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.

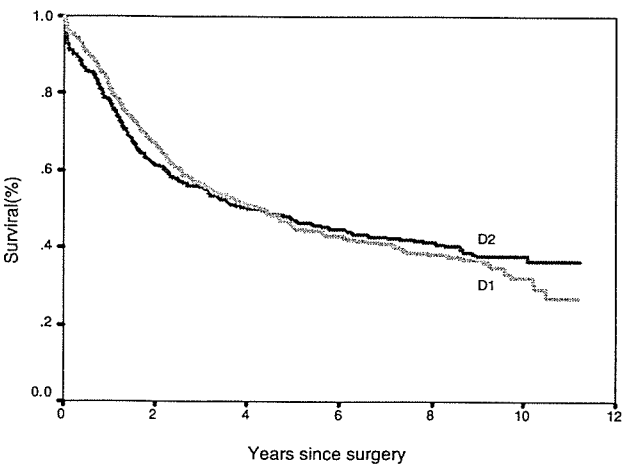
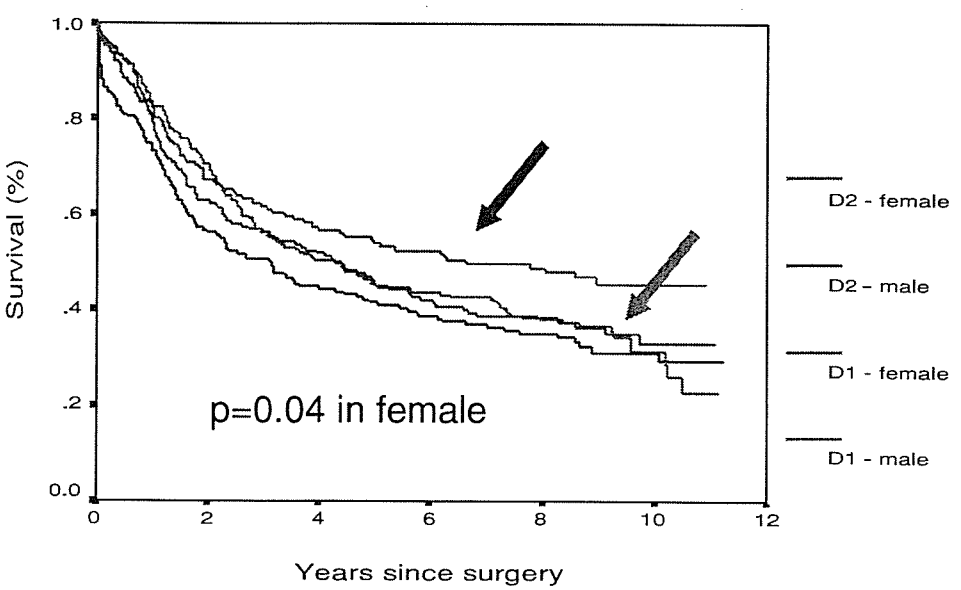


Fig. 2. Survival curves in the Dutch trial[9]

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

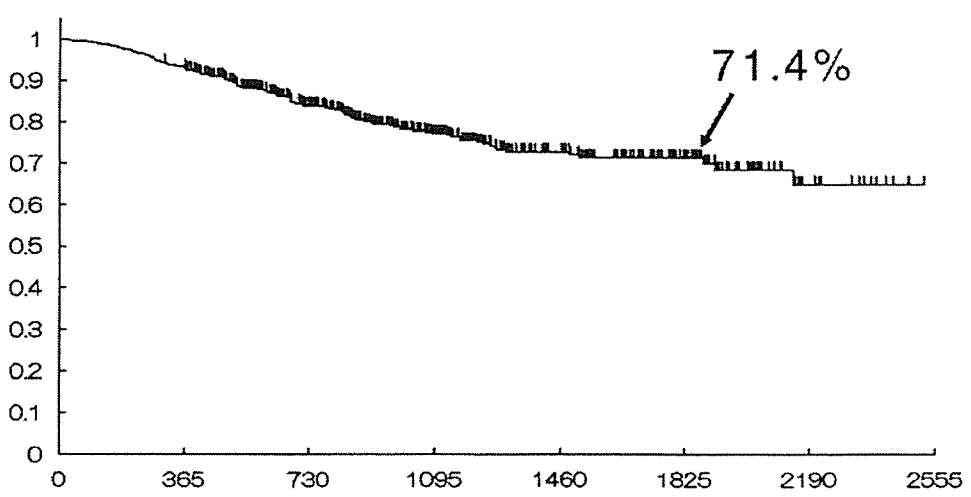


Fig. 4. Survival curve in all patients in the Japan Clinical Oncology Group (JCOG) 9501 trial. Actual proportion of 5 year survivors = 71.4%

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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Original article

Identification of risk factors for the development of complications following extended and superextended lymphadenectomies for gastric cancer

Y. Kodera[1], M. Sasako[2], S. Yamamoto[3], T. Sano[2], A. Nashimoto[4] and A. Kurita[5] on behalf of the Gastric Cancer Surgery Study Group of Japan Clinical Oncology Group

[1]Department of Gastroenterological Surgery, Aichi Cancer Centre, Nagoya, [2]Gastric Surgery Division, National Cancer Centre Hospital and [3]Cancer Information and Epidemiology Division, National Cancer Centre Research Institute, Tokyo, [4]Department of Surgery, Niigata Cancer Centre Hospital, Niigata, and [5]National Shikoku Cancer Centre, Matsuyama, Japan

Correspondence to: Dr Y. Kodera, Department of Surgery II, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 464-8550, Japan (e-mail: ykodera@med.nagoya-u.ac.jp)

Background: Extended lymphadenectomy for gastric carcinoma has been associated with high mortality and morbidity rates in several multicentre randomized trials.

Methods: Using data from 523 patients registered for a prospective randomized trial comparing extended (D2) and superextended (D3) lymphadenectomies, risk factors for overall complications and major surgical complications (anastomotic leakage, intra-abdominal abscess and pancreatic fistula) were identified by multivariate logistic regression analysis.

Results: Mortality and morbidity rates were 0·8 per cent (four of 523) and 24·5 per cent (128 of 523) respectively. Pancreatectomy (relative risk 5·62 (95 per cent confidence interval (c.i.) 1·94 to 16·27)) and prolonged operating time (relative risk 2·65 (95 per cent confidence interval 1·34 to 5·23)) were the most important risk factors for overall complications. A body mass index of 25 kg/m^2 or above, pancreatectomy and age greater than 65 years were significant predictors of major surgical complications.

Conclusion: Pancreatectomy should be reserved for patients with stage T4 disease. Age and obesity should be considered when planning surgery.

Paper accepted 24 January 2005

Published online in Wiley InterScience (www.bjs.co.uk). **DOI:** 10.1002/bjs.4979

Introduction

Despite a declining incidence in Western Europe[1] and the USA[2], gastric carcinoma remains the second commonest cause of cancer death worldwide, with over 600 000 deaths per year[3]. Given the poor outcome of irresectable disease treated by other therapeutic modalities in phase II and III trials[4,5], the curative treatment of gastric carcinoma remains primarily surgical. Although the presence of distant metastases usually precludes curative surgery, this does not necessarily apply to disease in the regional lymph nodes, which can be dissected *en bloc* with the primary lesion[6,7]. This type of resection may allow cure, provided that metastases are within the margins of dissection. Removal of a wider range of lymph nodes by extended lymph node dissection might increase the chance of cure, but is inappropriate if the cancer has spread systemically.

