric Cancer.⁸ These guidelines are also recommended by the American Joint Committee on Cancer, in its fourth Manual for Staging of Cancer, and by the International Union Against Cancer.^{9,10} In these guidelines, 16 different lymph node compartments (stations) are identified surrounding the stomach (Fig 1). In general, the perigastric lymph node stations along the lesser (stations 1, 3, and 5) and greater (stations 2, 4, and 6) curvature are grouped N1, whereas the nodes along the left gastric (station 7), common

hepatic (station 8), celiac (station 9), and splenic (stations 10 and 11) arteries are grouped N2.

D1 dissection entails removal of the involved part of the stomach (distal or total), including greater and lesser omentum. The spleen and pancreas tail are only resected when necessitated by tumor invasion. For a D2 dissection, the omental bursa is removed with the front leave of the transverse mesocolon, and the mentioned vascular pedicles of the stomach are cleared completely. Standard resection of the spleen and pancreatic tail was only done in proximal tumors to achieve adequate removal of D2 lymph node stations 10 and 11.

Patients were randomly assigned before surgery to ensure standardization of surgery. Patients randomly assigned to D1 dissection had their operation performed by their local surgeon, supervised by the trial coordinator. For D2 dissections, one of nine referent surgeons performed the operation at the local hospital. These referent surgeons had been trained in D2 dissection by a Japanese surgeon from the National Cancer Center Hospital in Tokyo. Apart from standardizing surgery, they ensured that the specimen was adequately divided into lymph node stations, which were then further investigated by the local pathologist. Operations were classified as R0 if there was microscopic complete tumor removal, without N3 or N4 involvement and no malignant cells on cytology of abdominal washing. For analysis of differences in relapse rates, only patients were included who had had a R0 resection and who did not die because of complications. None of the curative patients had adjuvant radiotherapy or chemotherapy.

In the hospital, death was defined as death within 30 days of surgery or during hospital stay, if this was longer than 30 days. For stage grouping, the new (2002) tumor-node-metastasis system classification system was used.¹¹ In this new classification lymph nodes are no longer characterized by location but by the number of metastatic regional lymph nodes. N1 stands for 1 to 6, N2 for 7 to 15, and N3 for more than 16 metastatic regional lymph nodes.

For statistical analysis the SPSS program (SPSS Inc, Chicago, IL) was used. A *P* value of .05 was considered statistically significant. Overall survival was calculated from the day of random assignment until either day of death (event) or day of last follow-up (censored). Relapse was also calculated from the day of random assignment; the data of a patient were censored when at last follow-up contact the patient was alive with no evidence of disease. The χ^2 test was applied to evaluate differences in proportions, and the Mann-Whitney test was used to assess the significance of differences in hospital stay. The log-rank test was used to evaluate difference between survival and relapse curves, although the assumption of proportional hazards was not always satisfied. The Cox proportional hazard model was used to test for interaction between prognostic factors and lymph node dissection.

For the subgroup analysis, no adjustment for multiple testing was applied. Interpretation of the results of subset analyses have to be judged carefully and any significant results must be viewed as hypotheses that require validation in subsequent studies. A *P* value of .05 may not be strict enough for these subgroups.

RESULTS

Of 1,078 patients randomly assigned in the DGCT, 996 were eligible. At the time of surgery, 285 patients (29%) had peritoneal, hepatic or distant lymph node metastasis, or

