Tumor stage

In the INT 0116 and ACTS-GC trials, only patients with pathologically confirmed stages after curative resection were recruited. More T3/T4 tumors were included in INT 0116 (69%) than in ACTS-GC (46%), but lymph node metastasis was less frequently detected in INT 0116 (85%) than in ACTS-GC (89%). It is well established that incidence and extent of nodal metastasis closely correlate with T stage of the primary tumor [12]; therefore, the above observation may appear contradictory. This may be explained by the fact that lymphadenectomy and postoperative nodal retrieval are more extensively performed in Japan; thus, small nodal disease possibly overlooked in the US trial could be detected.

In the MAGIC trial, it is difficult to determine the exact proportions of T and N stages of gastric cancer from the published data, partly because they were presented together with esophageal cancers and partly because there are several missing or "unknown" data. Nodal status is available in 156 of 187 gastric cancer patients in the surgery group, and only 114 (73%) had nodal metastasis, which is considerably lower than the other two trials (85% for INT 0116 and 89% for ACTS-GC). However, this is likely to be an underestimation because nonresectable cases with high probability of nodal metastasis were not included in this calculation.

A notable eligibility criterion used in ACTS-GC was the negative result of peritoneal cytology. Free cancer cells detected in the lavage fluid at the beginning of laparotomy or staging laparoscopy are a strong indicator of poor prognosis [13•], and the Japanese Classification [14] includes this as a determinant of the disease stage (ie, a tumor with positive cytology is staged as IV regardless of the T or N status). Exclusion of patients with positive cytology facilitates selection of patients with minimal residual disease who thus may benefit from adjuvant chemotherapy.

In all, Japanese patients in ACTS-GC were a highly selective population with the best prognosis among the three trials. Patients in MAGIC had the poorest prognosis at the time of registration because a considerable proportion had noncurative, even unresectable, disease. American patients in INT 0116 had more advanced T3/T4 disease than the Japanese patients but with better prognosis than the MAGIC population because they had undergone at least grossly curative resection.

Tumor site and type of surgery

Today, there is a remarkable difference between the East and the West in regard to the anatomical location of gastric cancer; in the West, a prominent shift to the proximal stomach exists [15,16]. Nevertheless, most tumors in the INT 0116 trial were located in the distal stomach, and 60% of the patients underwent distal gastrectomy. It is interesting that this rate of distal gastrectomy was very similar to that in the Japanese ACTS-GC trial (58%).

The MAGIC trial initially recruited only patients with gastric cancer, but extended the inclusion criteria to those with adenocarcinoma of the lower esophagus in the last 3 of the 8 accrual years. Fourteen percent of the tumors in the trial were lower esophageal cancer, and 22% of the patients in the surgery group underwent esophagogastrectomy. Of the other 146 gastric resections in this group, distal gastrectomy accounted only for 37%, indicating the predominance of proximal tumors in the trial.

The predominance of distal tumors in ACTS-GC and that of proximal tumors in MAGIC appears to reflect the general background of the disease in each region, although the patients in the INT 0116 trial may not represent American gastric cancer patients. The strict eligibility criteria of curative gastrectomy may have excluded many proximal or esophagogastric junction tumors which are, in general, locally more aggressive than distal tumors [17].

Lymphadenectomy

In adjuvant trials, surgery does not draw much attention because it is not a tested variable; rather it is a constant that is supposed to be the same or alike between the compared arms. However, when the results of separate studies are compared or combined for meta-analysis, the quality of surgery should be considered with great attention. In most solid tumors, including gastric cancer, surgery still plays the key role for cure, and the extent of surgery can easily alter the volume of residual tumor burden. If an adjuvant therapy aims at the systemically scattered cancer cells, the difference of surgery does not much matter. However, if the local residual disease is an important prognostic determinant to be targeted by adjuvant therapy, as in INT 0116, extent of surgery should be strictly controlled because it will directly affect the trial end points.

In the ACTS-GC trial, great attention was given to the quality assurance of surgery. Only high-volume centers participated in the study, the extent of lymphadenectomy was carefully reviewed, and the minimum requirement of D2 was confirmed before registration. In a D2 lymphadenectomy, the perigastric (N1) nodes and those along the branches of the celiac artery (N2) are completely removed [14].