In Japan, gastrectomy plus extended systematic lymphadenectomy (D2 resection) has long been the standard treatment, even for superficial cancers[8]. Success with D2 resection has led to the evolution of a superextended lymphadenectomy (D3 resection) and several feasibility studies evaluating dissection of para-aortic lymph nodes have been performed[9–12]. A randomized trial (Japan Clinical Oncology Group (JCOG) 9501) was launched in 1995, primarily to explore the potential survival benefit of D3 over D2 dissection[13]. This trial has provided the opportunity to evaluate prospectively collected data on gastric cancer surgery in Japan. The present study represents a detailed analysis of risk factors for overall and surgical complications following D2 and D3 resections.

Patients and methods

Between June 1995 and April 2001, 523 patients registered in the JCOG 9501 study were allocated randomly to either D2 (263 patients) or D3 (D2 plus para-aortic lymph node dissection; 260 patients) resection. Eligibility criteria and the method of randomization have already been reported in detail[13]. In brief, patients aged less than 75 years of age with histologically proven and resectable primary gastric carcinoma with an estimated depth of SS (penetrating the muscle layer), SE (penetrating the serosa) or SI (invasion to an adjacent organ) were recruited after giving informed consent. Patients found positive for free cancer cells by cytological examination of peritoneal washes and those with Borrmann type 4 tumours (linitis plastica type) were excluded. Twelve institutions participated in the trial initially and 12 other institutions were added to increase patient recruitment.

After laparotomy, cytological examination of peritoneal washes was performed, followed by gross examination of the abdominal cavity and the primary lesion. Only patients who were negative for free cancer cells in the abdominal cavity and without evidence of gross para-aortic lymph node spread, peritoneal carcinomatosis or other distant metastasis were eligible to participate. The patients were allocated randomly to either D2 or D3 resection by the minimization method of balancing the groups according to T stage (T2 *versus* T3/T4), gross appearance (Borrmann types 1 and 2 *versus* Borrmann types 3 and 5) and institution. The surgeons were notified immediately of the allocation results and completed the operation accordingly.

Patients underwent appropriate gastrectomy with systematic lymphadenectomy as allocated. Perigastric lymph nodes (nodal stations 1, 3, 4, 5 and 6 according to the Japanese Classification of Gastric Cancer[14]) and nodes at the base of the left gastric artery (7), along the common hepatic artery (8) and at the base of the splenic artery (11) were resected routinely. Lymph nodes along the hepatoduodenal ligament and behind the pancreatic head (12 and 13) were resected when the primary lesion was located in the lower third of the stomach. Lymph nodes along the left side of the cardia (2), within the splenogastric ligament (4sa) and at the splenic hilum (10) were resected with the spleen when total or proximal gastrectomy was performed. Concurrent resection of the pancreatic tail was not routine during either D2 or D3 resection and was reserved for patients with direct invasion to the pancreas. In patients randomized to superextended lymphadenectomy, para-aortic lymph nodes from the level of the coeliac trunk down to the root of the inferior mesenteric artery (16a2 and 16b1) were dissected. The mode of reconstruction following resection was not specified.

All information on complications was extracted from the case-report forms for the trial. Anastomotic leakage, intra-abdominal abscess and pancreatic fistula were considered to be major surgical complications. Anastomotic leakage was defined as dehiscence confirmed by radiographic examination using contrast medium. Pancreatic fistula was diagnosed if there was prolonged purulent discharge containing pancreatic juice from the drainage tube.

Factors that might affect the risk of overall and major surgical complications were evaluated by univariate analysis using cross-tabulations. Variables analysed included extent of lymphadenectomy, splenectomy, pancreatectomy, type of gastrectomy, pathological (p) T category (pT2 and pT3 *versus* pT4), sex, age, body mass index (BMI), operating time, amount of blood loss and need for autologous blood transfusion. Operating time and blood loss were divided into tertiles for analysis. Two factors associated with surgical experience were also evaluated: institutions that enrolled over 20 patients *versus* those with fewer patients and first and second halves of the trial (1995–1998 *versus* 1999–2001). The χ^2 test was used to assess differences in proportions. The independent contribution of various factors was assessed by multivariate logistic regression analysis, with mutual adjustment of potential risk factors for complications. All factors analysed in the univariate analysis were included as variables in the multivariate analysis. Two-sided P values are presented. Statistical analysis was performed using SAS® version 8.12 (SAS Institute, Tokyo, Japan).

Results

Total gastrectomy was performed in 199 (38·0 per cent) of 523 patients and proximal gastrectomy in four;

Table 1 Complications

Severe abdominal complications	
Pancreatic fistula	30
Abdominal abscess	29
Anastomotic leakage	11
Other complications	
Pneumonia	16
Anastomotic stenosis	14
Bowel obstruction/ileus	16
Lymphorrhoea	10
Thoracic effusion requiring thoracic drainage	7
Severe feeding problem requiring prolonged hyperalimentation	6
Wound abscess	5
Postoperative bleeding	3
Severe diarrhoea	3
Urinary tract infection	3
Catheter-induced sepsis	3
Pulmonary embolism	2
Cardiac failure	1
Cholecystitis requiring percutaneous drainage	1

the remaining patients underwent distal gastrectomy. Splenectomy was performed in 191 patients (36·5 per cent) and distal pancreatectomy in 22 (4·2 per cent). There was no significant difference in the type of gastrectomy and incidence of combined resection between the two groups. Details of patient demographics and tumour stages have been reported previously[13].

There were four hospital deaths (0·8 per cent), two in each group. Two patients suffered from rapid disease progression and died 3 and 5 months after surgery without being discharged from hospital. One patient died from pneumonia at 46 days and another died from massive bleeding from the gastroduodenal artery 24 days after operation. Complications were identified in 128 patients (24·5 per cent) and major surgical complications in 49 patients (9·4 per cent) (*Table 1*).

The results of univariate analyses of risk factors for overall postoperative complications are summarized in *Table 2*. Only pancreatic resection ($P = 0·001$) and

Table 2 Univariate and multivariate analysis of risk factors for overall complications