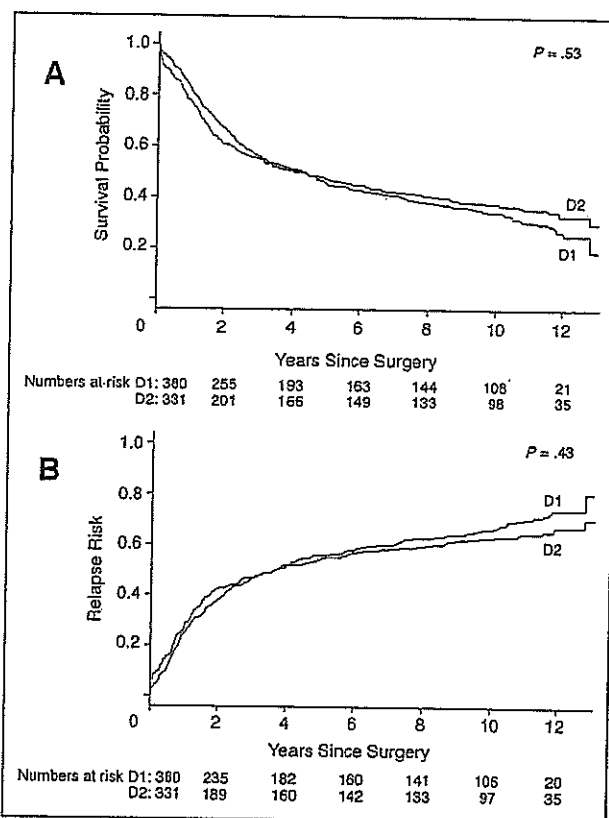


Fig 2. Survival probability (A) and relapse risk (B) of all patients treated with curative intent ($n = 711$). D1, limited lymph node dissection group; D2, extended lymph node dissection group.

locally irresectable tumor and they underwent noncurative treatment deemed appropriate by their surgeon.

This analysis focuses on the 711 patients (71%) who had a curative resection with D1 ($n = 380$) or D2 ($n = 331$) lymph node dissection. The characteristics of the 711 curative patients are well balanced between the two treatment groups, except for pancreatico-splenectomy, which was expected according to the protocol (Table 1).

Follow-up was continued until January 2003. Median follow-up for all eligible patients is 11 years (range, 6.8 to 13.1 years). Four-hundred eighty patients (68%) are now deceased, 35% without and 65% with recurrent disease (Table 1). In the hospital, death was 4% ($n = 15$) for the D1 group and 10% ($n = 32$) for the D2 group ($P = .004$). At 11 years, survival rates are 30% for D1 and 35% for D2 ($P = .53$). The risk of relapse is 70% for D1 and 65% for D2 ($P = .43$; Fig 2).

In a univariate analysis of all 711 patients, for none of the subgroups based on the selected prognostic variables was a significant impact found on survival rates between D1 and D2 dissection (Table 2). Analysis of interaction between covariates and lymph node dissection shows no significance. The only subgroup with a trend to benefit is the N2 disease group (Fig 3). Furthermore, there is no difference in survival after 11 years

D2 Dissection Beneficial for Some Patients

Table 2. Univariate Analysis of Survival Rates 11 Years After Resection With Curative Intent (N = 711)

Variable	Dissection Group				P*
	D1		D2		
	No. of Patients	Survival %	No. of Patients	Survival %	
Age, years					
≤ 70	252	37	229	41	.74
> 70	128	19	102	24	.68
Pathologic stage					
T1	98	57	85	55	.90
T2	181	28	152	35	.54
T3	94	8	82	17	.80
Lymph nodes					
Negative	171	52	144	51	.93
Positive	209	13	187	23	.28
Lymph node stage					
N0	171	52	144	51	.93
N1	138	20	113	30	.46
N2	50	0	47	21	.08
N3	21	0	27	0	.30
Tumor-node-metastasis stage‡					
IA	75	60	69	58	.84
IB	97	47	72	44	.65
II	93	23	77	37	.10
IIIA	60	4	54	22	.38
IIIB	24	0	20	10	.55
IV	28	0	36	3	.19
Gastrectomy					
Partial	265	35	205	43	.20
Total	115	20	126	24	.94
All patients	380	31	331	35	.53

Abbreviations: D1, limited lymph node dissection group; D2, extended lymph node dissection group; TNM, tumor-node-metastasis.
 *P values were derived by the log-rank test for the difference between the D1 and D2 groups.
 †Stages T0 and T4 (five patients in the D1 group and 12 in the D2 group) have been omitted.
 ‡Stages according to the sixth edition of the TNM classification manual.¹¹ TNM stage 0 (four patients in the D1 group and three in the D2 group) has been omitted.

whether less than 15 lymph nodes, between 15 and 25 lymph nodes, or more than 25 lymph nodes are harvested.