In the INT 0116 trial, the operative records were reviewed in terms of lymphadenectomy, and it was found that the vast majority (90%) of patients had undergone limited lymphadenectomy [18]. Considering the high incidence of pathological nodal involvement in these patients (85%), microscopic disease must have remained in the nodes around the celiac artery in a considerable proportion of cases. In the subset analysis of the long-term results, chemoradiation did not improve survival of patients undergoing D2 lymphadenectomy [19]. Thus, the positive results of this study could be interpreted to mean that chemoradiation therapy was effective in eradicating the residual local disease, thereby reducing local recurrence and subsequent systemic metastasis.

Table 1. Survival data of three pivotal trials

	INT 0116	MAGIC*	ACTS-GC
Surgery group			
3-year overall survival, %	41	31	70.1
3-year relapse-free survival, %	31	25	59.6
Chemo(radiation) group			
3-year overall survival, %	50	44	80.1
3-year relapse-free survival, %	48	40	72.2
Hazard ratios between arms			
Death	0.74	0.75	0.68
Progression	0.66	0.66	0.62

*Three-year survival rates in MAGIC trial were not shown (Cunningham et al. [4••]). The listed figures were estimations obtained from the survival curves presented.

In the MAGIC trial, the extent of lymphadenectomy was at the surgeon's discretion. Cunningham et al. [4••] reported that D2 lymphadenectomy was performed more frequently than D1 (96 and 50 cases, respectively, in the surgery group); however, this cannot be accepted at face value. First, these terms were used inaccurately (the researchers incorrectly termed "D1" as denoting limited lymph node dissection, and "D2" as denoting extended lymph node dissection), suggesting that a precise review of operative records, such as in the INT 0116 study, did not occur. Second, D2 lymphadenectomy, in its properly defined context, was not the standard of surgery in Europe at the time of the trial. Extremely high hospital mortality rates following D2 lymphadenectomy in both the Dutch D1/D2 trial and the British D1/D2 trial (10% and 13%, respectively) had been recently published (1995 and 1996) [20,21] at the time of MAGIC trial accrual (between 1994 and 2002); therefore, surgeons participating in the MAGIC trial had no strong reason to perform this dangerous surgery, especially after intensive chemotherapy. Indeed, the operative mortality of the MAGIC trial (5.4% in the chemotherapy group and 5.9% in the surgery group) was even lower than that of D1 group in the British D1/D2 trial (6.5%). Therefore, it seems inappropriate to consider that the surgery was more radical in MAGIC than in INT 0116 [22].

Survival

The survival data of the three trials are summarized in Table 1. Following publication of the INT 0116 and MAGIC trial data, many discussions have arisen regarding which therapy—adjuvant or perioperative—is superior in terms of survival [23]. However, this comparison requires special attention because these trials had essentially different populations in terms of curability and disease stages, as discussed above. Despite the difference in the survival rates between the two trials, the hazard ratios for both death and progression between the surgery and treatment arms were exactly the same.

There was a strikingly large difference in baseline survival between the Japanese study and the other two trials. The 3-year overall and relapse-free survival rates in the surgery group of ACTS-GC were almost twice as high as those in INT 0116 and MAGIC. Again, this should be attributed to the population differences discussed above. A more aggressive surgical approach in Japan may also have contributed to this survival difference. However, the 3-year survival of gastrectomy plus chemoradiation in INT 0116 (50%), which could be considered a result of optimal local therapy, was still far inferior to that of the Japanese surgery-only group (70.1%); the difference in local control alone cannot explain such a large survival difference.

Other Recently Concluded and Currently Ongoing Studies

In the time since the three pivotal studies discussed previously, other clinical studies in the United States, Europe, and East Asia have recently concluded or are ongoing (Table 2).

Studies in the United States

Following INT 0116, adjuvant chemoradiotherapy has become a standard treatment option in the United States; all ongoing clinical trials for localized gastric cancer now include chemoradiation. In a phase 3 trial (CALGB-80101), the chemoradiation regimen used in the INT 0116 trial is being compared with one in which the ECF regimen of the MAGIC trial is used rather than 5-FU/leucovorin [24].

