lung cancer has a very short span of limited disease, and most of the lesions of this cancer are already local regional disease plus systemic metastasis when diagnosed. At the opposite extreme is gastric cancer. In Japan, more than half of newly diagnosed lesions are T1, early gastric cancers. Advanced lesions of gastric cancer still have only local invasion and regional lymph node metastasis, which can often be cured by surgery alone. Squamous cell cancer of the esophagus would be situated between these two extremes.

Focus on gastric cancer

Table 1 shows the pattern and incidence of metastasis from gastric cancer, according to the tumor depth.[1] Lymph nodes, liver, and peritoneum are the three frequently involved sites. Other sites in the body, such as lung, bone, brain or skin, may have metastasis from gastric cancer, but only at the end of the disease development, at the terminal stage in these patients.

Table 1. Biological behavior of gastric cancer: incidence of metastasis and 5-year survival

Depth	*n*	LN	Liver	Peritoneum	5-Year survival
pT1					
M	1063	3.3	0.0	0.0	93.3
SM	881	17.4	0.1	0.0	88.9
pT2					
MP	436	46.4	1.1	0.5	81.3
SS	325	63.7	3.4	2.2	65.8
pT3					
SE	1232	78.9	6.3	17.8	35.5
pT4					
SI	724	89.8	15.5	41.6	10.1
Overall	4683	47.8	4.5	11.5	60.3

Patients operated on between 1972 and 1991, at the National Cancer Center Hospital (NCCH), including those with exploratory laparotomy: there were 22 non-resected patients, in whom T was unknown

As shown in Table 1, metastasis occurs almost exclusively to lymph nodes until the primary tumor becomes T3. Liver metastasis occurs in just 6% of the patients with T3 tumor, and in 15.5% of those with T4 tumor. Peritoneal metastasis occurs only after the tumor has reached the serosa, becoming a T3 tumor; the incidence remains at less than 20% in T3 tumors. On the other hand, the incidence of lymph node metastasis is rather high, even in the early stage of disease evolution. Even T1 submucosal invasive tumors have nodal metastasis in nearly 20% of cases. If the tumor becomes T2, over 50% of patients have regional lymph node metastasis. If these nodal metastases were to be left behind after surgery, they would metastasize and eventually become systemic disease.

So, if the patients are treated by D2 or more extensive surgery, which is the standard treatment in Japan, local regional recurrence is not common, as shown in Table 2.[1] This means that D2 dissection can provide rather good local control. By far the commonest site of recurrence is the peritoneum, and systemic and hematogenous metastases are rare (just 7% of all treated patients). Therefore, in patients with gastric cancer, local control can lead to a fairly high success rate for cure. Only 28% of patients developed recurrence; thus, over 70% of patients survived without recurrence. If these tumors are treated by very limited surgery, local regional recurrence could be a big problem.

Dr. Gunderson[2] reported the pattern of failure after limited surgery with curative intent at his institute. Fifty-four percent of recurrences occurred only in the gastric bed, and recurrences reached nearly 90% if all those with local regional failure were included regardless of other type of recurrence. This shows the importance of local control for gastric cancer.

In gastric cancer, the lymph nodes are the most important metastatic site. Table 3 shows the topographical pN stage according to the tumor depth.[1] The deeper the tumor, the more frequently lymph nodes are metastatic and the more frequently distant regional nodes become metastatic. If the tumor becomes T3, three-fourths of patients have nodal metastasis. If the tumor remains as T1 or T2, we do not see distant regional lymph node metastasis very often.

Table 2. Primary site of recurrence after ≥D2

Depth	*n*	Recurrence	LN + RF	Peritoneum	Hematogenous (%)
pT1					
M	1063	2	0	0	2 (0.2)
SM	881	18	6	3	9 (1.0)
pT2					
MP	436	45	10	9	26 (5.9)
SS	325	74	15	28	31 (9.5)
pT3					
SE	1232	625	146	330	149 (12.1)
pT4					
SI	724	562	173	283	106 (14.6)
Overall	4683	1326 (28.3%)	330 (7.0%)	635 (13.6%)	323 (6.9%)

Patients operated on between 1972 and 1991, at the NCCH, including those with exploratory laparotomy

A large proportion of patients have N2 disease; even in T2 tumor, over 20% of patients have N2 disease, and in the T3 tumors, over 40% of patients have N2 disease. This means that main target of local control in gastric cancer is lymph node metastasis. There are several grounds for saying that good local control is essential to cure this cancer. First, Professor Siewert reported that R0 resection is by far the most important prognostic factor after curative operation.[3] Second, the results of the Intergroup study (IT-0116) showed that adding irradiation to adjuvant chemotherapy could improve the results of limited surgery alone, which could not be achieved by adjuvant chemotherapy alone.[4] Good local control by radiation, together with chemotherapy, could improve the results of treatment remarkably. The researchers of the Intergroup study also carefully analyzed the prognostic factors in the patients treated in that trial, and found that surgical under-treatment was an independent prognostic factor. This theory can be applied to some other solid cancers as well.

The preferred method of local control depends on the efficacy of treatment other than surgery. If we see a non-Hodgkin's lymphoma in the stomach, we do not operate on the patients now, and chemotherapy alone can often control both the primary site and the metastasis. Of course, chemoradiotherapy does work, too. Regarding squamous cell carcinoma of the esophagus, chemoradiotherapy can often control the primary tumor and the nodal metastasis, although the local recurrence rate is as high as 20%–30% after chemoradiotherapy. For gastric cancer, even chemoradiotherapy can seldom control an advanced primary tumor, but it may well control nodal disease. Based on the results of the IT-0116 study, if gastric cancer is treated by limited surgery plus chemoradiation (CRT), the primary lesion is controlled by the surgery, and micrometastases in lymph nodes are controlled by the chemoradiation. If gastric cancer is treated by D2 surgery, both the primary and these metastases are controlled by surgery.

Table 4 shows a comparison of two studies, the IT-0116 study, and the Japan Clinical Oncology Group (JCOG) 9501 study.[5] The JCOG 9501 study is a trial organized by the Gastric Surgery Division of JCOG to evaluate the role of paraaortic lymph node dissection, which is quite extensive surgery. There are remarkable differences between these two trials: in the IT-0116, surgery was rather limited (D0; very limited resection) in 54% of patients, and D1 surgery was done in 36%, while so-called Japanese-type surgery was done in only 10%. But in the JCOG 9501 study, half of the patients underwent D2 dissection, the standard surgery in Japan. The other half underwent much more extensive surgery (D3 dissection). Regarding adjuvant treatment, those allocated to the test arm in the IT-0116 study underwent 45-Gray radiotherapy together with chemotherapy (5-fluorouracil [5-FU] and leucovorin). In the JCOG 9501 trial, none of the patients underwent adjuvant treatment until they developed recurrence. There was no difference in tumor locations between these two trials, although researchers in the United States always say that they have more proximal tumors than antral tumors. Unlike the pattern of tumor location in the general population, a much larger proportion of patients in this American trial had antral tumors, while more tumors of the body were seen in the Japanese trial. Tumor depth is shown in Table 4: 14 T1, 74 T2, 175 T3, and 18 T4 in the IT-0116 study; and 23 T1, 257

Table 3. Lymph node metastasis according to the depth of tumor invasion

Depth	No.	pN+ (%)	pN0	pN1	pN2 (%)	pN3	pN4
T1							
M	619	14 (2)	605	9	5 (0.8)	0	0
SM	499	89 (18)	410	60	29 (5.8)	0	0
T2							
MP	276	126 (46)	150	74	47 (17)	5	0
SS	207	130 (63)	77	65	57 (28)	3	5
T3							
SE	646	484 (75)	162	171	266 (41)	28	19
T4							
SI	152	121 (80)	31	31	65 (43)	12	13
Total	2399	964 (40)	1435	410	469 (20)	48	37

In gastric cancer, the main target of local control is lymph node metastasis

Table 4. Comparison of the results of IT-0116 and JCOG 9501

	IT-0116	JCOG 9501
Surgery	D0/D1/D2-54%:36%:10%	D2/D3-50%:50%
Adjuvant	Radiation 45 Gy Chemotherapy 5-FU + LV	None
No of patients	281 (Test arm)	523
Tumor location	Antrum, 53%; corpus, 24%; cardia, 21%; multiple, 2%	Lower third, 41%; middle third 39%; upper third, 19%
pT stage (1:2:3:4)	14:74:175:18	23:257:230:13
Treatment-related deaths	3 (1.1%) + Postop.	4 (0.8%)
Survival	3-Year: 50% 5-Year: 42%	5-Year: 71.4 (66.5%–76.3%)

Table 5. Estimated 5-year survival of the IT-0116 patients if they would have undergone D2-3 surgery

IT-0116 patients	NCCH[a] 5-Year survival	Calculated survival proportion	CIH[b] 5-Year survival	Calculated survival proportion
T1, 14	92.2	12.9	96.6	13.5
T2, 74	77.5	57.4	80.6	59.6
T3, 175	47.1	82.4	40.2	70.4
T4, 18	29.9	5.4	17.4	3.1
42%		56.3%		52.2%

[a] Results of National Cancer Center Hospital[6]
[b] Results of Cancer Institute Hospital[7]