			Univariate analysis		Multivariate analysis	
	n	No. with complications	Relative risk	*P*	Relative risk	*P*
Extent of lymphadenectomy						
D2	263	55	1		1	
D3	260	73	1·48 (0·99, 2·21)	0·057	0·93 (0·58, 1·51)	0·776
Splenectomy						
No	332	64	1		1	
Yes	191	64	2·11 (1·41, 3·17)	< 0·001	2.05 (0·52, 8·01)	0·304
Pancreatectomy						
No	501	115	1		1	
Yes	22	13	4·85 (2·02, 11·63)	< 0·001	5·62 (1·94, 16·27)	0·001
Extent of gastrectomy						
Distal	320	62	1		1	
Total or proximal	203	66	2·01 (1·34, 3·00)	< 0·001	0·84 (0·22, 3·27)	0·804
Invasion to adjacent organs						
T2, T3	501	123	1		1	
T4	22	5	0·90 (0·33, 2·50)	0·846	0·37 (0·11, 1·24)	0·107
Sex						
M	358	94	1		1	
F	165	34	0·73 (0·47, 1·14)	0·163	0·73 (0·45, 1·19)	0·207
Age (years)						
< 56	160	33	1		1	
56–65	207	48	1·16 (0·70, 1·92)	0·557	1·26 (0·73, 2·17)	0·403
> 65	156	47	1·66 (0·99, 2·77)	0·053	1·63 (0·92, 2·89)	0·092
Body mass index						
< 25	446	101	1		1	
≥ 25	77	27	1·85 (1·10, 3·10)	0·019	1·75 (0·99, 3·08)	0·054
Operating time (min)						
< 240	167	23	1		1	
240–297	179	43	1·98 (1·13, 3·46)	0·016	1·77 (0·96, 3·25)	0·068
> 297	177	62	3·38 (1·97, 5·78)	< 0·001	2·65 (1·34, 5·23)	0·005
Blood loss (ml)						
< 395	174	27	1		1	
395–710	174	42	1·73 (1·01, 2·97)	0·045	1·05 (0·58, 1·90)	0·886
> 710	175	59	2·77 (1·65, 4·64)	< 0·001	1·11 (0·58, 2·12)	0·754
Blood transfusion						
Yes	408	87	1		1	
No	115	41	2·04 (1·31, 3·20)	0·002	1·53 (0·92, 2·56)	0·102
Case volume*						
< 20	147	41	1		1	
≥ 20	376	87	0·78 (0·51, 1·20)	0·256	0·83 (0·51, 1·34)	0·437
Period						
1995–1998	295	75	1		1	
1999–2001	228	53	0·9 (0·59, 1·33)	0·566	0·87 (0·56, 1·35)	0·539

Values in parentheses are 95 per cent confidence intervals. *No. of patients registered.

Table 3 Univariate and multivariate analysis of risk factors for major surgical complications

	n	No. with major complications	Univariate analysis		Multivariate analysis	
			Relative risk	*P*	Relative risk	*P*
Extent of lymphadenectomy						
D2	263	23	1		1	
D3	260	26	1·16 (0·64, 2·09)	0·623	0·67 (0·32, 1·39)	0·279
Splenectomy						
No	332	20	1		1	
Yes	191	29	2·79 (1·53, 5·09)	< 0·001	1·08 (0·15, 7·56)	0·941
Pancreatectomy						
No	501	43	1		1	
Yes	22	6	3·99 (1·49, 10·74)	0·003	6·90 (1·86, 25·58)	0·004
Extent of gastrectomy						
Distal	320	19	1		1	
Total or proximal	203	30	2·74 (1·50, 5·03)	< 0·001	2·15 (0·31, 15·20)	0·442
Invasion to adjacent organs						
T2, T3	501	47	1		1	
T4	22	2	0·97 (0·22, 4·26)	0·964	0·37 (0·067, 2·01)	0·246
Sex						
M	358	38	1		1	
F	165	11	0·60 (0·30, 1·21)	0·150	0·57 (0·25, 1·27)	0·169
Age (years)						
< 56	160	7	1		1	
56–65	207	20	2·34 (0·96, 5·67)	0·061	3·06 (1·15, 8·20)	0·026
> 65	156	22	3·59 (1·49, 8·66)	0·005	4·04 (1·48, 11·02)	0·006
Body mass index						
< 25	446	34	1		1	
≥ 25	77	15	2·93 (1·51, 5·69)	0·001	3·32 (1·54, 7·12)	0·002
Operating time (min)						
< 240	167	8	1		1	
240–297	179	14	1·69 (0·69, 4·13)	0·252	1·60 (0·60, 4·27)	0·350
> 297	177	27	3·58 (1·58, 8·12)	0·002	2·96 (1·03, 8·55)	0·045
Blood loss (ml)						
< 395	174	10	1		1	
395–710	174	11	1·11 (0·46, 2·68)	0·822	0·47 (0·17, 1·30)	0·145
> 710	175	28	3·12 (1·47, 6·65)	0·003	0·86 (0·32, 2·31)	0·767
Blood transfusion						
Yes	408	29	1		1	
No	115	20	2·75 (1·49, 5·08)	< 0·001	1·99 (0·97, 4·08)	0·061
Case volume*						
< 20	147	16	1		1	
≥ 20	376	33	0·79 (0·42, 1·48)	0·457	0·76 (0·36, 1·57)	0·454
Period						
1995–1998	295	30	1		1	
1999–2001	228	19	0·80 (0·44, 1·47)	0·475	0·83 (0·43, 1·61)	0·575

Values in parentheses are 95 per cent confidence intervals. *No. of patients registered.

prolonged operating time (patients in the upper tertile for whom the operating time was more than 297 min; $P = 0·005$) were identified as significant independent risk factors for overall complications (*Table 2*). A BMI of 25 or more was close to significance ($P = 0·054$).

The results of univariate analyses of risk factors for major surgical complications are summarized in *Table 3*. Multivariate analysis identified BMI ($P = 0·002$), pancreatic resection ($P = 0·004$), age (56–65 years, $P = 0·026$; over 65 years, $P = 0·006$) and operating time over 297 min ($P = 0·045$) as significant independent risk factors for major surgical complications (*Table 3*).

Discussion

Gastrectomy plus extended systemic lymphadenectomy (D2 resection) is the standard procedure for gastric carcinoma in Japan. This approach has resulted in superior stage-by-stage survival than that observed in most Western countries and has led to cure for a

proportion of patients with nodal disease beyond the perigastric region, although this has not been confirmed in Western randomized trials[15,16]. Although long-term follow-up revealed significantly better disease-free survival for the D2 group in the subset with node-positive cancer[17], this difference did not extend to all patients in the trial, in part owing to the unacceptably high mortality rate associated with D2 resection[8]. JCOG 9501, a Japanese multi-institutional prospective randomized trial comparing D2 with more extended resection, has superior quality control of surgical procedures and reliability of data[13] than retrospective Japanese studies and Western prospective trials.

The most significant risk factor for both surgical and overall complications in the present study was pancreatic resection, although it should be noted that this was performed in only 4·2 per cent of patients, compared with 30·3 and 15·2 per cent in the UK Medical Research Council (MRC) and Dutch trials respectively[15,16]. The rate of pancreatectomy was lower in the present series because a pancreas-preserving technique[18,19] was generally used, whereas distal pancreatectomy and splenectomy were integral parts of D2 dissection in the Dutch trial unless cancer was located in the distal stomach. The low morbidity rate in the present study may well be related to pancreas preservation[18,19]. The success of this approach has also been reported in a multicentre phase II trial of D2 dissection in Northern Italy[20].

Splenectomy, on the other hand, was not an independent determinant of risk, possibly because it was never performed with distal gastrectomy in the present series. In the Dutch randomized trial a high mortality rate after distal gastrectomy was attributed in part to necrosis of the remnant stomach as a result of splenectomy and division of the short gastric arteries[21]. The survival benefit of splenectomy performed solely to facilitate dissection of lymph nodes close to the splenic hilum has been questioned, however, and a randomized trial to explore this issue is ongoing[22].