Neoadjuvant chemoradiation is a new subject drawing great attention. A phase 2 trial (RTOG 9904) in a cooperative study setting tested a regimen consisting of 5-FU/leucovorin/cisplatin induction followed by concurrent 45-Gy radiation and 5-FU, as well as weekly paclitaxel prior to surgical resection. Results showed pathological complete response in 26% and favorable survival of responders [11•]. Other chemotherapeutic regimens currently being evaluated in combination with radiation include capecitabine and oxaliplatin (SWOG-S0425) [25].

Table 2. Currently active phase 3 trials on (neo)adjuvant therapy for gastric cancer

Study	Country	Patients, *n*	Disease	Therapeutic modes
CALGB-80101 [24]	USA	∂24	Stage Ib–IV M0	Surgery + chemoradiation (RT + 5-FU/leucovorin) vs surgery + chemoradiation (ECF)
MRC-ST03 [29]	United Kingdom	1100	Stage Ib–IV M0	ECX + surgery + ECX vs ECX/bevacizumab + surgery + ECX/bevacizumab + bevacizumab
CRITICS [30]	The Netherlands	788	Stage Ib–IVa M0	ECC + surgery + ECC vs ECC + surgery + chemoradiation (RT + capecitabine/cisplatin)
CLASSIC [31]	Korea	1024	Stage II, III	Surgery vs surgery + capecitabine/oxaliplatin
SMC IRB [33]	Korea	490	Stage Ib–IV M0	Surgery + capecitabine/cisplatin vs surgery + chemoradiation (RT + capecitabine/cisplatin)
SAMIT [34•]	Japan	1480	T3–4, N0–2	Surgery + UFT vs surgery + S-1 vs surgery + paclitaxel + UFT vs surgery + paclitaxel + S-1
JCOG 501 [36]	Japan	316	Linitis plastica/large ulcerative tumor	Surgery + S-1 vs S-1/cisplatin + surgery + S-1

The ECC and ECX regimens comprise the same chemotherapy elements; however, because different trials use these agents in different doses or timings, the abbreviations have been set to match the original expressions used in the respective citation and/or trial registration.
5-FU—fluorouracil; ECC/ECX—epirubicin, cisplatin, capecitabine; ECF—epirubicin, cisplatin, 5-FU; RT—radiation therapy; UFT—tegafur–uracil.

Studies in Europe

The results of a French neoadjuvant randomized controlled trial were presented at the American Society of Clinical Oncology meeting in 2007 [26]. A total of 224 patients with adenocarcinoma of the lower esophagus (11%), esophagogastric junction (64%), or stomach (25%) were enrolled between 1995 and 2003. The chemotherapy group received two to three courses of 5-FU/cisplatin before surgery, whereas the surgery group immediately proceeded to surgery without additional chemotherapy. The responders of the neoadjuvant group also received postoperative chemotherapy. The 5-year overall survival rate was 38% in the chemotherapy group and 24% in the surgery group (HR 0.69; $P = 0.02$). Although the publication of the details is awaited, this can be considered supportive evidence for the MAGIC trial.

The ECF regimen is now undergoing modifications, as the UK National Cancer Research Institute REAL-2 study for advanced disease showed noninferiority of oral capecitabine to infusional 5-FU [27]. In the "MAGIC-B" trial (MRC-ST03), the 5-FU component of ECF is substituted by capecitabine (ECX). The perioperative ECX is to be compared with ECX plus bevacizumab in a phase 3 setting [28•,29].

Adjuvant chemoradiation is also being tested in Europe. In the Dutch CRITICS trial, patients with resectable gastric cancer receive neoadjuvant ECC and surgery, and then either adjuvant ECC or adjuvant 45-Gy radiation with cisplatin and capecitabine [30].