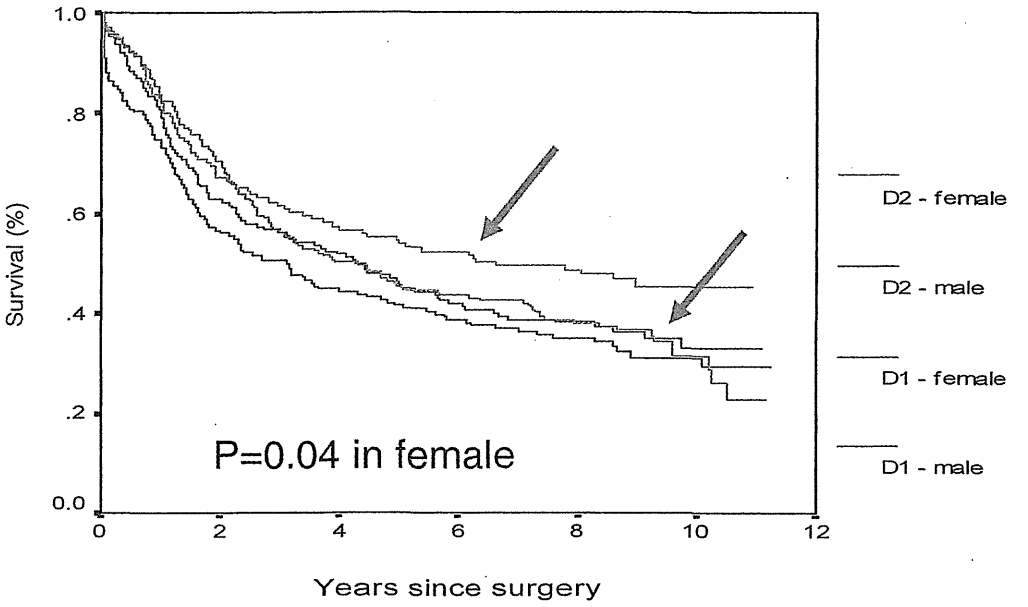

Fig. 1. D1 vs D2 for males and females. *High postoperative mortality did not confound comparison in female patients*

T2, 230 T3, and 13 T4 in the JCOG 9501. As to the treatment-related death rate (TRD), 1.1% was reported in IT-0116, and 0.8% in JCOG 9501. However, if the total population that could be candidates in this trial is considered, the TRD should be higher in IT-0116, because some postoperative deaths that occurred before enrolment in this trial were not counted. The survival results of IT-0116 are 50% at 3 years and 42% at 5 years, while the overall survival rate at 5 years is 71.4% in the JCOG 9501 study, although the observation time is not sufficient. As there is a non-inegligible difference of T-stage distribution between the two trials, this survival comparison is not fair. It is possible, however, to calculate the survival proportion by applying the survival rates of Japanese institutes by pT stage. The hypothetically estimated survival rates are then over 52%, which is about 10% better than the actual survival rate of the patients in the IT-0116 study (Table 5).

The results of the IT-0116 trial are interpreted as follows: (1) D0/1 surgery is proven to be inadequate treatment in terms of local control, (2) the results achieved are worse than the standard level of those treated by D2 surgery, (3) surgical under-treatment clearly undermined survival, (4) whether D0/1 + CRT can be as good as D2 alone should be tested by a RCT, (5) whether CRT after D2 can improve the results of this type of surgery alone is another question. At the same time, another question arose. Why was D2 not better than D1 in the western RCTs?

In fact, the Dutch and Medical Research Council (MRC) trials did not prove the effect of D2 dissection.[8,9] However, the quality of D2 dissection in these trials was questionable, with quite high postoperative mortality with extremely small hospital volume. The TRD rate of D2 was as high as 10% and the quality of postoperative care to avoid operative deaths was very poor, due to the small hospital volume. Not only in these trials but also in several other RCTs in surgery, a high TRD rate offsets the long-term effect of treatment. In the two trials on squamous cell carcinoma of the esophagus reported at the 39th annual meeting of the American Society of Clinical Oncology (ASCO), i.e., the German[10] and French[11] trials, a benefit of surgery after CRT was not seen in long-term survival, with a remarkable difference of the TRD rates between CRT alone versus CRT plus surgery. Based on the experience in these RCTs, we may say that proper D2 dissection is technically demanding surgery, requiring experience and specific postoperative care, and it should be carried out at specialist centers in the west.

In the Dutch trial, D2 started with a handicap of about 6%, within 3 months, but caught up with the curve of D1,

Table 6. Morbidity and mortality after D2 dissection for gastric cancer

Trial	Type	Number of patients	Number of D2 dissections per hospital/year	Mortality	Morbidity	Reference
Hong Kong[12]	RCT	30	7.5	3%	57%	Ann Surg
MRC[7]	RCT	200	1.5	13%	46%	Lancet
Dutch[6]	RCT	331	1.0	10%	43%	Lancet
Italian[13]	Phase II	191	8.0	3%	21%	JCO
Sue-Ling[14]	Retrospective	142	14.2	5%	17%	BMJ
Pacelli[15]	Retrospective	157	15.7	4%	22%	Br J Surg

Table 7. Mortality after major postoperative complications

Complications	Dutch trial (n = 711)		NCCH (1980s) (n = 1197)		P Value
Leakage	19/46	41.3%	12/84	14.3%	0.0005
Distal	9/22	40.1%	2/23	8.7%	0.012
Total	10/24	41.7%	10/60	16.7%	0.0047
Abscess/pancreatic fistula	19/91	20.9%	2/75	2.7%	0.0004

Experience is needed to manage major adverse effects to avoid treatment-related deaths TRD, which occur slightly more often in surgery than in chemotherapy. Hospital volume is a concern

although the difference never reached statistical significance. The hospital mortality for D2 and D1 showed a large difference, at nearly 10% for D2, and 4% for D1. But this difference was seen only in male patients, in whom hospital mortality was 4.2% for D1 versus 14% for D2. There was no difference in mortality between D1 and D2 in female patients. Accordingly, the hazard ratio between D1 and D2 by time for each sex is completely different. In female patients, the hazard ratio is almost constant. The survival curves by procedure by sex are shown in Fig. 1. As we would expect, the survival curves of the female patients do not cross, as typical model curves of survival showing a constant hazard, and the P value is 0.04. We can confirm that high immediate mortality easily offsets the long-term effect of any cancer treatment.

Table 6 shows the relation between the hospital volume and the TRD rates in many trials or consecutive series of D2 dissection for gastric cancer. The Dutch and MRC trials show extremely low numbers of patients treated per year, per hospital, and show extremely high hospital mortality, compared with other reports.

Table 7 shows the mortality after major complications, comparing the results of the Dutch trial and those of the National Cancer Center Hospital (NCCH) in the 1980s.[1] Even in a high-volume hospital, major complications, such as anastomotic leakage or intraabdominal abscess, were not rare. However, in the Dutch trial, over 40% of patients died when they developed anastomotic leak, while only 14% of such patients died in the NCCH. As to mortality after abdominal abscess, a difference of nearly ten times was observed. Experience is needed to manage major adverse effects to avoid TRD, which occurs slightly more often in surgery than in chemotherapy or CRT. In this regard, hospital volume is a concern.

The Japanese perspective of the role of D2 dissection in multidisciplinary treatment for advanced gastric carcinoma can be summarized as follows. The superiority of D2 has not been proven by RCTs. But all RCTs so far have a crucial problem in regard to the quality of treatment given in the D2 arm. D2 is not a dangerous procedure if it is done by specialists in large-volume hospitals. D0/1 plus CRT is better than D0/1 alone, but it may be worse than D2 alone. The survival benefit of CRT after D2 is an open question. Establishing standard adjuvant chemotherapy after D2 is a more urgent clinical issue. There is no reason to abandon D2 gastrectomy for curable gastric cancer in Japan.

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Gastric cancer surgery in the elderly without operative mortality

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Abstract

Background: Surgeons are increasingly being faced with the problem of treating elder gastric carcinoma patients. Recent improvements in the techniques for preoperative diagnosis and perioperative management have been made. The purpose of this study was to elucidate whether these improvements have produced a decrease in postoperative complications and mortality and resulted in a better clinical outcome.

Methods: Between 1993 and 2003, 141 elderly patients (aged 80 years or above) with gastric cancer underwent operation under the care of dedicated staff surgeons. The results of treatment were analysed.

Results: 52 (36.9%) patients had a diagnosis of gastric cancer during a health-check. Only 19 patients (13.5%) had no preoperative risk factors. The ASA score was II in 80%. Approximately 35% of the patients had early gastric cancer. Nodal metastasis was observed in 56% of the patients. The proportion of stage I patients was 40%.

Resection rate was 95.7%. Reduced nodal dissection (<D2) was common (47%). The surgery-related complication rate was as low as 8% and the number of operation-related deaths was zero. The 3 (5) year survival rates were 59.0 (48.2–69.8), 48.8 (36.0–61.6) % overall, and 70.0 (58.3–81.7), 56.6 (41.4–71.8) % after curative resection. The 3 (5) year survival rate was 80.3 (63.9–96.7), 73.6 (54.0–93.2) % for early gastric cancer.

Conclusions: Gastrectomy for elder patients can be carried out very safely by specialists with an excellent patient prognosis.