Age was not an independent risk factor for overall complications in this study, in contrast to the Dutch trial in which age over 65 years was a significant risk factor for hospital death and overall complications[21]. This discrepancy may be attributed to the fact that only patients aged 75 years or less were eligible for inclusion in the JCOG 9501[13], whereas other trials have included older patients[15,16]. Japanese patients were, on average, 8 years younger than Dutch patients[23]; consequently the proportion of patients over 65 years of age was 29·8 per cent in the present series as opposed to 51·3 per cent in the Dutch trial[16]. This age distribution may account for the very low incidence of perioperative cardiovascular events in the present series, another factor that may have influenced the low morbidity and mortality rates.

Extended lymph node dissection may be hampered by excess bodyweight[24–26] and in the present study BMI was a significant risk factor for major surgical complications. Caucasians in general have a higher BMI than Japanese and the incidence of morbid obesity is significant among patients in the USA and Europe. Only 14·7 per cent of the present patients had a BMI of 25 kg/m^2 or greater, whereas one-third of the US population is obese (BMI over 27 kg/m^2)[27]. These data suggest that the patients' physique favours Japanese patients when major gastric cancer surgery is performed.

The extent of lymph node dissection (D2 *versus* D3), surgical volume and the period in which the operation was performed had no impact, suggesting that there were no learning curve issues. Although D2 resection has long been a standard procedure in Japan, all surgeons in the trial were experts from specialized centres who had sufficient experience with D3 resection through numerous other studies. Of the variables reflecting difficulties encountered during surgery, prolonged operating time was identified as a significant independent risk factor for both overall and major surgical complications. However, amount of blood loss and blood transfusion were significant only in univariate analysis; this may be attributable to multicolinearity, as these two factors are closely related.

Gastrectomy with extended lymphadenectomy is feasible and safe in Japan, provided that older patients with co-morbidity are excluded and pancreatectomy is reserved for lesions with direct invasion to the pancreas. Obese patients should be treated with caution, however, as they have a significant risk of developing major surgical complications. Hopefully, with careful patient selection, appropriate surgical expertise and pancreas and spleen preservation[8] where possible, equally good results, rarely achieved previously[20,28], will be realized in the West.

Acknowledgements

The authors thank Dr Yoshimura for help with the statistical analysis, Ms Hongo for data management and Ms Sugimoto for secretarial assistance. This study was supported by a Grant-in-Aid for Cancer Research from the Ministry of Health and Welfare and the Second Term Comprehensive 10-year Strategy for Cancer Control by the Ministry of Health and Welfare, Japan.

Participating institutions and chief participants: National Cancer Center Hospital (M. Sasako, T. Sano), Niigata Cancer Centre Hospital (A. Nashimoto, H. Yabuzaki), National Shikoku Cancer Centre (A. Kurita, Y. Kubo), Osaka Medical Center for Cancer and Cardiovascular Diseases (M. Hiratsuka, I. Miyashiro), Osaka National Hospital (K. Kobayashi, T. Tsujinaka), National Cancer Centre Hospital East (T. Kinoshita), Tokyo Metropolitan Komagome Hospital (K. Arai, Y. Iwasaki), Aichi Cancer Centre (T. Kito, Y. Yamamura), Osaka Medical College (K. Okajima, M. Tanigawa), International Medical Centre of Japan (O. Kobori, T. Shimizu), Sakai City Hospital, Kanagawa Cancer Centre (H. Furukawa, H. Imamura), Tokyo Metropolitan Bokuto Hospital (M. Kitamura, S. Inoue), Nagaoka Chuo General Hospital (T. Yoshikawa, T. Shimizu), Niigata City General Hospital (K. Aizawa), Cancer Institute Hospital (K. Ota, S. Oyama), Kyoto Second Red Cross Hospital (H. Tokuda, S. Takahashi), Saitama Cancer Centre, Hiroshima City Hospital (Y. Tanaka, K. Uchida), Kanazawa University (K. Miwa, T. Fujimura), Gifu Municipal Hospital (H. Tanemura, H. Oshita), Kagoshima University (T. Aiko, S. Hokita), Iwate Medical University (M. Terashima, K. Saito) and Okayama University (H. Isozaki).

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Seminars in Oncology

Overview of Adjuvant Therapy for Resected Gastric Cancer: Differences in Japan and the United States

Atsushi Ohtsu[a] and Mitsuru Sasako[b]

Survival in adjuvant chemotherapy following resected gastric cancer has been studied by both Japanese and Western investigators using varied chemotherapy regimens in different target patients. Gastrectomy with D2 lymphadenectomy is the standard in Japan, and trials of adjuvant therapy in these patients have shown no survival advantages over surgery alone. In the United States, where 5-year survival rates in patients with gastric cancer are much lower following potentially curative surgery, adjuvant therapy has shown a survival benefit. The differences observed in these trials may result from the additional experience that Japanese surgeons have gained because of the higher incidence of gastric cancer there, or because of this increased incidence, there are more stringent screening guidelines in place and these cancers are possibly being diagnosed at an earlier stage. The Japanese viewpoint on the use of adjuvant therapy in patients with gastric cancer following potentially curative resection is that the quality of surgery, including diagnostic and pathologic procedures, is a more important prognostic factor than adjuvant chemotherapy. Also, they have determined from previously conducted clinical trials that patients with stage 1–2 tumors should be excluded from the target populations of randomized trials. Until the results of INT-0116 became available, there had been no improvement, or only marginal improvement, in overall or disease-free survival for patients receiving adjuvant chemotherapy following gastric cancer resection in the United States and Europe.
Semin Oncol 32(suppl 9):S101-S104

Gastric cancer is the fourth most common cancer worldwide and the second leading cause of cancer death, accounting for 10.4% of cancer deaths globally. In 2000, there were an estimated 865,000 new cases of gastric cancer.[1] Approximately 50% of patients with gastric cancer have metastasis at diagnosis, and of those without metastasis at diagnosis, only 50% are eligible for gastric resection. In fact, gastric cancer resection typically occurs in late-stage cancer, when the cancer has already spread to the peritoneal cavity, lymph nodes, or blood vessels.[2] The 5-year survival rate in the United States and most Western countries is between 5% and 15%.[3] Age-standardized incidence rates of gastric cancer are highest in Japan; however, because of mass screening that leads to earlier disease stage at diagnosis, the 5-year survival rate is approximately 52%.[1] Adjuvant therapy for gastric cancer after surgical resection has been investigated for many years. Its efficacy in gastric cancer remains questionable because no concrete evidence exists to show that adjuvant therapy for resected gastric cancer improves survival. Questions exist regarding the necessity, most useful chemotherapy combinations, worldwide standardization of lymph node dissection grade, eligibility for surgery based on tumor stage, and the benefit of individualization of therapy for adjuvant chemotherapy for gastric cancer.

Adjuvant Therapy for Resected Gastric Cancer

Early trials of adjuvant therapy for gastric cancer in Japan evaluated the use of mitomycin-C (MMC), and later, a combination of MMC and oral fluoropyrimidines. These studies showed a small survival benefit compared with surgery alone. Re-examination of these data led to additional studies of these agents. Pooled data showed borderline survival benefit for oral fluoropyrimidines compared with surgery alone.