Lymph node stations 10 and 11 were resected in 112 and 124 patients, respectively. In the group of 18 patients with metastasis in station number 10, survival after 11 years is only 11%. In the group of 24 patients with lymph node metastasis in station 11, survival after 11 years is only 8%. If there are no metastases in lymph node stations 10 and 11, the 11-year survival is 27% and 35%, respectively.

The relative risk ratio for morbidity and mortality is significantly greater than one for D2 dissections, splenectomy, pancreatectomy, and age older than 70 years (mortality only; Table 3).

Patients older than 70 years have significantly higher morbidity and hospital mortality and significantly shorter survival compared with patients younger than 70 years. (Table 4).

DISCUSSION

For many years it has been debated whether an extended lymph node dissection for gastric cancer is beneficial. The-

oretically, removal of a wider range of lymph nodes by extended lymph node dissection increases the chances for cure. Such resection, however, may be irrelevant if there are no lymph nodes affected, if the cancer has developed into a systemic disease, or if resection increases morbidity and mortality substantially.

Long-term follow-up of the largest randomized study of D1 and D2 dissection now clearly demonstrates that overall, no improved survival or decreased relapse rates can be obtained by D2 dissection. Extended lymph node dissection is even harmful in terms of increased morbidity and hospital mortality, although many reports deny this. Specifically, Japanese investigators have reported low operative morbidity and mortality,¹² but so far, studies have not been randomized. A randomized Japanese study between D2 and D4 dissections, that included 523 patients and closed in April 2001 found a hospital mortality of 0.8% in both groups. Dedicated centers in Western Europe have reported hospital mortality rates of less than 5% for extended lymph node dissections in selected patients.¹³⁻¹⁵ In our study, patients younger than 70 years had a hospital mortality rate of 5.9%.