Keywords: Gastric carcinoma; The elderly

1. Introduction

The Japanese population is ageing. Life-expectancy is currently 78.36 years for men and 85.33 years for women [1]. Despite a decrease in the incidence of gastric carcinoma, the number of patients aged 80 years and older (elder patients) with this disease is increasing. We previously reported the outcome of 112 elderly gastric cancer patients treated between 1971 and 1990 and showed gastric cancer surgery in elderly patients without co-morbidities was safe [2]. Since then, improvements have been made with regard to socioeconomic conditions, medical progress for perioperative care and operative apparatus, and preventive medicine. The purpose of this study was to elucidate whether these improvements have produced a decrease in postoperative complications and mortality, and resulted in a better clinical outcome.

2. Patients and methods

Out of 4395 patients with gastric adenocarcinoma who underwent laparotomy under our care (5 dedicated staffs, specialists in gastric cancer) between 1993 and 2003, 141 patients (3.2%) were 80 years of age and older. Since 2001, we have recorded every patient with gastric carcinoma who has visited our hospital. One hundred and seventy-two elderly patients with gastric carcinoma visited our hospital between 2001 and 2003. Sixty patients (35%) were operated upon by us and other 112 patients (65%) were treated either by

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endoscopic mucosal resection for early gastric cancer or best-supportive care for advanced tumours.

Curative operations were our aim, even in the elderly patients. However, we did try to perform limited dissection and to avoid total gastrectomy as long as curability was preserved [2].

Surgical specimens were examined and scored according to the Japanese Classification of Gastric Carcinoma [3]. Medical records were reviewed for preoperative medical conditions, further histological, and follow-up data. The latest follow-up was July 24, 2004. The conclusive physical status of patients and their surgical risks were classified according to the American Society of Anesthesiology classification of physical status (ASA class I–V). Survival rate was calculated using the Kaplan-Meier method with 95% Confidence Limits (CL).

3. Results

3.1. Patients' characteristics

The median age was 83 years (80–94 years). There were 95 male and 46 female patients. Eighty-nine patients (63.1%) visited hospital with symptoms. However, 52 (36.9%) patients had a diagnosis of gastric cancer during a health-check. Twenty patients (14.2%) were treated for other cancers before the diagnosis of gastric cancer. Median Body Mass Index (BMI) was 21.4 (11.7–32.5) Kg/m^2: BMI <20 ($n=50$), $20 \leq$ BMI <24 ($n=62$), BMI ≥ 24 ($n=29$).

3.2. Preoperative morbidity (Table 1)

Table 1 Nineteen patients (13.5%) had no preoperative risk factors. Over 20% of the elderly patients had hypoalbuminaemia (<35g/l), and 16% had anaemia (haemoglobin <100 g/l). Electrocardiogram (ECG) abnormalities were detected in 55 patients (39.0%). Master's two-step exercise test was positive in 18 patients (12.8%). Abnormalities detected by echocardiography were mild in all cases. More than 35% of patients had abnormal respiratory function test. Fifty-seven patients (40.4%) had chronic diseases such as hypertension (22.7%), ischaemic heart disease (3.5%), and diabetes mellitus (9.9%). The ASA score was either II or III. in every patient.

3.3. Extent of tumour spread (Table 2)

Table 2 Approximately 35% of the patients had early gastric cancer. Nodal metastasis was observed in 56% of the patients. Distant metastasis was observed in liver up and peritoneum. We did not operate upon patients with

Table 1
Preoperative co-morbidities

	No. of patients	(%)
Hypoalbuminaemia Alb <35g/l	30	(21.3)
Anaemia Hgb <100 g/l	22	(15.6)
Abnormal heart evaluation		
ECG abnormalities	55	(39.0)
Master's two-step test-positive	18	(12.8)
Echocardiography		
Valve diseases	22	(15.6)
Low ejection fraction	3	(2.1)
Respiratory function test abnormal	53	(37.6)
Liver dysfunction	0	(0)
Creatinine clearance < 0.83 ml/s	21	(14.9)
Hypertension	32	(22.7)
Ischaemic heart disease	5	(3.5)
Abdominal aorta aneurysm	3	(2.1)
Diabetes Mellitus	14	(9.9)
ASA score = III	28	(19.9)

ASA, see text for definition.

Table 2
Extent of tumour spread

	No. of patients	(%)
Depth of tumour invasion		
T1	50	(35.5)
T2	28	(19.9)
T3	49	(34.8)
T4	14	(9.9)
Nodal involvement		
N0	62	(44.0)
N1	34	(24.1)
N2	33	(23.4)
N3	12	(8.5)
Peritoneal seeding		
P0	134	(95.0)
P1	7	(5.0)
Liver metastasis		
H0	137	(97.2)
H1	4	(2.8)
Other distant metastasis		
M0	141	(100)
M1	0	(0)
Lavage cytology		
CY0	125	(88.7)
CY1	16	(11.3)
Stages		
IA	44	(31.2)
IB	13	(9.2)
II	21	(14.9)
IIIA	20	(14.2)
IIIB	13	(9.2)
IV	30	(21.3)

Table 3
Surgical procedures

Type of operation	No. of patients	(%)
Total	44	(31.2)
Distal	81	(57.4)
Other resection	10	(7.1)
Bypass or exploration	6	(4.3)
Extent of dissection		
<D2	63	(46.7)
≥D2	72	(53.3)
Curability		
Curative resection (R0)	107	(75.9)
Non-curative resection (R≥1)	28	(19.9)
Bypass and exploration	6	(4.3)
ICU stay		
Elective	8	(5.7)
Emergency	1	(0.7)
No	132	(93.6)
Re-operation	2	(1.4)
Operation time (min)	194 (30–357) minutes	
Blood loss (ml)	310 (15–2572) ml	
Postoperative hospital stay (days)	17 (10–79) days	

Other resections includes surgical mucosectomy, wedge resection, and proximal gastrectomy.
Elective intensive care unit (ICU) stay was decided before the operation when the patients had severe co-morbidities.

other distant metastases. The predominant stage was stage I, followed by stages III, IV, and II.

3.4. Surgical procedures (Table 3)

Table 3 More than half of the patients underwent a distal gastrectomy. 53.3% of patients had resection with D2 lymph node dissection. Resection rate was 95.7% (135/141). One hundred and seven patients underwent operation with curative intent. The operation for the patients with positive lavage cytology was regarded as non-curative. The median operation time was 194 min Median blood loss was 310 ml. Postoperative hospital stay period was 17 days.

3.5. Early results (Table 4)

Table 4 Postoperative morbidity rate was 27.0% (38/141) overall, 28.0% (30/107) for the operations with curative intent, and 23.5% (8/34) for the palliative operations. There was no difference between curative and palliative operations. Surgery-related complications were less common. Pancreatic-related abscess was the most common. Pneumonia, regardless of the existence of aspiration, was most frequent postoperative complication. There was only one patient, who required intensive care unit (ICU) management due to postoperative complications.

Table 4
Postoperative complications

	No. of patients	(%)
Surgery-related		
Pancreatic-related abscess	10	(7.1)
Anastomotic leakage	1	(0.7)
Bleeding	0	(0)
Others	0	(0)
Non-surgery-related		
Pneumonia	13	(9.2)
Pulmonary embolism	0	(0)
Cardiac	5	(3.5)
Liver	2	(1.4)
Delirium	4	(2.8)
Empty disturbance	5	(3.5)
Others	2	(1.4)
Overall	38	(27.0)

The operation-related death was zero. The hospital mortality rate was also zero.

3.6. Survival

Fifty-nine patients died during the follow-up period. Forty-three of the deaths were related to gastric cancer. Twelve of the patients died of other causes (20.3%). Six were due to other malignancies (10.1%), six were due to other diseases (10.1%). Four occurred for unknown reasons (6.8%). Twenty-nine patients died within one year of their operation.

The 3-year survival rates were 59.0 (48.2–69.8)% for the whole population, 70.0 (58.3–81.7)% after curative resection and 16.1 (0–33.7)% after non-curative operations. After operations with curative intent, the 3-year survival rate was 80.3 (63.9–96.7)% for early gastric cancer, and 61.8 (45.7–77.9)% for advanced gastric cancer. The 5-year survival rates were 48.8 (36.0–61.6)% for the whole population, 56.6 (41.4–71.8)% after curative resection and 16.1 (0–33.7)% after non-curative operations. After operations with curative intent, the 5-year survival rate was 73.6 (54.0–93.2)% for early gastric cancer, and 41.7 (20.0–63.4)% for advanced gastric cancer.

4. Discussion

The Japanese population is ageing. However, they are still educated enough to be interested in health-checks for gastric cancer. A better public education of the elderly has increased cancer awareness, and thereby decreased the risk of developing symptoms, cases that are traditionally associated with a poor prognosis.

The increased age of the population is accompanied by an increase in age-related diseases. The preoperative surgical risk is often high, as has been reported in

Refs. [2,4,5]. However, the grade of complications were usually not severe in our series. Although we observed a high incidence of hypoalubuminaemia and low BMI, nutritional support via intravenous hyperalimentation was not essential before the operation. The ASA score was II in 80% and they did not have severe complications. They were only classified as score II because of their age i.e. 80 years and older.

The number of patients with stage I disease was 40% and less than that of previous study reported in Ref. [2]. Widespread use of endoscopic treatment has contributed to a decrease in gastrectomy for patients with early gastric cancer [6].