Recent studies have shown either no differences or marginal improvement in overall survival (OS) with adjuvant chemotherapy compared with surgery alone.[4–6] Three meta-analyses of randomized, controlled clinical trials comparing surgery alone with adjuvant chemotherapy showed only

[a]National Cancer Center Hospital East, Kashiwa, Japan.
[b]National Cancer Center Hospital, Tokyo, Japan.
Dr Ohtsu has no significant financial relationships to disclose.
Address reprint requests to Astushi Ohtsu, MD, National Cancer Hospital East, 6-5-1, Kashiwanoha, Kashiwa, Chilea, 277-8577 Japan; e-mail: aohursu@east.ncc.go.jp

0093-7754/05/$-see front matter
doi:10.1053/j.seminoncol.2005.06.001

Table 1 Meta-Analyses Randomized Clinical Trials in Patients With Resected Gastric Cancer (Adjuvant Chemotherapy v Surgery Alone)

Study	Trials Analyzed (No.)	HR	95% CI
Hermans et al (1993)[7]	11	0.82	0.68–0.97
Earle and Maroun (1999)[8]	13	0.80	0.66–0.97
Mari et al (2000)[6]	20	0.82	0.75–0.89

Abbreviations: CI, confidence interval; HR, hazard ratio.

marginal advantages of adjuvant chemotherapy (Table 1).[6–8] As a result of these meta-analyses, adjuvant chemotherapy following curative surgery for gastric cancer continues to be an investigational approach.[6] The use of meta-analysis has been the trend in determining benefits of adjuvant chemotherapy for resected gastric cancer, but recent studies suggest standardization of lymph node dissection protocols worldwide, tumor stage qualification for target populations of randomized trials, and surgery quality along with diagnostic procedures are all needed to qualify the results of these meta-analyses.

Adjuvant Therapy for Resected Gastric Cancer in Japan

Three randomized controlled clinical trials have been conducted or are currently underway in Japan comparing surgery with or without adjuvant chemotherapy (Table 2).[9,10]

Nashimoto et al[9] conducted a randomized, multicenter, phase III study ([Japan Clinical Oncology Group] JCOG-9206-1) to evaluate the survival benefit of adjuvant chemotherapy in patients with serosa-negative gastric cancer following curative resection. Patients were randomly assigned to observation or chemotherapy with MMC 1.33 mg/m^2, 5-fluorouracil (5-FU) 166.7 mg/m^2, and cytarabine 13.3 mg/m^2 twice weekly for the first 3 weeks after surgery, and oral 5-FU 134 mg/m^2 daily for the next 18 months. The primary endpoint was relapse-free survival. The 5-year relapse-free survival among patients who received chemotherapy in addition to surgery was 88.8% versus 83.7% in patients who underwent surgery alone; these differences were not statistically significant ($P = .14$). The 5-year survival in the chemotherapy plus surgery group was 91.2% versus 86.1% in patients who had surgery alone ($P = .13$). Fewer patients who received the combination of chemotherapy plus surgery experienced cancer recurrence (7.1%) than did patients who received surgery alone (13.8%). Because there was no relapse-free or OS benefit with this adjuvant chemotherapy regimen in patients with macroscopically serosa-negative gastric cancer after curative resection, and there were no remarkable differences in modes of cancer recurrence between the arms, the investigators concluded that adjuvant chemotherapy with this regimen is not recommended for this patient population in clinical practice.

Nakajima et al[10] conducted a randomized, phase III trial (JCOG-8801) in patients with T1 and T2 gastric tumors, who were either observed or received chemotherapy following resection to assess the survival benefit of adjuvant chemotherapy after curative gastrectomy for macroscopically serosa-negative gastric cancer. Patients who were randomly assigned to the chemotherapy group received MMC 1.4 mg/m^2 and 5-FU 166.7 mg/m^2 twice weekly for 3 weeks and oral uracil-tegafur (UFT) 300 mg daily for 18 months following surgery. At the median follow-up time of 72 months, 5-year survival was 82.9% for the observation group versus 85.8% for patients receiving chemotherapy. This difference in survival was not significant (log-rank test, $P = .17$; hazard ratio, 0.738; 95% confidence interval, 0.498–1.093). Toxic effects were generally mild. For patients with T1 (mucosal or submucosal) gastric tumors, 5-year survival was 94.9% in the observation group and 92.0% in the chemotherapy-treated group. Survival for T2 (muscularis propria or subserosa) was 76.9% and 83.0% for the observation and chemotherapy treated groups, respectively; the differences observed between the two groups were not statistically significant. The respective cancer recurrence rate was 13.7% versus 10.1% of the observation and chemotherapy-treated groups. Death from cancer occurred in 0.4% versus 1.0% of the observation and chemotherapy groups, respectively. The investigators concluded that there was no survival benefit with this adjuvant chemotherapy regimen for patients with macroscopically serosa-negative gastric cancer (T1 and T2) after surgery. They also recommended that T1 cancer patients be excluded

Table 2 Japanese Studies of Adjuvant Chemotherapy Versus Surgery Alone in Patients With Resected Gastric Cancer

Study/Trial	Target Patients	Treatment	No. of Patients	5-Year Survival (%)	*P* Value
Nashimoto et al/JCOG-9206-1[9]	T1-T2	5-FU plus MMC plus cytarabine followed by oral 5-FU	127	91.2	.13
	T1-T2	Observation	123	86.1	
Nakajima et al/JCOG-8801[10]	T1-T2	5-FU plus MMC followed by UFT	288	85.8	.17
	T1-T2	Observation	285	82.9	
JCOG 9206-2	T3-T4	5-FU plus cisplatin followed by UFT	135	*	*
	T3-T4	Observation	133	*	

Abbreviations: 5-FU, 5-fluorouracil; JCOG, Japan Clinical Oncology Group; MMC, mitomycin-C; UFT, uracil-tegafur.
*Not yet available: data will be available in 2005.

from future trials because surgery alone resulted in a good survival rate.

Results of a randomized phase III clinical trial evaluating patients with T3 and T4 gastric tumors in Japan will be available in 2005. This ongoing study has enrolled 133 patients who are being observed post-surgery and 135 patients who are receiving 5-FU plus cisplatin followed by UFT.

Another phase III study of adjuvant chemotherapy for gastric cancer in Japan (Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer [ACTS-GC])[11] began accruing patients with stage II, IIIA, or IIIB gastric cancer in October 2001. Anticipated accrual is 1,000 patients (500 patients per arm), and the primary objective is to assess OS. Expected 5-year survival of the control arm compared with the test arm is 70% versus 78%, respectively. There are 108 institutions involved in the study, 825 patients have been accrued, and the expected final accrual was completed in the third quarter of 2004. Table 2 summarizes the results of these studies.

Adjuvant Therapy for Resected Gastric Cancer in the United States

The development of adjuvant chemotherapy for gastric cancer in the West was not based on combinations with MMC, but rather 5-FU. While sometimes showing a survival benefit compared with surgery alone, these 5-FU–containing regimens have been criticized for lack of regimen standardization as adjuvant chemotherapy.