Studies in East Asia

In Korea, where D2 gastrectomy is routinely performed as in Japan, an adjuvant randomized controlled trial is currently evaluating capecitabine/oxaliplatin after curative surgery for stage II and III gastric cancer (CLASSIC trial) [31]. This is an international study involving institutions in China and Taiwan, and would be the last large-scale randomized controlled trial with a control arm of surgery alone (as further discussed in the Future Perspectives section). Adjuvant chemoradiotherapy is being evaluated in the Samsung Medical Center (Seoul, South Korea) a mega-volume center for gastric cancer surgery (1000 gastrectomies/year). The center published a nonrandomized study using the same regimen as the INT 0116 trial, and results suggested the survival benefit of this regimen even after D2 gastrectomy [32•]. Currently, a randomized controlled trial in a single-institutional setting is under way at the Samsung Medical Center to compare D2 gastrectomy plus adjuvant capecitabine/cisplatin with D2 plus chemoradiation [33].

Following the ACTS-GC trial, adjuvant S-1 has become a standard treatment in Japan, and various trials are active or being planned with S-1 as the reference arm. An adjuvant study (SAMIT) is evaluating the sequential use of paclitaxel and S-1 or oral UFT (tegafur–uracil) for T3/T4 gastric cancer in a 2 × 2 factorial design, expecting that adding paclitaxel to a fluoropyrimidine may reduce peritoneal recurrence [34•]. Following the SPIRITS trial, in which the superiority of S-1/cisplatin to S-1 alone was proven for advanced gastric cancer [35], a phase 2 trial is under way to confirm the feasibility of adjuvant S-1/cisplatin after D2 curative gastrectomy for stage III gastric cancer.

Neoadjuvant chemotherapy has also been evaluated in phase 2 settings. The Japan Clinical Oncology Group (JCOG) completed four trials recruiting high-risk gastric cancer patients (ie, linitis plastica, large diffuse ulcerative tumors, or tumors with bulky nodal metastasis). Three regimens were used: S-1 alone, cisplatin/irinotecan, and S-1/cisplatin. A high pathological response rate with low toxicity was observed with S-1/cisplatin, and a phase 3

trial (JCOG 0501) has started to compare immediate D2 gastrectomy plus adjuvant S-1 with neoadjuvant S-1/cisplatin followed by D2 gastrectomy plus adjuvant S-1 [36].

Future Perspectives

Although the treatment modalities and populations studied were all different, the three trials clearly showed a survival benefit of adjuvant or perioperative therapy for gastric cancer. With the exception of the Korean CLASSIC trial, a control arm of surgery alone has already disappeared in recently launched randomized controlled trials [31]. Large-scale trials will be conducted to compare various combinations of chemotherapy and radiotherapy before and/or after surgery, possibly including new molecular targeting agents.

In the West, the American principle of adjuvant chemoradiation and European principle of perioperative chemotherapy will certainly merge in the near future through cooperative randomized controlled trials. The Dutch CRITICS trial is such an example [30]. International cooperation may become mandatory in the West because of the relatively low incidence of gastric cancers, especially those that are localized.

The increasing trend of esophageal adenocarcinoma and esophagogastric junction tumors in the West are also expected to change the target population. In the middle of the trial, MAGIC extended its inclusion criteria to include esophageal cancer. Currently, there are several phase 2 studies that recruit patients with only esophageal and junctional adenocarcinomas. Application of the results of these trials to stomach cancer merits attention.

In Eastern Asia, the evolution of adjuvant therapy is also awaited, but from a different standpoint. In the INT 0116 and MAGIC trials, the 5-year overall survival rates of the surgery groups are less than 30%, even after curative resection. For a population with such a poor prognosis, toxic combination therapy is warranted even despite the possibility of treatment-related death. However, for a population in which a majority survives by surgery alone, physicians may hesitate about the blind use of highly toxic therapy for all patients, especially before surgery. These physicians would likely prefer primary D2 gastrectomy, careful pathological staging, and selection of high-risk tumors for adjuvant therapy. Simple regimens with high compliance and low toxicity are desirable, and in this regard, oral S-1 monotherapy is acceptable.

According to the Japanese Gastric Cancer Association's nationwide registry of gastric cancer, the 5-year overall survival rate of resected stage IIIb and IV tumors (International Union Against Cancer's TNM [tumor, node, metastasis] staging) was 30.5% and 9.9%, respectively; for resected linitis plastica tumors, it was 16.2% [37•]. Together, these populations would have a comparable prognosis to those of the INT 0116/MAGIC trials, and will likely become a target of toxic combination therapy before and/or after surgery. The JCOG 0501 is such an example [36]. Thus, (neo)adjuvant regimens in Japan and Korea will probably evolve depending on tumor stages, based on the premise that D2 gastrectomy provides sufficient local tumor control and accurate staging.