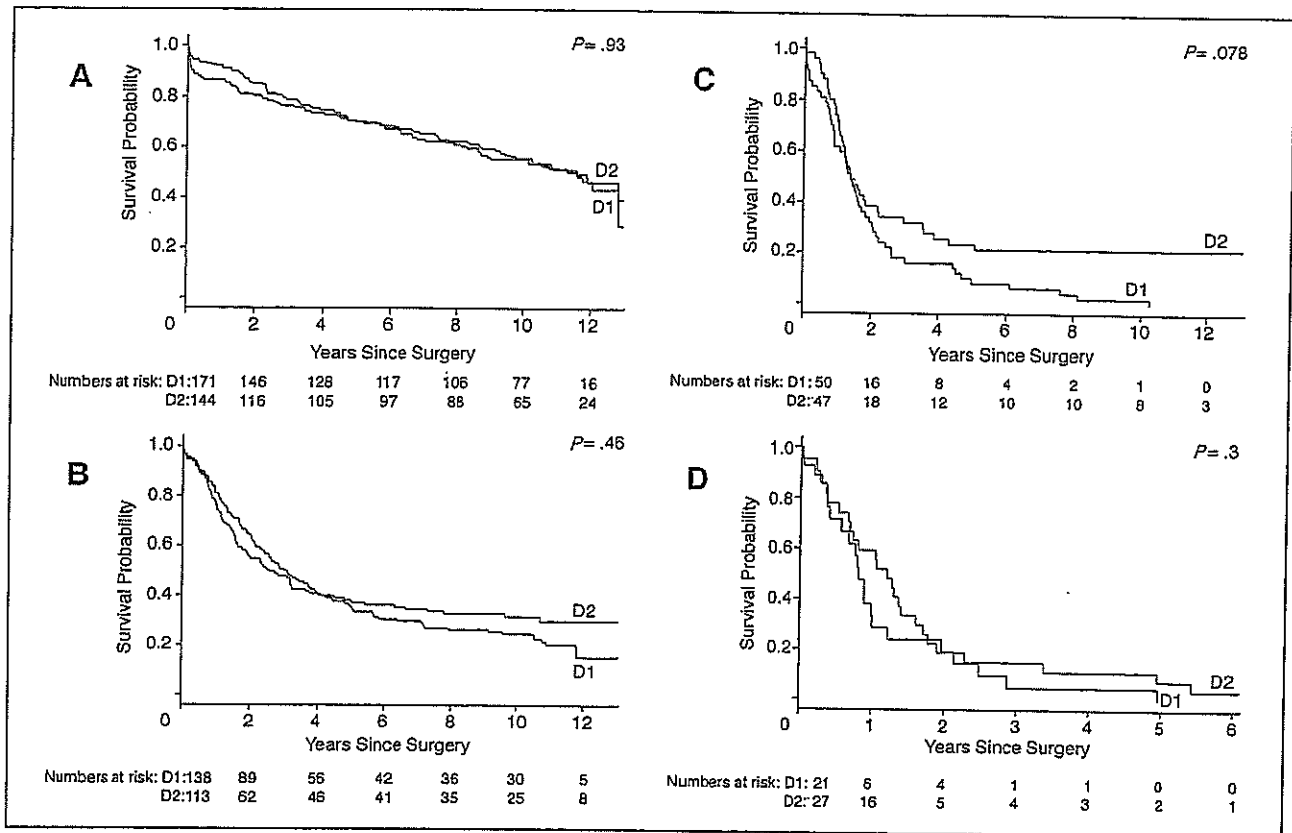


Fig 3. Survival of patients treated with curative intent according to N stage. (A), N0; (B), N1; (C), N2; (D), N3. D1, limited lymph node dissection group; D2, extended lymph node dissection group.

Splenectomy and pancreatectomy are important risk factors for morbidity and hospital mortality after D2 dissection,^{16,17} with a significant adverse effect on survival as well.¹⁸ Two Japanese studies showed no beneficial effect on survival if pancreatectomy was combined with total gastrectomy, whereas morbidity was increased in these patients.^{19,20} A randomized trial in Chile found no survival benefit from a splenectomy in patients with total gastrectomy, whereas morbidity was again significantly increased.²¹ Another randomized trial to study the effect of splenectomy is underway in Japan.²² In our study the risk ratio for morbidity and mortality was significant for pancreatectomy and splenectomy. The question is whether a survival benefit can be achieved with an extended lymph node dissection, if morbidity- and mortality-increasing procedures such as pancreatectomy and splenectomy can be avoided. A randomized English study supports this hypothesis for patients with stage II and III disease.²³ Pancreas and spleen sparing procedures have now become standard in Japan as well as many Western countries.

The main reason to do pancreatectomy and splenectomy in D2 dissection was not to compromise an adequate dissection of lymph node stations 10 and 11. Metastasis in

these lymph nodes, however, confers a poor prognosis. In our study, patients with metastasis in these lymph nodes have a survival rate at 11 years of 8% and 11%, respectively, whereas patients without metastases have a survival rate of 27% and 35%, respectively. So the relevance of the dissection of these nodes has to be questioned as the survival benefit is small and morbidity and hospital mortality are significantly increased.

Total gastrectomy has a higher morbidity and hospital mortality rate than partial gastrectomy. A randomized trial in Italy showed that there is no survival benefit from a total gastrectomy if resection margins are free of tumor.¹⁸ So total gastrectomy should only be performed if the localization of the tumor requires to do so.