Macdonald et al[12] conducted the randomized, multicenter, phase III intergroup INT-0116 study that evaluated survival at 3 and 5 years following adjuvant chemoradiotherapy (chemoRT) in patients with adenocarcinoma of the stomach or gastroesophageal junction after curative resection. A total of 556 patients were enrolled in the trial; 275 patients were randomly assigned to receive surgery only, and 281 patients received surgery plus chemoRT. Patient tumor stage was 1 (n = 14), 2 (n = 74), 3 (n = 175), and 4 (n = 18). Of the 552 patients whose surgical records were reviewed, 10% had undergone a formal D2 lymph node dissection, 36% a D1 dissection, and most patients (54%) a D0 dissection. Adjuvant chemotherapy consisted of 5-FU 425 mg/m^2 plus leucovorin 20 mg/m^2 per day, for 5 days, followed by 4,500 cGy of radiation therapy (RT) (180 cGy/day), given 5 days per week for 5 weeks. Modified doses of 5-FU and leucovorin were given on the first 4 and the last 3 days of RT. One month after the completion of RT, two 5-day cycles of 5-FU (at 425 mg/m^2/day) plus leucovorin (20 mg/m^2/day) were given 1 month apart. The median 5-year survival was 36 months in patients who received chemoRT plus surgery versus 27 months in patients who received surgery alone. The 3-year survival rates were 50% versus 41% in the chemoRT plus surgery groups and surgery-only groups, respectively. The median duration of relapse-free survival was significantly longer in patients who received chemoRT plus surgery versus those receiving surgery only (30 v 19 months; $P < .001$, log-rank test). Relapses were reported in 64% of patients who received surgery only versus 43% of patients who received surgery plus chemoRT. The investigators concluded that local-regional RT plus fluoropyrimidine-based chemotherapy as adjuvant treatment significantly improves OS and relapse-free survival in patients with gastric cancer. This study also showed that the most frequently performed lymph node dissection in the United States was a D0 lymphadenectomy.

Table 3 Comparison of Results of INT-0116 and JCOG-9501[16]

	INT-0116	JCOG-9501
Surgery (%)	D0: 54 D1: 36 D2: 10	D2: 50 D3: 50
Adjuvant therapy	CT: 5-FU and LV RT: 45 Gy	None
No. of patients	281 (CT arm)	523
Tumor location (%)	Antrum: 53 Gastric body: 24 Cardia: 21 Multiple lesions: 2	Lower-third: 41 Middle-third: 39 Upper-third: 19
pT stage (1:2:3:4)	1: 14 pts 2: 74 pts 3: 175 pts 4: 18 pts	1: 23 pts 2: 257 pts 3: 230 pts 4: 13 pts
Survival (%)	3-yr: 50 5-yr: 42	5-yr: 71.4

Abbreviations: CT, chemotherapy; 5-FU, 5-fluorouracil; LV, leucovorin; pT, pathologic tumor stage; RT, radiation therapy; pts, patients.

Future Directions

Individualizing chemotherapy in various types of cancers has recently received much focused interest. In gastric cancer, individualized chemotherapy is based on subgroups of patients who are evaluated through molecular targeting that includes the use of the epidermal growth factor and vascular endothelial growth factor receptors. Recent studies have confirmed that: (1) the use of cDNA microarray analysis to detect expression files of cancer tissues improves the understanding of molecular changes during the development of gastric cancers, and (2) the expression of the S100A11 gene was useful to distinguish lymph node metastases of gastric cancers.[13–15] The evaluation of individual genetic information may prompt the future development of more personalized adjuvant chemotherapy regimens.

Discussion

In the United States, adjuvant chemoRT is considered a standard treatment and is based largely on the results of INT-0116, whereas in Japan the use of adjuvant therapy is the standard. Sasako[16] compared the results of INT-0116 with those of JCOG-9501 (Table 3).[16] INT-0116 showed a survival advantage with chemoRT plus surgery in patients with gastric cancer following curative resection; however, the 3-year survival rate in INT-0116 was only 50% which, when compared with Japanese studies, is lower than the 3-year

survival rate in patients who received surgery alone. The JCOG-9501 trial was designed to compare survival in patients with D2 versus D3 lymph node dissection without adjuvant chemotherapy or RT, while in INT-0116 the majority of patients had a D0 or D1 lymph node dissection and also received chemoRT. In the Japanese trial JCOG-9501 there was a higher proportion of patients with T2 disease than in the INT-0116 trial (49% v 26%) and also a lower proportion of patients with T3 disease (44% v 62%), respectively. Five-year survival rates were considerably higher (71%) in patients who received surgery only in the Japanese trial versus 42% in patients who received surgery plus chemoRT in the US trial. The Japanese interpretation of these results are that D0 or D1 lymph node dissection plus chemoRT is better than D0 or D1 lymph node dissection alone, but may be worse than D2 surgery alone. Determining whether a D0 or D1 lymph node dissection can replace a D2 lymph node dissection should be evaluated in a randomized, controlled clinical trial; however, D2 lymph node dissection in the United States appears difficult to achieve. Also, whether chemoRT after D2 surgery can improve the results of surgery alone is another unresolved issue.

Several factors should be considered when interpreting the differences in the results of these trials. Because the incidence of gastric cancer is several times higher in Japan than in the United States there are more stringent screening programs in place that may affect the baseline condition of patients accrued onto clinical trials. Moreover, the standard curative resection in the United States is gastrectomy plus D0 or D1 lymphadenectomy, whereas in Japan gastrectomy plus D2 lymphadenectomy with en bloc dissection of the lymph nodes around the common hepatic artery and the splenic artery is used. Japanese surgeons believe that these differences may be because of the additional experience they have acquired due to the higher incidence of gastric cancer in Japan.

The Japanese viewpoint on the use of adjuvant therapy in patients with gastric cancer following curative resection is that the quality of surgery, including diagnostic procedures or pathologic procedures, will be a more important prognostic factor than adjuvant chemotherapy because no survival advantages have been shown in patients with gastrectomy and D2 lymph node dissection in clinical trials. However, standard adjuvant chemotherapy after good local control by surgery (D2 or more) has yet to be established and remains an urgent issue. Also, data from clinical trials indicate that patients with stage 1–2 tumors should be excluded from the target populations of randomized, controlled clinical trials. In the United States and Europe there had been either no or only marginal improvement in OS or disease-free survival for patients receiving adjuvant chemotherapy following gastric cancer resection, until the results of INT-0116 became available, at which time the issue of postoperative chemoRT became the standard treatment for patients with gastric carcinoma. The question as to whether or not chemoRT can improve the results of D2 surgery alone remains unsolved.

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特集 臨床腫瘍学の現状と展望

V．がん薬物療法の実際
4．消化器癌
2）胃　癌
b）進行胃癌のアジュバント療法

Saka Makoto 阪　眞　Sasako Mitsuru 笹子三津留*
*国立がんセンター中央病院外科

はじめに

明らかな遺残腫瘍のない手術，すなわち治癒切除後の再発予防を期待して行われるのが補助療法である．胃癌治療におけるその歴史は長く，1950年代から，様々な臨床試験が行われてきた．しかし，統計学的にその有用性を実証した研究は少なく，欧米では長い間，その有効性に対し否定的な風潮であった[1,2]．2001年に日本胃癌学会から出された『胃癌治療ガイドライン』でも，補助化学療法について，「現在まで確実な延命効果を証明したevidenceは乏しい．しかし複数の無作為化比較対照試験のmeta-analysisでは延命効果を示唆する結果が報告され，延命効果を指標とした臨床試験を引き続き施行すべきである」と記載されている．しかし近年になり，良くデザインされた質の高い無作為化比較対照試験(randomized controlled trial：RCT)のいくつかが，補助療法の延命効果を肯定する結果を報告するようになり，状況は大きく変化してきた．