The resection rate of gastric carcinoma in the elderly has reached 95.7%, due to the early detection of disease and the ability to perform extensive resections, as well as the enormous improvements in preoperative staging.

Studies from other countries have reported high morbidity and mortality rates [4,5], especially in emergency cases. However, surgery-related complications were decreased in our study compared with those in previous series and the operation-related death rate was zero.

We previously reported that total gastrectomy and extended nodal dissection were both associated with a high operation-related death rate, especially in patients with preoperative morbidity. Therefore, curative operations were our aim, but at the same time, making efforts to perform limited dissections and to avoid total gastrectomy whilst preserving curability. The proportions of extended dissections was as low as 53% in our series.

There were very few obese patients in our series and these cases have higher morbidity and mortality rates [7]. In addition, the grade of preoperative co-morbidities was not severe in most of our patients. Our operations were all elective. In our institution, operation for gastric carcinoma is carried out only by specialists since 1993. Our stapling technique has improved and reduced the anastomotic leak rate [8]. Abscesses were common in the past after total gastrectomy with splenectomy. However, management of the abscess has been standardised as a result of a careful evaluation of past cases [9]. These factors have contributed to a decrease in our morbidity and mortality rates.

Gastrectomy can be carried out very safely in elderly patients by specialists. The survival rate was better than in the previous series. Life-expectancy for the general population of 80 years and older has increased and is now 8.26 years for males and 11.04 years for females. Therefore, death by other causes has decreased in this study. The 3(5)-year survival rate for early gastric cancer was excellent; 80.3 (73.6)%. Overall, 3(5)-year survival rates for the Japanese general population are 79 (61)%. There was no significant difference in survival between the early gastric cancer group and the general population.

Studies from the literature have reported that even patients with early gastric cancer usually die within 3 years without treatment [10]. Achievement of a curative R0 resection is always important, even for elderly patients.

Survival after non-curative resection is very poor. There is seldom an indication for a palliative distal or total gastrectomy. Preoperative staging, including laparoscopic exploration, is important to find candidates for surgical resection.

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Original article

Pancreaticoduodenectomy for advanced gastric cancer

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Abstract

Background. **Although pancreaticoduodenectomy has been rarely performed for gastric caner because of frequent morbidity and mortality, some favorable results after this procedure have been reported recently. Our objective was to present our data that might aid in the selection of patients to undergo this procedure.**

Methods. **Between 1970 and 2001, 23 patients who had pancreaticoduodenectomy for gastric cancer with tumor invading the pancreatic head were identified, and they were the subjects of this study. Clinical, operative, and pathological data, and morbidity and mortality rates were collected and analyzed. Survival outcome was also calculated and analyzed.**

Results. **Five patients underwent this procedure for disease in the gastric remnant, 18 undergoing the procedure for primary tumors. Median operating time was 8 h (range, 6–13 h), and median blood loss was 1600 ml (range, 700–16 000 ml). Regarding extent of gastrectomy, all patients with primary cancer ($n = 18$) underwent a distal gastrectomy and patients with disease in the gastric remnant ($n = 5$) underwent a completion gastrectomy. Incurable factors, including paraaortic lymph node metastasis, positive lavage cytology, or peritoneal dissemination were found in 8 patients. The postoperative morbidity rate was 73.9%; however, operation-related death was zero. The overall 5-year survival rate was 34.3%. The 5-year survival rate of the 8 patients with incurable factors was 0%, while that of the 15 patients without incurable factors was 47.4%.**

Conclusion. **If an R0 resection can be achieved by pancreaticoduodenectomy, this procedure should be performed for patients with tumor invading the pancreatic head. Patients with incurable factors should not be considered for pancreaticoduodenectomy.**

Key words Gastric cancer · Pancreaticoduodenectomy · Combined resection of adjacent organs

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Introduction

Complete removal of all evaluable disease, i.e., R0 resection, is vital to a successful outcome in gastric cancer treatment. Extended surgery is occasionally required for advanced gastric cancer with infiltration of adjacent organs to achieve complete tumor clearance. For locally advanced gastric cancer with infiltration of the pancreatic head or duodenum, pancreaticoduodenectomy (PD) is required. However, this procedure has been rarely performed because of substantial morbidity and mortality [1]. Prior to the 1990s, few reports regarding PD for gastric cancer had been published [2]. Only Kishimoto et al. [3] and Scott et al. [4] referred to a long survivor after this procedure in their reports about gastrectomy with combined resection. Recently, with current advances in operative techniques and in nutritional support, some favorable results of the patients undergoing this procedure have been reported [5–7]. However, only a few reports with a large number of cases have been published so far. In the current study, we present our data that might aid in the selection of patients to consider who should undergo this procedure.

Subjects and methods

A retrospective review of our prospective database, spanning from 1970 to 2001 and containing 9349 patients, identified 195 (2.1%) who had locally advanced cancer with macroscopically suspected infiltration of the pancreatic head. We included patients with pancreatic head invasion from metastatic lymph nodes, and excluded type 4, linitis plastica cancer. Of the 195 patients identified, 23 underwent PD with presumed curative intent, and they were the subjects of this study.

In these 23 patients, clinical data, including age, sex, symptoms, and primary tumor or tumor in the gastric remnant, were collected and analyzed, using the appro-

Table 1. Patients undergoing pancreaticoduodenectomy

		Disease	Stage	pT	pN	P	CY	Adjuvant Chemo.	Combined resection	Recurrence	FUT (months)	Status
1	63/F	Primary	IV	4	1	0	0	−	Liver	N	13	DOD
2	42/M	Primary	IIIB	3	1	0	ND	−		—	157	DOC
3	64/M	Primary	IIIB	2	2	0	0	−		—	182	NED
4	67/M	Primary	IV	3	2	0	ND	−		—	87	DOC
5	76/M	Primary	IV	4	3	0	0	−	Colon	Unclear	4	DOD
6	67/M	Primary	IIIB	4	0	0	0	+		—	26	DOC
7	65/M	Primary	IV	4	3	0	1	+		N	6	DOD
8	74/F	Primary	IV	2	3	0	0	−	Colon	H	34	AWD
9	70/M	Primary	IV	4	2	0	0	−	Colon	N, H	14	DOD
10	62/M	Primary	II	2	0	0	0	−	Colon	—	52	NED
11	65/M	Primary	IV	4	2	0	0	−		N	36	AWD
12	65/F	Primary	IV	4	2	0	0	−		N, H, spleen	12	DOD
13	58/M	Primary	IV	4	3	0	0	−	Colon	N	6	DOD
14	60/M	Primary	IIIB	2	2	0	0	−	Colon	—	12	NED
15	64/M	Primary	IV	4	2	1	1	−	Colon	Unclear	19	DOD
16	51/F	Primary	IIIB	2	2	0	0	−		H	11	DOD
17	61/M	Primary	IV	4	1	0	ND	−		H	4	DOD
18	70/M	Primary	IV	4	3	0	1	−		N, lung	4	DOD
19	60/M	Remnant	IV	4	2	1	1	−		N	13	DOD
20	57/M	Remnant	IV	4	1	0	0	−	Liver, colon	N, H	26	DOD
21	64/F	Remnant	IIIB	4	0	0	0	−		N	64	DOD
22	47/M	Remnant	IV	4	3	0	0	−		N	17	DOD
23	60/M	Remnant	IIIB	4	0	0	0	−	Colon	P	4	AWD

Primary, Primary tumor; remnant, tumor of the gastric remnant; P, peritoneal dissemination; CY, lavage cytology; ND, not done; N, lymph node; H, liver; FUT, follow-up time; NED, no evidence of disease; AWD, alive with disease; DOC, dead of other cause; DOD, dead of disease; unclear, site of recurrence unclear

priate nonparametric tests. Operative data, including operating time, blood loss, hospital stay, extent of gastrectomy, extent of lymphadenectomy, and combined resection with PD, were also evaluated. Pathological data, including pT, pN stage, site of tumor, and incurable factors, such as paraaortic lymph node metastasis (pN3), peritoneal dissemination, and positive lavage cytology, were analyzed according to the Japanese classification. Perioperative morbidity and mortality were also investigated.

The survival data of the 195 patients with tumors invading the pancreatic head, including the 23 PD patients, were calculated by the Kaplan-Meier method and analyzed by the log-rank method.

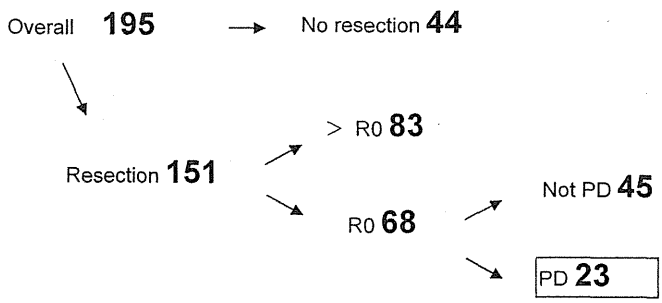

Fig. 1. Patients with tumors invading the pancreatic head. *No resection*, patients undergoing only exploration or bypass operation. *Not PD*, patients undergoing R0 resection, but with a lesser pancreatic resection than pancreaticoduodenectomy (*PD*)

Results

Demographics

Of the 195 patients with tumors invading the pancreatic head, 151 (77%) underwent resection, and the remaining 44 underwent only an exploration or a bypass surgery. In 68 patients, an R0 resection was carried out. In 45 patients with R0 resections, a lesser pancreatic resection (not PD) was performed because of a slight degree of tumor infiltration. The remaining 23 patients (12%) underwent PD (Fig. 1).