Conclusions

As a result of three pivotal trials, adjuvant and neoadjuvant therapies for gastric cancer have entered a new era. Large-scale, randomized controlled trials should further produce evidence of benefits from various combination regimens. The East and the West have different patient populations and surgical approaches with different baseline survival rates; therefore, despite some cross-over, their studies are likely to move forward in separate directions. Research on molecular prognostic/predictive markers may be helpful in bridging the gap.

Clinical Trials Acronyms

ACTS-GC—Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer; CALGB—Cancer and Leukemia Group B; CLASSIC—Capecitabine and Oxaliplatin Adjuvant Study in Stomach Cancer; CRITICS—Chemoradiotherapy after Induction Chemotherapy in Cancer of the Stomach; INT—Intergroup; JCOG—Japanese Clinical Oncology Group; MAGIC—Medical Research Council Adjuvant Gastric Infusional Chemotherapy; MRC-ST—Medical Research Council Study; REAL—Revised European American Lymphoma Classification; RTOG—Radiation Therapy Oncology Group; SAMIT—Stomach Cancer Adjuvant Multi-institutional Trial; SMC IRB—Samsung Medical Center Institutional Review Board; SPIRITS—S-1 Plus Cisplatin vs S-1 in RCT in the Treatment of Stomach Cancer; SWOG—Southwest Oncology Group.

Disclosure

No potential conflict of interest relevant to this article was reported.

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D2 Lymphadenectomy Alone or with Para-aortic Nodal Dissection for Gastric Cancer

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ABSTRACT

BACKGROUND

Gastrectomy with D2 lymphadenectomy is the standard treatment for curable gastric cancer in eastern Asia. Whether the addition of para-aortic nodal dissection (PAND) to D2 lymphadenectomy for stage T2, T3, or T4 tumors improves survival is controversial. We conducted a randomized, controlled trial at 24 hospitals in Japan to compare D2 lymphadenectomy alone with D2 lymphadenectomy plus PAND in patients undergoing gastrectomy for curable gastric cancer.

METHODS

Between July 1995 and April 2001, 523 patients with curable stage T2b, T3, or T4 gastric cancer were randomly assigned during surgery to D2 lymphadenectomy alone (263 patients) or to D2 lymphadenectomy plus PAND (260 patients). We did not permit any adjuvant therapy before the recurrence of cancer. The primary end point was overall survival.

RESULTS

The rates of surgery-related complications among patients assigned to D2 lymphadenectomy alone and those assigned to D2 lymphadenectomy plus PAND were 20.9% and 28.1%, respectively (P=0.07). There were no significant differences between the two groups in the frequencies of anastomotic leakage, pancreatic fistula, abdominal abscess, pneumonia, or death from any cause within 30 days after surgery (the rate of death was 0.8% in each group). The median operation time was 63 minutes longer and the median blood loss was 230 ml greater in the group assigned to D2 lymphadenectomy plus PAND. The 5-year overall survival rate was 69.2% for the group assigned to D2 lymphadenectomy alone and 70.3% for the group assigned to D2 lymphadenectomy plus PAND; the hazard ratio for death was 1.03 (95% confidence interval [CI], 0.77 to 1.37; P=0.85). There were no significant differences in recurrence-free survival between the two groups; the hazard ratio for recurrence was 1.08 (95% CI, 0.83 to 1.42; P=0.56).

CONCLUSIONS

As compared with D2 lymphadenectomy alone, treatment with D2 lymphadenectomy plus PAND does not improve the survival rate in curable gastric cancer. (ClinicalTrials.gov number, NCT00149279.)