本稿では，欧米と日本で行われた過去のRCTのレヴューと，最近の臨床試験について概説する．

欧米における胃癌補助化学療法

補助療法の有効性を評価するためには，手術単独群を対照としたRCTが必要である．日本に比べ，手術単独の成績が悪い欧米では，真に有効な補助療法が求められ，行われたRCTはほぼ一貫して手術単独群を対照としている．欧米における胃癌補助化学療法は1960年代にThio-TEPAを用いた研究から始まり[3]，その後は5-FUを中心として5-FU＋MeCCNU，MFC，FAMなどの多剤併用療法が研究された[4-20]．しかし，多くの研究はその有用性を示すことができなかった．その中で，1983年にAlcobendasら[6]がMMC(mitomycin C)の，1996年にNeriら[17]がEPI＋LV＋5-FU(epirubicin＋leucovorin＋5-fluorouracil)の，1999年にCirerasら[20]がMMC＋tegafurの，手術単独に対する有意な効果を報告している(表1)．しかし，いずれの研究も，サンプルサイズが小さく，明らかなevidenceにはなり得ていない．

2001年，Macdonaldら[21]は，手術単独群を対照にした大規模RCTで初めてのpositive dataを報告した．これは術後化学放射線療法のRCT(SWOG 9008/INT 0116)で，手術単独群を対照とし，治療群は，術後5-FU＋LV療法に総量45 Gyの体外照射を組み合わせた治療を受けた．手術単独群275例，治療群281例と十分なサンプルサイズをもつこの研究で，overall survival ($p=0.005$)，relapse-free survival ($p<0.001$)ともに有意差をもって治療群の成績が対照を上回り，胃癌に対する術後補助化学放射線療法として，初めて生存期間延長効果を示した．この研究が欧米の臨床腫瘍医に与えた影響は大きく，米国のNational Cancer Institute (NCI)が提供する癌治療ガイドラインであるPhysician Data Query(PDQ)において，胃癌の術後補助化学放射線療法はstandard treatment optionとして採用

0287-3648/05/¥500/論文/JCLS

表1　手術単独群を対照に有意差がみられた欧米の補助化学療法RCT

筆頭著者	掲載誌(掲載年)	症例数	レジメン	有効性の評価
Alcobendas	Ann. Surg.(1983)	70	MMC	$p<0.001$
Neri	Br. J. Cancer(1996)	103	EPI+LV+5-FU	$p<0.001$
Cirera	J. Clin. Oncol.(1999)	148	MMC+tegafur	$p=0.04$

MMC：mitomycin C, EPI：epirubicin, LV：leucovorin, 5-FU：5-fluorouracil.

されている．

しかし，わが国にも導入できるかどうかは疑問である．なぜなら，この研究では90%の症例がD0，D1のリンパ節郭清しか受けておらず，わが国で標準的であるD2郭清が行われた症例は10%にすぎない．局所コントロールが不十分なD0，D1手術を局所治療である放射線治療で補いつつ，化学療法の効果を示したともとれる．実際，Hundahlら[22]はこの臨床試験の登録症例を用いて，個々の症例で大きさ，組織型，肉眼型，占拠部位などから各リンパ節の部位別の転移の可能性を評価し，実際の手術で郭清を受けていない場合を理論的遺残と計算して，遺残腫瘍指数を算出した結果，この指数が5を超えると予後が有意に不良となることを発表している．この指数は，D2郭清を行った症例ではほぼ0となる．図らずも，局所コントロールの重要性，ひいてはD2郭清の必要性を示唆する結果となっている．わが国では，D2郭清の安全性は高く，むしろ放射線治療を導入することでmorbidityが高くなる危険性がある．D2郭清に不向きな肥満症例(BMI>30)が30%を占める欧米諸国においてこそ，意味がある結果であると思われる．

日本の胃癌補助化学療法に関するRCT

わが国における胃癌術後補助化学療法の臨床試験の歴史は，1959年の国立病院癌化学療法共同研究班(小山班)[23]より始まる．このRCTは，MMC群，Thio-TEPA群およびMMC+5-FU群など，2～3年ごとに化学療法のレジメンを変え，1978年の第7次研究まで手術単独群を対照として行われたが，化学療法群の優位性を示すことはできなかった．

小山班に少し遅れ，1965年に厚生省今永班の多施設共同RCT[24]がスタートする．今永班は，1973年に終了した第4次研究まで，すべて手術単独群を対照とし，MMC中心のレジメンとの比較を行った．割り付け症例全体で化学療法群の優位性を示す研究はなかったが，後層別解析を行い，StageⅡあるいはStageⅢにおいて，化学療法群が対照に比し良好な生存率であったと報告した．しかし，この当時の臨床試験は大半が封筒法で行われ，除外脱落率が極めて高く，試験の信頼性は低い．1980年に報告されたNakajimaら[25]の研究で，初めて化学療法群(MFC：MMC+5-FU+cytarabine)が手術単独群を上回ったが，サンプルサイズが小さく，さらに同一レジメンで，より大規模に行われた今永班第4次研究で差が出なかったために，evidenceとはなり得なかった．しかし，当時は医師が統計学に関して無知で，臨床試験に対する理解が不足していたために，初期RCTのsuggestive dataをもって，補助化学療法は標準治療として広く普及してしまった．経口フッ化ピリミジン剤や様々な免疫賦活剤の開発も相まって，1970年代後半以降，わが国のRCTは補助(免疫)化学療法同士の比較となる[26-39]．1980年代は，MMC単独あるいは多剤併用療法をactive controlとし，tegafur，免疫療法剤の付加効果を検討した報告が数多く行われたが，当然のごとく補助療法の真の有効性を証明することはできなかった．また，多くの研究が一流誌に投稿されることなく終わり，「薬剤販売のための試験」という痛烈な批判を浴びた．

わが国の癌治療専門施設で構成される日本臨床腫瘍研究グループ(Japan Clinical Oncology Group：JCOG)の胃癌外科グループは，1980年代初めからESAC(Exploratory Study Group of Adjuvant Chemotherapy)として共同研究を展開していた．当初から胃癌術後補助化学療法のRCTでは，対照に手術単独群を置くことが重要であると認識し，1988年から漿膜浸潤陰性胃癌でT2またはリンパ節転移陽性の症例を対象に，手術単独群を対照とするRCTを施行した(JCOG 8801)[40]．補助化学療法としてMMC+5-FU+UFTを採用したが，手術単独群との間に有意な生存率の差を見出すことはできなかった．後層別解析で，pT1はリンパ節転移の有無にかかわらず手術単独でも予後良好であり，補助化学療法が予後を改善する余地がないことが示された．しかし，pT2，pN+では5年生存率で10%以上の差(78%対67%)が認められ，この結果は後述するN・

表2　最近の日本の手術単独群を対照にした補助化学療法RCT

	対　象	症例数	レジメン	有効性の評価
JCOG 8801	漿膜浸潤陰性pT2 or pN+	573	MMC+5-FU+UFT	NS
JCOG 9206-1	漿膜浸潤陰性	252	MFC+oral FU	NS
JCOG 9206-2	漿膜浸潤陽性	268	CDDP ip+CDDP iv +5-FU iv+oral FU	NS
N・SAS-GC	pT2, pN1～2	188	UFT	p=0.0176
ACTS-GC	StageⅡ, Ⅲ	1,000	TS-1	?