In the 23 patients undergoing PD, the median age at the time of resection was 64 years (range, 42–76 years), with a male-to-female ratio of 18:5 (Table 1). Twenty-one patients (91.3%) were symptomatic, most commonly with abdominal pain ($n = 13$) and symptoms due to obstruction, including fullness and vomiting ($n = 11$).

Eighteen patients underwent the PD procedure for primary cancer and 5 for gastric remnant cancer following previous Billroth I gastrectomy. Of the 5 patients with gastric remnant cancer, 4 had undergone distal partial gastrectomy for gastric cancer. Two of these

patients had early cancers, and the other 2 had advanced disease. The disease-free intervals were 1.5 and 6 years for those with advanced cancers and 8 and 10 years in those with early cancers. The fifth patient had had a partial gastrectomy for a benign gastric ulcer 30 years previously.

Operative data

The median operating time for PD was 8h (range, 6–13h), with a blood loss of 1600ml (700–16000ml). The median length of postoperative hospital stay was 37 days (range, 25–92 days). Regarding extent of gastrectomy, patients with primary cancer ($n = 18$) underwent a distal gastrectomy and those with gastric remnant cancer ($n = 5$) underwent a completion gastrectomy. As to extent of lymph node dissection, 14 patients underwent D2 lymphadenectomy and 9 underwent D3. In 9 patients, a combined resection of the colon was performed because of direct infiltration of the mesocolon (Table 1). Two patients underwent a partial hepatectomy because of a direct invasion of the liver. Modified Child's method was selected for a reconstruction for all patients. Two patients received postoperative adjuvant chemotherapy of 5-fluoruracil (5-FU) after surgery.

Pathology

Resection specimens from all patients revealed adenocarcinoma of gastric origin. In 7 patients, infiltration of the pancreatic head could not be confirmed histopathologically. Regarding site of tumor, 18 primary tumors involved the antrum, and 11 of these tumors extended into the duodenum.

Incurable factors, including pN3, peritoneal dissemination, and positive lavage cytology were found in eight patients (Table 1). No patient in this series had a visceral metastasis. In 6 patients, pN3 was found. These patients had been considered as negative for pN3 intraoperatively, but the finding was changed to positive by pathological examination postoperatively. Of these 6 patients, 2 also had positive lavage cytology. Two patients had positive lavage cytology and peritoneal dissemination synchronously; the peritoneal dissemination was a single nodule that was removed easily at operation.

Seventeen patients developed recurrences. The most common recurrence sites were nodal, in 11 patients, followed by liver, in 6; peritoneum in 1; lung in 1, spleen in 1, and unclear, in 2.

Morbidity and mortality

Postoperative complications were seen in 17 patients (73.9%; Table 2). Pancreatic fistula was the most common. All patients who developed this complication recovered, after receiving drainage and continuous irrigation, using double-lumen drainage tubes. No operation-related death occurred in this series.

Regarding the long-term postoperative morbidity, body weight at 12 months was maintained within 10% of the preoperative weight in all patients who lived for more than 1 year. Serum albumin levels were not decreased. However, two patients who underwent PD with completion gastrectomy required total parenteral nutrition (TPN) at home, for 1 and 3 years, respectively, after discharge from hospital, because of malnutrition. Postoperative pancreatic endocrine function was adequate in all patients, but three patients required pancreatic exocrine enzyme support postoperatively.

Table 2. Postoperative morbidity

	n
Postoperative morbidity	17 (73.9%)
Pancreatic fistula	10 (43.5%)
Abdominal abscess	3 (13.0%)
Anastomotic or jejunal stenosis	3 (13.0%)
Cholangitic infection	3 (13.0%)
Anastomotic leakage	2 (8.7%)

Table 3. Survival of patients with tumor invading the pancreatic head

	n	Median survival (months)	5-Year survival rate (%)
Overall	195	10	13.6
No resection	44	7	0
Resection	151	12	17.7
>R0	83	8	7.9
R0	68	21	29.3
Not PD	45	22	28.1
PD	23	17	34.3

No resection, Patients who underwent only exploration or bypass operation; not PD, patients who underwent R0 resection but received a lesser pancreatic resection than PD

Survival

In the 195 patients with tumors invading the pancreatic head, the 5-year survival rate was 13.6%. Of these 195 patients, the 68 patients who underwent an R0 resection showed a better survival outcome, with a 5-year survival of 29.3%. In patients who had R0 resections, there was no significant difference in survival between patients who underwent PD and those not receiving PD (Table 3).

In the 23 PD patients, the median follow-up time was 13 months (range, 4–182 months). The status of the

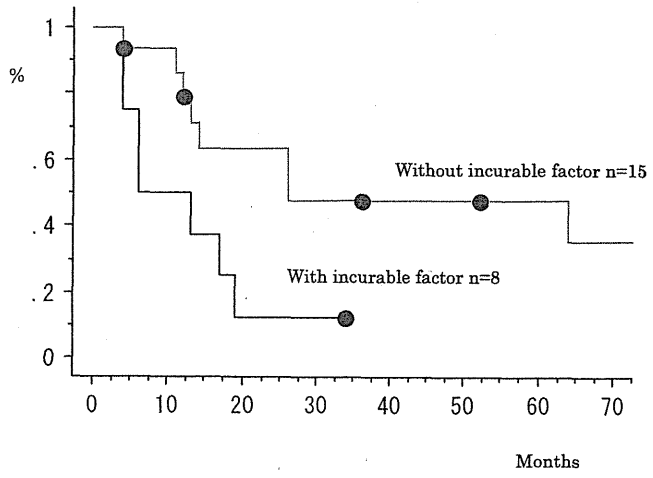

Fig. 2. Survival curves of patients undergoing pancreaticoduodenectomy (*PD*). The overall 5-year survival rate and the median survival of the 8 patients with incurable factors were 0% and 6 months, respectively, and these values in the 15 patients without incurable factors were 47.4% and 26 months ($P = 0.035$)

patients was as follows: no evidence of disease, 3; alive with disease, 3; dead of other causes, 3; and dead of disease, 14. The overall 5-year survival rate was 34.3%. The 5-year survival rate and the median survival of the 8 patients with incurable factors (pN3, positive lavage cytology, and peritoneal dissemination) were 0% and 6 months respectively, while these values in the 15 patients without incurable factors were 47.4% and 26 months (Fig. 2). Four patients have survived for more than 5 years.

Discussion

In our data, of 195 patients with tumors invading the pancreatic head, 23 (12%) underwent PD. This procedure has been rarely performed because of high morbidity and mortality rates. Prior to the 1990s, there had been only a few reports about this procedure [2–4]. Recently, with current advances in operative techniques, nutritional support, and antibiotics, some favorable results have been reported [5–11]. Ohashi [9] reported a large number of patients (145) undergoing this procedure. The 5-year survival rate of patients undergoing PD in that study was 6%, and it was approximately equal to the result for patients undergoing more than R0 resection in our data. Thus, it is inferred that Ohashi's subjects included patients with far-advanced tumors that could not be removed by this procedure. With proper indications, PD could account for 10% of surgeries for tumors invading the pancreatic head, and the number of patients who would have this procedure would be around 30, even at a large institution.

In our study, tumor infiltration of the pancreatic head could not be confirmed in 7 patients (30%) histopathologically. Such patients, theoretically, could have avoided this procedure; however, inconsistency between macroscopic and microscopic findings of infiltration has been reported to be 30%–50%, often because of inflammatory reactions surrounding the tumor [8,12]. Even if the latest diagnostic modalities, such as computed tomography (CT), magnetic resonance imaging (MRI), and endoscopic ultrasound (EUS) are used, it is very difficult to distinguish between inflammatory reactions and tumor infiltration before operation. Intraoperative ultrasound could be more helpful than these modalities, but it was not used in any patients in the present series. It seems that inconsistency at a level of around 30% is unavoidable at present.

Morbidity after PD was in Ohashi's study [9] 51.6% and 37.8% in that of Shchepotin et al. [11]. Regarding mortality, these authors reported rates of 6.3%, and 10.8%, respectively. Buchholtz et al. [1] recommended that PD should not be performed for gastric cancer because of an unacceptable risk, with no greater degree of palliation. The morbidity rate in our series (73.9%) was higher than the rates in these previous reports [9,11], to be sure. However, the operative mortality rate was 0% and all surviving patients could resume a regular life. Pancreatic fistula was the most common complication in this series. This is critical, as it may lead to intraabdominal abscess and rupture of arterial aneurysm. This complication was diagnosed by the detection of infectious drain discharge with a high concentration of amylase (>10000IU/l). For the early detection of pancreatic fistula, the concentration of amylase in the drain discharge is checked routinely after PD. When pancreatic fistula has developed, continuous drainage is performed, initially. If there is infection, continuous irrigation, using double-lumen drainage tubes, is done. To achieve better control of this complication, the medical staff including not only the surgeon but also nursing staff, have to be skilled at careful drain management. Therefore, this procedure should be performed only at institutions where PD for pancreatic cancer is frequently performed.