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GASTRIC CANCER IS THE SECOND LEADING cause of cancer death worldwide, although its incidence is decreasing.[1] About 60% of new cases of gastric cancer occur in eastern Asia; the incidence of new cases in Japan is 100,000 per year. Chemotherapy helps to prolong survival in cases of advanced disease, but surgical resection is the most effective treatment for curable gastric cancer. Reports from the Gastric Cancer Registry and other retrospective studies[2-4] have made radical gastrectomy with extended (D2) removal of regional lymph nodes the standard for the treatment of curable gastric cancer in Japan. Two randomized, controlled European trials that compared the less extended D1 dissection with the D2 procedure failed to show a survival benefit for D2 dissection,[5,6] but lack of experience with the surgical procedure and with postoperative care were thought to account for the poor outcome of patients who underwent D2 lymphadenectomy.[7-9] In 2001, the American Intergroup 0116 study showed that chemoradiotherapy after limited lymphadenectomy (D0 or D1) decreased the local recurrence rate and increased long-term survival,[10] a result suggesting that chemoradiotherapy eliminates the residual lymph-node metastases that could be removed by D2 lymphadenectomy. In 2006, a randomized trial in Taiwan showed a significant benefit in overall survival for a D2 or D3 procedure as compared with D1 dissection, with no increase in operative mortality.[11] These trials indicate that adequate local control is essential for the treatment of gastric cancer. Hence, the standard of care for curable gastric cancer in eastern Asia and the United States is either gastrectomy with D2 lymphadenectomy and without postoperative chemoradiation or D0 or D1 gastrectomy with postoperative chemoradiation.[12-14]

Once the gastric tumor invades the subserosa (stage T2b), the serosa (stage T3), or the adjacent structures (stage T4), metastases can spread to the para-aortic lymph nodes, which are termed N3 nodes according to the *Japanese Classification of Gastric Carcinoma*, second English edition,[15] and M1 nodes according to the International Union Against Cancer (UICC) tumor–node–metastasis (TNM) classification.[16] In advanced gastric cancer, the incidence of microscopic metastases in the para-aortic region is 10 to 30%.[17-19] Because the 5-year overall survival rate of patients with para-aortic nodal metastases can be as high as 20% after systematic dissection,[20] extensive surgery has been performed in Japan since the 1980s for stage T2b, T3, and T4 gastric cancers. However, to our knowledge there has never been a large prospective study to investigate whether para-aortic nodal dissection (PAND) for gastric cancer has a survival benefit. Here we report the final results of a multi-institutional, randomized, controlled trial by the Japan Clinical Oncology Group (JCOG9501) that was conducted to determine whether the addition of systematic PAND to standard gastrectomy with D2 lymphadenectomy improves survival rates among patients with curable gastric cancer. An interim analysis found no differences between the two procedures in the rates of short-term major complications or in-hospital death.[21]

METHODS

ELIGIBILITY

In this trial, we enrolled patients who were younger than 75 years of age and who had histologically proven gastric adenocarcinoma that was considered potentially curable. Additional eligibility criteria, as determined from intraoperative findings, were the presence of a stage T2b, T3, or T4 tumor, the absence of gross metastases to the para-aortic nodes, and negative cytologic findings in peritoneal-lavage fluid. Diagnosis of metastases by examination of frozen sections of para-aortic nodes was not allowed, because sampling of the nodes would involve dissection. The study protocol was approved by the JCOG protocol review committee and the institutional review boards of each of the 24 participating hospitals. In accordance with JCOG policy in 1995 (the year in which enrollment began), all patients gave written informed consent before undergoing randomization.

RANDOMIZATION AND DATA MANAGEMENT

After confirming the eligibility of the patient during surgery, the surgeon contacted the JCOG Data Center by telephone to receive a randomly generated assignment of the patient to standard D2 lymphadenectomy alone or D2 lymphadenectomy plus PAND. Assignments were made by the minimization method according to clinical T stage (T2b vs. T3 or T4), Borrmann macroscopic type (type 0, 1, or 2 vs. type 3 or 5), and institution (patients with Borrmann type 4 tumors were excluded because there was no chance of cure for such patients if they had para-aortic nodal metastases). The surgeon then performed the assigned operation according to the methods described in the protocol.