MMC：mitomycin C, 5-FU：5-fluorouracil, UFT：tegafur-uracil, MFC：MMC+5-FU+cytarabine, CDDP：cisplatin, TS-1：tegafur-gimeracil-oteracil potassium.

SAS-GC(1997年～)の対象絞り込みの根拠となった.

1992年より始まったJCOG 9206では，漿膜浸潤陽性胃癌と陰性胃癌の再発様式のリスクの違いを考慮して，全く別個のプロトコールが用意された．漿膜浸潤陰性例を対象としたJCOG 9206-1[41]はMFC+oral FUを，漿膜浸潤陽性例を対象としたJCOG 9206-2[42]はCDDP(cisplatin)ip+CDDP iv+5-FU iv+oral FUを治療レジメンとして行われたが，いずれの試験でも全体としての有意差はみられなかった．しかしJCOG 9206-1では，pT2，pN+で5年生存率90%対81%という差を認め，JCOG 8801と同様に，このサブグループに対する補助化学療法の有用性を示唆した．反対に，pN－では92%対91%と差を認めず，前述のJCOG 8801の結果と併せて，pT1症例とpT2，pN0症例は手術単独でも十分に予後良好であり，今後，補助療法の臨床試験の対象にしないことが確認された.

フッ化ピリミジンの経口剤は，単独投与の延命効果の報告がないのにもかかわらず，その使いやすさを理由に，あたかも胃癌術後の標準治療のごとくわが国で広く施行されてきた．N・SAS-GCは最も繁用されているtegafur-uracil(UFT®)を取り上げ，単独投与の有用性について手術単独群を対照に比較したRCTである．前述したJCOG 8801のsubset analysisの結果をもとに，対象はpT2, pN1～2とされた．予定症例数を500例として1997年に始まったが，症例の集積スピードが遅く，1999年にS-1(TS-1®)が発売されると，これを用いたRCTを優先させるために，N・SAS-GCは2001年3月に190例の時点で症例登録を中止した．その結果が，2005年のASCO(American Society of Clinical Oncology)総会でKinoshitaらによって報告された[43]．Overall survival(p=0.0176)，relapse-free survival(p=0.0040)ともに有意差をもって，治療群が対照群を上回っていた．しかし，予定症例数の半数にも満たない症例数で試験が終わっていること，手術単独群の成績がJCOG 9206-1での同サブグループに比較して5年生存率で約10%も下回ることなどの問題がある．とてもpivotal studyといえない試験であり，この結果をもって補助化学療法の有効性が証明されたとは解釈されていない．JCOGでは早急に大規模な追試のRCTを行う予定である.

一方，第Ⅱ相試験で45%という経口抗がん剤としては驚異的な奏効率をたたき出したTS-1を用いたRCT(ACTS-GC)が，2001年10月に始まり，2004年12月に1,000例の予定症例数を達成して登録を終了している．対象はStageⅡ(ただしpT1は除く)，ⅢとN・SAS-GCよりも広く設定されているが，これほど大規模な試験は過去になく，pivotal studyとしてその結果が待たれるところである(表2).

術前補助化学療法

術前補助化学療法には2つの目的がある．1つは本来治癒切除可能な進行癌に対して術前化学療法を行い，再発率を低下させようとするもの，2つ目は治癒切除不能と思われる高度局所進行癌に対して術前化学療法を行い，腫瘍の縮小を図って治癒切除に持ち込もうとするものである．いずれについても過去に多くの第Ⅱ相試験が行われてきたが，その評価は定まっていない.

標準治療の確立には，治癒切除可能症例を対象とする場合は，術前化学療法対手術単独，あるいは術後化学療法を含めた3アームによる第Ⅲ相試験が必須である．一方，高度進行胃癌症例では，ほかに良い治療もなく，比較的症例数の多い第Ⅱ相試験でも十分なevidenceたり得ると考えられる．JCOGでは，過去の第Ⅱ相試験の結果から，十分な奏効率と有害反応の少なさから，TS-1+CDDPをレジメンとして選択し，高度リンパ節転移を伴う進行胃癌に対する術前化学療法の第Ⅱ相試験(JCOG 0405)を2005年3月より開始してい

る．さらに，同じくTS-1＋CDDPを治療レジメンとした大型3型および4型胃癌に対する術前化学療法の手術単独群を対照とした第Ⅲ相試験(JCOG 0501)を計画中である．

英国で行われたMAGIC trialは，ECF(EPI＋CDDP＋5-FU)を術前術後に3クールずつ行う術前術後化学療法のRCTである．1994年に始まったこの試験は，8年をかけて予定の500例を集積し，2005年のASCO総会でその結果が報告された[44]．Overall survival(p＝0.009)，progression-free survival(p＝0.0001)ともに，有意差をもって治療群が手術単独群を上回り，周術期化学療法の有効性を肯定している．しかし，治療対象に1/3の非治癒切除症例が含まれること，25%が食道浸潤胃癌あるいは食道腺癌であること，手術内容が不明であることなど，わが国に当てはめられる内容かどうかはかなり疑問がある．

Meta-analysis

Meta-analysisは，論文として報告され，質の保証された複数のRCTにおける登録症例のオリジナルデータを統計学的に処理して，全体としての傾向を引き出すことを目的とした手法である[45]．

1993年，Hermansら[46]は，手術単独群を対照とした13研究についてmeta-analysisを行い，odds ratio 0.82(95% CI：0.68～0.98)と，補助化学療法の有用性を示唆する結果を報告した．その後も，1999年にEarleら[47]が(odds ratio 0.80，95% CI：0.66～0.97)，2000年にMariら[48]が(odds ratio 0.82，95% CI：0.75～0.89)同様の報告を行っている．

Meta-analysisは，一定の治療法に関するいくつかの臨床試験を合同して，意義のある結論を導く方法論であるが，胃癌に関するこれらの結果は多種多様な治療法を集計したもので，全体として胃癌術後補助化学療法の有用性を示唆はするが，臨床現場で必要な実際の治療選択には直結しない．この示唆を受けてわれわれが行うべきことは，第Ⅱ相試験や進行胃癌での有用性が示されている治療レジメンを用いて，あくまで手術単独群を対照に置いたpivotal studyといえる大規模RCTを実施することである．

おわりに

胃癌補助化学療法の研究が始まってから半世紀が過ぎようとしている．過去のRCTには，①対象群の設定，②レジメンの選択根拠，③サンプルサイズの算定，④適格性と除外脱落，⑤サブセット解析とその解釈，といった基本的な方法論に問題があったため，補助化学療法の有効性に関するevidenceが未だに得られていないという現状を作り出した．

RCTに関する正しい理解がようやく普及の兆しをみせ，大規模で質の良いRCTが徐々に増えてきた．そのうちのいくつかは肯定的な結果を報告しており，補助療法の有効性は証明されつつある．

しかし，外国で行われたRCTの結果を無批判にわが国に導入することはできない．国により，早期癌と進行癌の比率や，リンパ節郭清などの治療法が大きく異なるからである．D2郭清が標準的に行われ，手術単独群の治療成績が優秀なわが国の胃癌患者に適用できるような，わが国独自のevidenceを確立する必要がある．

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