No patient in our series developed diabetes mellitus after PD, and only three required pancreatic exocrine enzyme support postoperatively. However, after PD with completion gastrectomy, two patients required TPN at home for a long period because of malnutrition. Total gastrectomy combined with PD should be considered very carefully, as nutritional problems may be severe.

The overall prognosis of patients with tumors invading the pancreatic head was poor; however the 5-year survival rate of patients undergoing R0 resection was about 30% in this series. In the patients with R0 resec-

tions, there was no significant difference in survival between those requiring PD and those not requiring PD. Thus, to achieve R0 resection is an important objective, irrespective of whether or not PD is performed.

Ajisaka et al. [5] and Shchepotin et al. [11] reported that the 5-year survival rates of patients undergoing PD were 35% and 17%, respectively. In a study of 26 patients undergoing PD combined with right hemicolectomy, Yonemura et al. [10] reported that the 5-year survival rate of 13 patients with tumors infiltrating the pancreatic head was 55%. In our series, the 5-year survival rate for such patients was 34.3%. In PD patients without incurable factors, the 5-year survival rate was higher, at 47%, and 4 patients have survived for more than 5 years. Careful application of the PD procedure can achieve improved survival outcome. Kodama et al. [13] and Habu et al. [14] mentioned that a small amount of peritoneal dissemination and limited liver metastasis, respectively, were not contraindications for PD. However, most patients in the present series who had incurable factors died of the disease soon after operation. Incurable factors, such as pN3, positive lavage cytology, peritoneal dissemination, and visceral metastasis, should be regarded as a contraindication for PD.

In summary, the results after PD for patients with advanced gastric cancer with tumors invading the pancreatic head were acceptable from the aspects of morbidity, mortality, and survival benefit. If an R0 resection can be achieved by PD in such patients, this procedure should be performed. Patients with incurable factors should not be considered for PD. The combination of PD and total gastrectomy should be considered with caution.

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Mitsuru Sasako

Clinical trials of surgical treatment of malignant diseases

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Abstract The Dutch Gastric Cancer Study Group Trial was the first clinical phase III trial to be carried out in the field of cancer surgery. In spite of the excellent quality of the trial, it was heavily criticized for the poor quality of the treatment itself. Actually, the hospital mortality after the new surgical treatment (D2 lymph node dissection for gastric cancer) was unacceptably high. In surgical trials, special attention should be paid to quality issues specific to surgery. The first and the most important issue is the quality of treatment given. Reproducibility, homogeneity, and verifiability are the greatest problems in surgical trials. There are also some patient factors. If the patient is old, or fragile, or obese, the results of the surgical treatment can easily be affected by these factors. The surgeon can also be a prognostic factor, especially in complicated procedures or those requiring experience and training. Experience, including postoperative care, and dexterity affect the results. If surgeons do not know how to manage complications, mortality becomes very high. Because blinding is impossible in surgical trials, the treatment may easily be affected by personal preference or prejudice. To minimize the influence of these hampering factors, the procedures should be defined in as detailed a way as possible. If pretrial training or a feasibility study (phase II) is needed, it should be carried out properly for the patients' sake. An excellent design and excellent statistical analysis cannot lead to meaningful results if the quality of treatment is poor. Nonsense in, nonsense out.

Key words Clinical trials of surgical treatment · Quality assurance of treatment · Gastric cancer · Lymph node dissection

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Quality control in the Dutch Gastric Cancer trial

The Dutch Gastric Cancer Study Group Trial was the first well-designed, large-sized, randomized clinical trial (RCT) comparing the surgical procedures in cancer treatment (Fig. 1). In this trial, randomization was carried out before surgery, because the quality controller of the surgery, who usually came from outside the hospital, should be in the operation theater at every D2 dissection. So the group randomized patients before operation, based on the clinical staging, but they expected that some of these patients, about 30% of them, might have peritoneal seeding, and the operation would turn out to be non-curative in such patients. The estimated survival rates of the D1 and D2 surgery arms were 20% and 32%, respectively, but with these non-curative cases, the rates were 14% and 21% for D1 and D2, respectively in all randomised patients. The projected sample size was 531 in each arm.[1]

Not following the principles of phase III clinical trials, even the first patient in this RCT was randomized. When this trial started, only one Dutch surgeon knew what a D2 dissection was and had some experience of carrying out D2 gastrectomy. Although none of the other surgeons involved had ever had experience of D2 gastrectomy, they did not plan any feasibility study before starting a phase III study. Instead, they invited the author (M.S.) to carry out D2 dissections and to teach them how to do it. Therefore, they could randomize the first patient in whom he carried out a D2 dissection for the Dutch surgeons. Inviting a surgeon who knows well the new treatment seemed to be a good option and was much better than letting surgeons do a new treatment after just looking at a videotape of the procedure. However, the tutor could not stay there to participate in all D2 surgery during the entire period of the trial. Therefore, in just 4 months he had to teach them how to carry out the procedure. Surgery of this type is not easy to learn without doing it oneself. It was obvious that he could not teach all the participating surgeons of about 80 hospitals. This length of time was not sufficient to teach even the 12 quality controllers of the D2 surgery.[2] A feasibility study or intensive

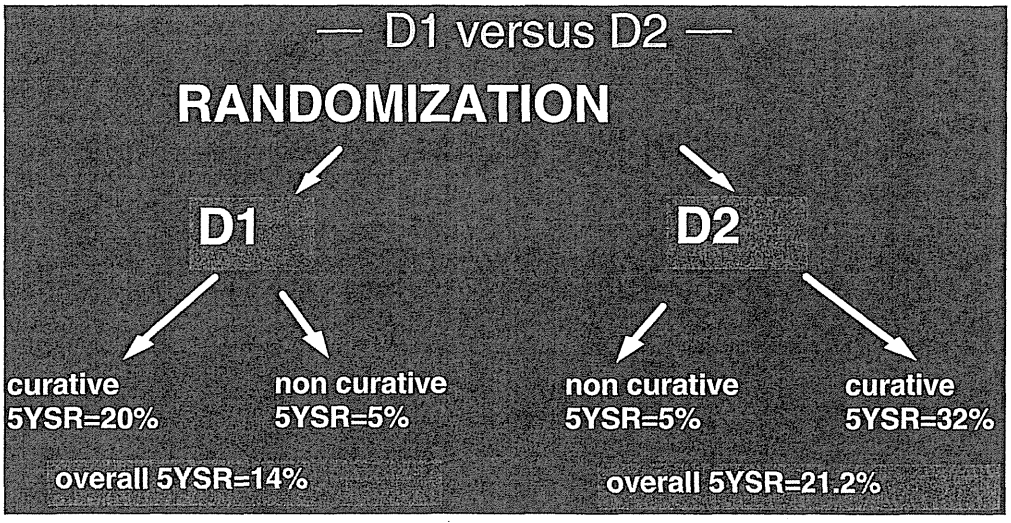


Fig. 1. Dutch trial on lymphadenectomy for gastric cancer.[1] Alpha = 0.05, power = 0.90, 531 patients in each arm requested; *5YSR*, 5-year survival rate

Table 1. Morbidity and mortality after D2 dissection for gastric cancer

Trial	Type	Number of patients	Number of patients per hospital/year	Mortality	Morbidity
Hong Kong[4]	RCT	30	7.5	3%	57%
MRC[5]	RCT	200	1.5	13%	46%
Dutch[1]	RCT	331	1.0	10%	43%
Italian[6]	P-II	191	8.0	3%	21%
Sue-Ling et al.[7]	Retro	142	14.2	5%	17%
Pacelli et al.[8]	Retro	157	15.7	4%	22%

pretrial training should have been carried out. From the scientific and ethical points of view, this kind of setting for a phase III trial of a new surgical technique is not allowed anymore.

The author's major task in this surgical trial was to teach the surgeons how to do a D2 gastrectomy. He himself did 27 operations and instructed the Dutch surgeons as the first assistant in operations for six patients. He also gave many lectures, using videotapes of this operation; the organizers distributed a videotape of the D2 operation on a Dutch patient, which was filmed during this period of the trial, and also distributed a booklet with detailed color photographs showing the anatomy and the technique. This is all that we did for teaching. However, this was not good enough for many of the quality controllers to master the technique sufficiently. Actually, in spite of all the efforts, the morbidity and mortality of this trial was shockingly high for the organizers. Postoperative hospital deaths reached nearly 10% in the D2 arm, much higher than in the D1 arm. This was something unexpected by them before they started this trial. Retrospectively, they should have stopped this trial much earlier and gone back to the feasibility study for the sake of the patients.