With the aging of the populations of industrialized countries, more elderly patients with gastric cancer will be diagnosed. Population-based data from the Netherlands show that from 1982 to 1992, 27% of newly diagnosed patients were older than 80 years.²⁴ In a study on gastric cancer in the elderly by Klein Kranenburg et al,²⁵ it was shown that there is no difference in resectability and curability rate between different age groups, but hospital mortality increases with increasing age, especially older than 70

D2 Dissection Beneficial for Some Patients

Table 3. Relative Risk Ratio for Morbidity and Mortality After Resection With Curative Intent (n = 711)

Factor	Total No. of Patients	Morbidity				Mortality			
		No. of Patients	%	RR	95% CI	No. of Patients	%	RR	95% CI
Dissection									
D1	380	94	25			15	4		
D2	331	142	43	1.73	1.40 to 2.15	32	10	2.45	1.35 to 4.44
Splenectomy									
D1	41								
D2	124								
No, both groups	546	59	11			26	5		
Yes, both groups	165	54	33	3.03	2.19 to 4.19	21	13	2.67	1.55 to 4.62
Pancreatectomy									
D1	10								
D2	98								
No, both groups	603	70	12			34	5		
Yes, both groups	108	43	40	3.43	2.49 to 4.72	13	12	2.14	1.17 to 3.91
Age, years									
≤ 70	481	152	32			20	4		
> 70	230	80	37	1.10	0.88 to 1.37	27	12	2.82	1.62 to 4.93

Abbreviations: RR, relative risk; D1, limited lymph node dissection group; D2, extended lymph node dissection group.

years. Differentiation between D1 and D2 dissections for the age groups younger and older than 70 years shows that the morbidity and hospital mortality is higher in the D2 dissection group compared with the D1 dissection group. Although some authors do not regard age as an important prognostic variable for survival, we believe that gastrectomies should not be withheld from elderly patients but that extended lymph node dissection should be avoided in Western patients older than 70 years.

The new (2002) tumor-node-metastasis system classification system¹¹ offers a better insight in subgroups with different prognosis.²⁶⁻²⁸ Using this new classification system, we studied the effect of D1 and D2 dissections in the N0, N1, N2, and N3 groups and found what theoretically might be expected—that the largest advantage is for the N2 disease group if they had a D2 dissection. This advantage was less for the N0, N1, and N3 groups. So a D2 dissection probably is the only possible cure for N2 patients. Given that only 12% of all patients had N2 disease, it is not possible to find this difference through the randomized groups. We calculated that with exclusion of postoperative deaths, 21% of the population ought to have N2 disease to make an overall difference between D1 and D2 significant. Including postoperative death, no such percentage will make the difference between the D1 and D2 significant.

At this moment N classification can only be concluded postoperatively after histologic examination. Although we have tested many possible prognostic factors and their combinations, such as T stage, tumor location in the stomach, histologic characteristics (well v poorly differentiated, WHO classification, Lauren classification, and Goseki classification), oncogene markers (p53, Rb, Myc, and Nm23),

adhesion molecules (Ep-CAM, E-Cadherin, CD44v5, and CD44v6), and sucrose maltase expression, we have so far not been able to identify any factor that can identify N2 patients preoperatively.^{29,30} We hope that promising results from genomic profiling in the near future may help to discriminate between patients with a high risk of lymph node metastasis.³¹

The extent of surgery will especially be of influence on locoregional control. Relapse after curative surgery because of local recurrence or regional lymph node metastasis has been shown in up to 87.5% of patients.³² In our trial, locoregional recurrence was registered in 58% of the D1 group and in 45% of the D2 group. In studies with extensive surgery (D2 or more) local recurrence rates of less than 1% are reported.³³ Another approach to improve locoregional control is postop-

Table 4. Impact of Age on Morbidity, Mortality, and Survival After Resection With Curative Intent (N = 711)

	Age (years)		P
	≤ 70	> 70	
Morbidity, %			
D1	20.4	31.7	.01
D2	41.1	46.4	NS
Mortality, %			
D1	1.7	7.6	.005
D2	5.9	17.0	.002
Mean survival, years			
D1	6.27	4.43	.0001
D2	6.13	4.73	.009

Abbreviations: D1, limited lymph node dissection group; D2, extended lymph node dissection group; NS, not significant.