Causes of mortality and hospital volume

Theoretically, factors which may influence the morbidity and mortality after this type of surgery are patient factors, tumor factors, operative procedures, and hospital and surgeon factors. Obviously, older patients and obese patients may have more morbidities. But, unexpectedly, sex actually influenced the mortality in this trial very much. And, of course, so did tumor location and histology, the procedures, lymph node dissection, the type of gastrectomy (total or distal), and combined organ resection. Postoperative hospital mortality after D2 in women was as low as that for D1 dissection, but that in male patients reached 14%, or three times higher than that for D1.[3]

Table 1 shows the postoperative hospital mortalities after D2 dissection in various reports.[1,4–8] In the Dutch trial and the MRC (Medical Research Council) trial (British trial), each hospital had very small numbers of cases annually (hospital volume). These two trials had smaller hospital volumes and much higher hospital mortality than in other reports. With such a limited case load, learning how to manage these complications was almost impossible. Actually, the mortality after major surgical complications in the Dutch trial was significantly higher than that experienced at the National Cancer Center Hospital Tokyo (NCCH). The mortality after anastomotic leak and after intraabdominal abscess or pancreatic juice leakage was 41% and 20%, respectively, in the Dutch trial. But, in the same period, the 1980s, the corresponding figures at the NCCH showed much lower 14% after anastomotic leak, and only 3% after intraabdominal abscess.[3] This suggests that experience is needed to manage these major adverse effects to avoid treatment-related deaths. Even in patients with medical treatment, we should know how to manage febrile neu-

tropenia. If not, the patient may die. Greater effort and more experience are needed in the treatment of complications after surgical treatment.

High treatment-related death (TRD) rate offsets treatment effect

Figure 2 shows the survival curves of the Dutch trial.[9] The curve of the D2 arm started at 10% below the D1 arm but caught up with the D1 curve at about 4 years after surgery. However, the difference between the two arms did not become statistically significant at any time. As expected from this, the hazard ratio between the two treatments changed with time; at the beginning, three to four times higher risk for D2 was observed, but the hazard ratio of D2/D1 became less than 1 after 3 years, even with the upper limit of the 95% confidence interval below 1. So, after 3 years, patients who underwent D2 had a significantly lower risk of death than those who underwent D1. These hazard ratio curves by time were completely different for men and women. The curve for women showed a more or less constant hazard ratio, suggesting the applicability of statistical methods based on the hypothesis of a constant hazard ratio. The most common method used to evaluate two survival curves is the log rank test, which is based on the assumption that the hazard ratio is roughly constant. This means that the above statistical methods cannot be properly applied to survival analyses in male patients.

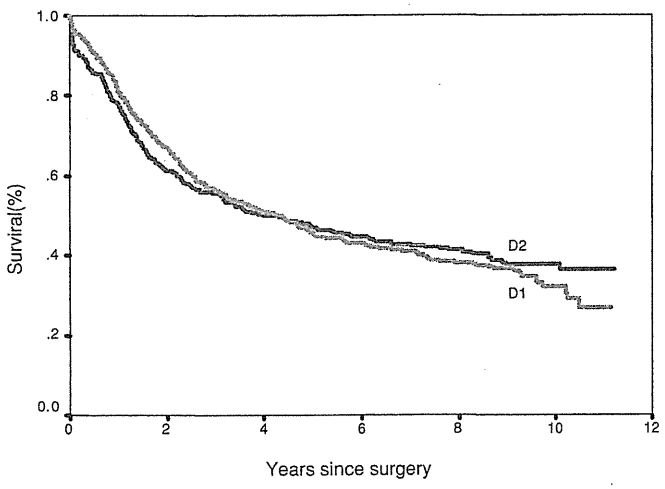
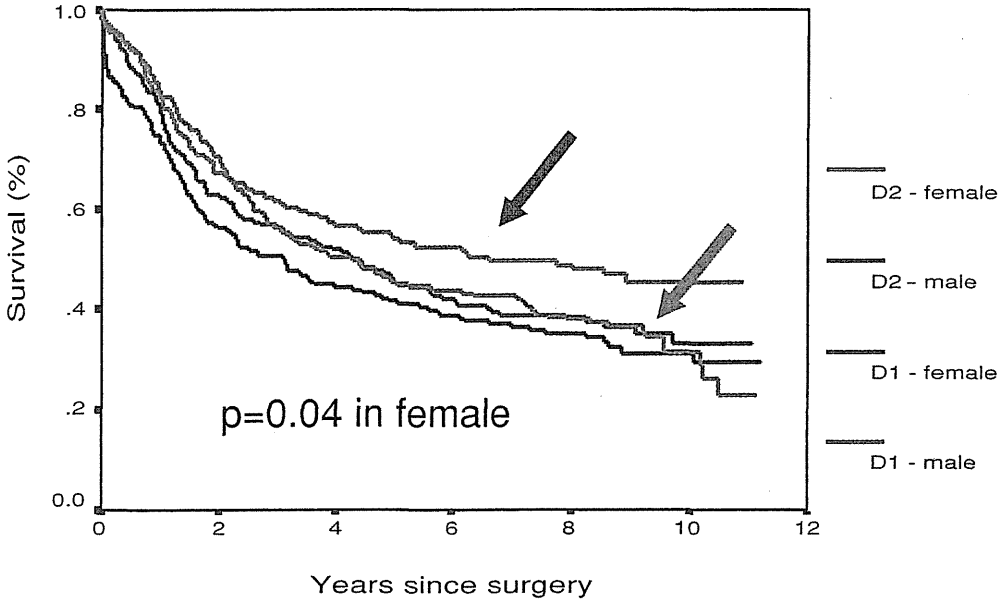


Fig. 2. Survival curves in the Dutch trial[9]

Figure 3 shows the survival curves by treatment by sex in the Dutch trial.[3] The survival curve for the female patients in the D2 arm shows clearly better survival than that for the female patients in the D1 arm. Although the *P* value of the difference by log rank test was 0.04, this cannot be regarded as statistically significant because of the multiplicity of the analysis.

In summary, the conclusion which should be drawn at the moment is that all the RCTs of lymphadenectomy for curable gastric cancer failed to prove the effect of D2 dissection.[10] As discussed already, however, the quality of D2 dissection in these trials was questionable, especially that in the MRC trial. With quite small hospital volumes, each of these trials had treatment-related death (TRD) rates after D2 as high as 10%. The quality of postoperative care to avoid TRD was very poor, and the high TRD rate offset the long-term effect of treatment. This was also confirmed in the French and German studies of squamous cell cancer, reported at Americal Society of Clinical Oncology (ASCO) meetings in 2002[11] and 2003, respectively.[12] Proper D2 dissection is a technically demanding procedure, requiring experience in postoperative care, and should be carried out at specialized centers, at least in low-volume areas.

Fig. 3. Survival curves by treatment (D1 or D2) by sex in the Dutch trial.[3]



Surgical trials with low TRD rate

The results of a Japanese trial, Japan Clinical Oncology Group (JCOG) 9501, a study comparing standard D2 gastrectomy with D2 plus paraaortic lymph node dissection (D3), made a clear contrast to these trials.[13] Unlike the Dutch trial, it was possible to randomize the patients during surgery after confirming the absence of the peritoneal seeding and negative cytology of the peritoneal washing fluid, because every participating surgeon knew the technique and therefore a quality controller from outside the hospital was not needed. This randomization during surgery was done at the central data center by telephone. The primary endpoint was survival and morbidity/mortality, and the projected sample size was 412 at the beginning. But the sample size was amended in June 2000, to increase the statistical power, and we can now evaluate an 8% difference between the two treatment arms. Five hundred twenty-three patients were enrolled, and the results of the survival analysis in 2006 are awaited. The postoperative morbidity and mortality of this trial is shown in Table 2. The D2 arm showed 20% morbidity, including all complications and although slightly more complications were observed in the D3 arm, there was no difference in mortality, at 0.8%, in the two arms. No differences were observed in major surgical complications such as anastomotic leak or pancreatic juice fistula, but an increased of diarrhea juice and ileus was observed after D3.

Table 2. Morbidity and mortality: JCOG 9501 (523 patients)

	D2	D3	All
Morbidity (any*)	20.9%	28.1%	24.5%
Anastomotic leak	2.3%	1.9%	2.1%
Pancreatic fistula	5.3%	6.2%	4.0%
Abdominal abscess	5.3%	5.8%	5.5%
Pneumonia**	4.6%	1.5%	3.2%
Miscellaneous***	9.1%	20.0%	14.5%
Reoperation	1.9%	2.7%	2.3%
Mortality (in hospital)	0.8%	0.8%	0.8%

* $P = 0.067$; ** $P = 0.0724$; *** $P = 0.0005$ (ileus, lymphorrhea, diarrhea)

Figure 4 shows the survival curve for all the patients in JCOG 9501. The investigators do not know yet how are the survival curves for the two treatment arms, but the survival curve for all the patients is quite good, considering the T stage of the patients. So far, from this result, it can be said that morbidity and mortality after extended surgery did not increase much, if the surgery was done by experienced surgeons in countries of high incidence. The incidence of the major complications was the same in both arms, with a slight increase of minor complications in the D3 arm. D3 increased the operation time by 60 min and the blood loss by 230 ml. Unlike the two trials in Europe (Dutch trial[1] and MRC trial[5]), postoperative mortality will not affect the results in the long term.

The only clinical phase II trial of D2 dissection was carried out by the Italian Gastric Cancer Study Group in Turin.[6] This was carried out to confirm the feasibility of D2 carried out by Italian surgeons after the reports of the Dutch[1] and MRC[5] trials. The Italian group achieved 3% mortality. In the Dutch trial, the number of participating hospitals was 80 and the number of D2 dissections per year per hospital was just 1, while in the Italian trial, the number of hospitals was 9 and the number of D2 dissections per year was 7. The hospital volume differred enormously between these two trials. Another important difference that may have affected the morbidity and mortality was the indication for pancreas tail resection. In the Dutch trial, a total gastrectomy was always combined with pancreaticosplenectomy, but in the Italian trial, the pancreas was preserved in principle.

After achieving this 3% mortality, the Italian group started a phase III trial, comparing D1 versus D2 dissection. However, they have actually had much difficulty in enrolling patients. As there was no difference between the mortality rates of D1 and D2, some surgeons had refrained from enrolling patients with a preference for D2. The feeling was, why should they go back to D1 when there

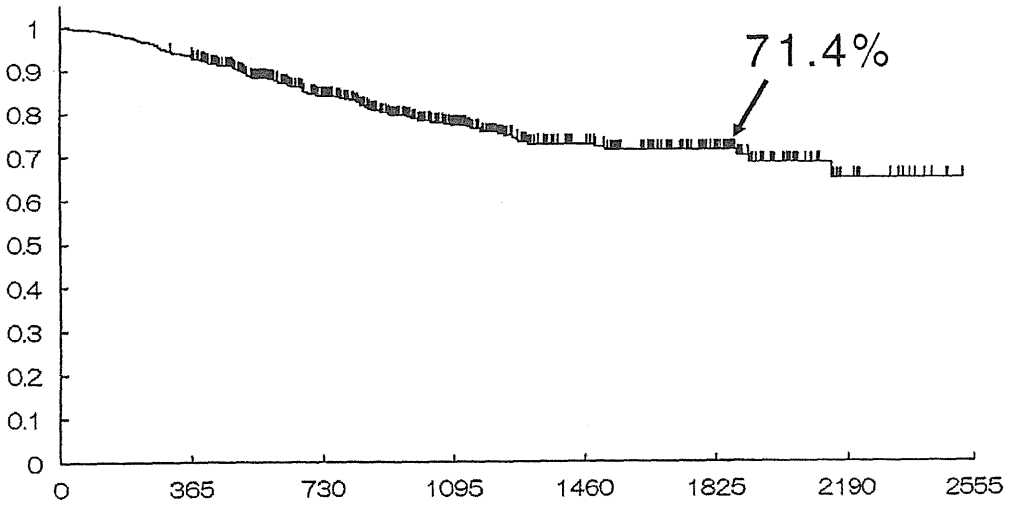


Fig. 4. Survival curve in all patients in the Japan Clinical Oncology Group (JCOG) 9501 trial. Actual proportion of 5 year survivors = 71.4%

is a low mortality for D2 in their hands. If they do enroll patients, it is questionable whether D1 performed by such surgeons can be real D1. If the mortality rates after pancreatico-duodenectomy or three-field dissection for esophageal cancer (major surgery) at specialist institutes in Japan, and in Western countries are compared, they are less than 5%.

Why did the Dutch and the MRC trials have higher mortality than pancreatico-duodenectomy or three-field dissection? Radical pancreatico-duodenectomy is usually more aggressive than D2 gastrectomy. The only difference was that the patients with esophageal or pancreatic cancer were treated at specialist centers, while those with gastric cancer were treated at general hospitals. In both the MRC and the Dutch trials, many hospitals had very low hospital volumes. On the other hand, in the Japanese JCOG trial, both procedures (i.e., D2 and D3 gastrectomy) have commonly been carried out, and all participants had high hospital volumes. Besides, in this trial, together with strict patient selection and quality assurance, according to the number of dissected nodes, each participant showed their operative procedure on videotapes in regular group meetings.

Factors hampering surgical trials

There are several factors which make clinical trials in surgery difficult.[14,15] First of all, skill and experience affect the results. In this aspect, all surgeons cannot be the same. So inter-surgeon variation is unavoidable; some are dexterous and some are "all thumbs" by nature, and techniques suitable only for dexterous surgeons exist. Experience is also a very important factor – knowledge, familiarity, and knacks included. There is a learning curve for most surgical techniques. Surgery is usually followed by sequelae, and, therefore, quality-of-life evaluation is essential in surgical trials when comparing surgical techniques. However, there is no well-established measurement to assess these sequelae. Unlike medical treatment, masking of the allocated arm is impossible, and auditing the treatment given is very difficult in surgical trials.

In the past, we surgeons have experienced the introduction of laparoscopic cholecystectomy, and in this procedure, we heard for the first time, the term, "learning curve". Many articles state that at least 30 cases are needed to reach the plateau of the curve, while some argue that 250 cases are needed. We also observed expansions of indications of this procedure. At the beginning, this technique was not indicated for gallstone disease with acute cholecystitis, or for patients with previous operations in the upper abdomen, or during pregnancy. But actually, many surgeons are now doing laparoscopic cholecystectomy, even in patients with these conditions. Finally, in regard to laparoscopic cholecystectomy, RCTs were carried out, but they were only small trials and the results were reported only after an NIH consensus meeting, and, actually, these RCTs did not have any impact on clinical practice.[16]

Quality of surgical trials

The quality of surgical trials can be summarized in two categories. One category is quality issues that are common to all clinical trials. Indicators of the quality of a trial are, for example, the randomizing of patients (either by the envelope method or by a central computer system), the blinding of the arms, the proportion of excluded cases or protocol violations, sample size projection, the quality and independence of the data center and respect for multiplicity in the analysis, the prospective setting of the interim analysis, and the existence of an independent monitoring committee. If all these factors are fulfilled, the quality of the trial itself should be regarded as excellent. The South West Oncology Group (SWOG), the East Clinical Oncology Group (ECOG), the European Organization for Reseach and Treatment of Cancer (EORTC) and the JCOG are good examples of organizations which support various subgroups of different specialties and can carry out high-quality clinical trials.

The second category is specific to surgical trials. First, and most important, is the quality of treatment given. Reproducibility, homogeneity and verifiability are the greatest problems in surgical trials. There are also some patient factors. If the patient is old, or fragile, or obese, the results of the surgical treatment can easily be affected by these patient factors. Some surgery in obese patients is much more difficult than in slim patients. The surgeon can also be a prognostic factor, especially in complicated procedures or those requiring experience and training.

In surgical trials, quality control should include postoperative care as well. If surgeons do not know how to manage complications, mortality becomes very high, especially in intra-abdominal or intra-thoracic surgery. Therefore, experience and hospital volume are very important factors in surgical trials. Because blinding is impossible in surgical trials, the treatment may easily be affected by personal preference or prejudice. When surgical trials are planned, details of each procedure in each arm should be defined carefully after discussion among the participants to avoid unacceptable heterogeneity. For example, the Gastric Surgery Division of the JCOG now is carrying out an RCT of total gastrectomy with or without splenectomy, and there are several possible techniques in each procedure to be decided among the participants. They had to decide whether or not mobilization of the spleen was allowed for dissection of lymph nodes along the distal pancreas, whether or not a frozen section for splenic hilum node was acceptable, and where the splenic artery and vein should be divided, and also the indications for splenectomy in the spleen-preserving arm. This is because the spleen occasionally has to be taken out if it is injured, to control bleeding, even if the patient is allocated to the spleen-preserving arm. When these details are decided, leading surgeons should demonstrate to all participants, the procedures in detail on a videotape and each step of the procedures should be decided as precisely as possible. Even after starting the trial, it is recommended that the participating surgeons should

visit reciprocally to see others' operations. At each regular meeting among the participants, some of them, perhaps three or four, demonstrate their operation on videotape and discuss the technical details, repeatedly. Each participating center should demonstrate the technique at least once in the course of a trial, and any technical issue should be reevaluated, if needed, even after starting the trial, which may lead to protocol revision. Another difficult issue in surgical trials is how to audit the treatment given. Videotape recording for every patient is the best way. But, as this is not realistic, an onsite visit by referees is also another good way of auditing, but this is also very difficult to perform. Checking a close-up photograph of the operation field after dissection is one of the possible options. Actually, the Colorectal Surgery Division of the JCOG is adopting this method for an ongoing trial of rectal surgery. Close and intensive assessment of resected material, including lymph nodes, is a feasible technique if collaboration of pathologists is available, and was adopted in the Dutch trial on rectal surgery. All these methods to evaluate the quality of surgery become effective when proper feedback of the results to the operators is given regularly.

How to set up clinical trials in surgery

When surgical trials are set up, the following points should be considered. First, when to start phase III trial should be decided. For some surgical techniques that are complicated and surgically demanding, a feasibility study is absolutely needed, because there is usually a learning curve. Assessment of the experience of each participant is also important. Even if the procedures in each arm of a study are familiar to the surgeons, each participant's experience of each technique has to be assessed. A phase III trial should be started after sufficient experience of the procedures. In this regard, a phase III trial comparing two commonly performed operations is much easier than a comparison of old and new techniques. Open colon surgery versus laparoscopic colon surgery for colon cancer is a good example of a difficult trial, because the learning curve is a serious issue for laparoscopic colectomy. Selection of participants is also very important. The more institutes are involved, the faster is the accrual. On the other hand, the more institutes are involved, the more difficult is the quality control of surgery. Careful selection of participating hospitals which have acceptable quality of surgery is essential. The two procedures compared in a trial should be defined in every detail and in each technical point. Some method to verify the treatment given should be included, and the maximum effort should be made to avoid personal preferences affecting the results. Quality-of-life evaluation (i.e., a quality-of-life score or symptom score) should be included in most surgical trials.

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