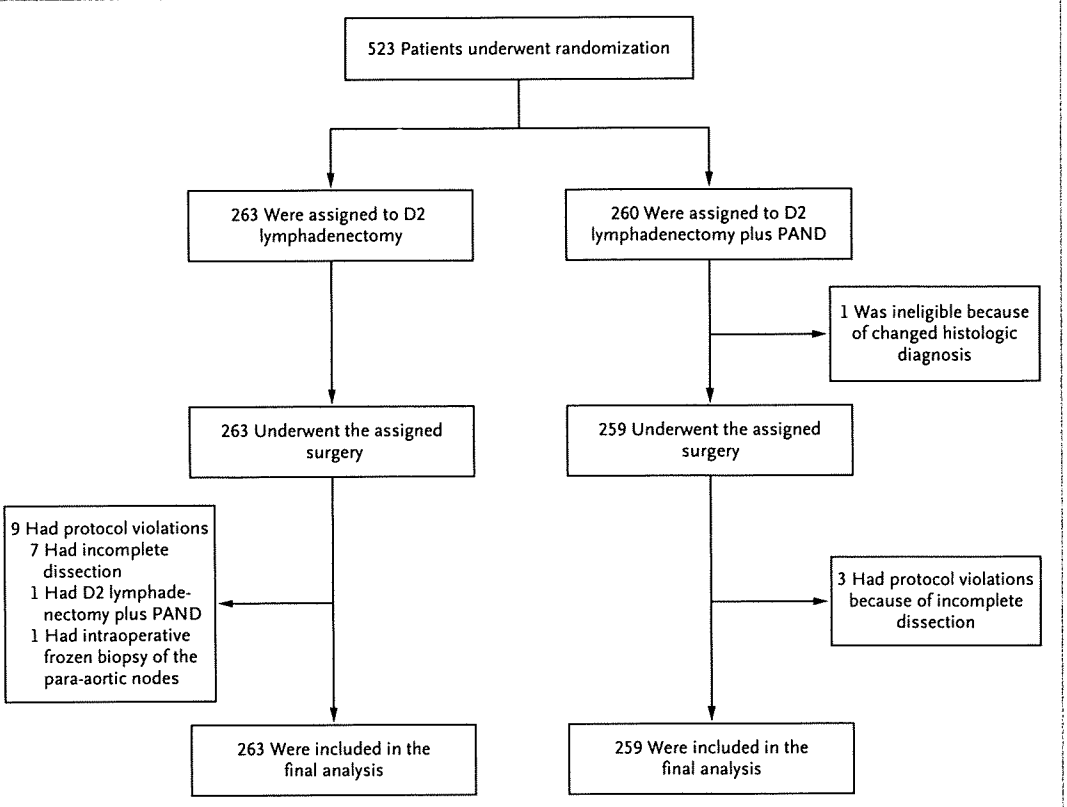

Figure 1. **Disposition of the Patients.**
PAND denotes para-aortic nodal dissection.

The JCOG data center performed data management, central monitoring, and statistical analysis. The center also provided twice-yearly monitoring reports, each of which was submitted to and reviewed by an independent JCOG data and safety monitoring committee. None of the surgeons who performed the operations were involved in data analysis. For quality assurance, the JCOG audit committee made site visits to monitor whether the study was being conducted according to protocol.

SURGERY

D2 lymphadenectomy alone and D2 lymphadenectomy plus PAND were performed as described previously.[21,22] The dissected lymph nodes were classified according to the *Japanese Classification of Gastric Carcinoma*, first English edition.[23] The method of reconstruction of the gastrointestinal tract was not specified.

During the planning of the study, all participating surgeons reached agreement concerning the technical details of both procedures. All operations either were performed by surgeons who had previously performed more than 100 gastrectomies with D2 dissection or took place at institutions with specialized units where more than 80 gastrectomies were performed annually. In addition to reviewing the twice-yearly monitoring reports, the surgeons observed videos of both types of procedures obtained in a sample of patients (at least three patients from each institution during the course of the study) and discussed the technical details of the operations to ensure uniformity of treatment. To assess adherence to the lymphadenectomy protocol, the dissection status of all regional nodal stations and the number of dissected nodes in the para-aortic area were recorded on case report forms, which were also reviewed by the surgeons.

POSTOPERATIVE EVALUATION

Pathologic findings were categorized according to the first English edition of the *Japanese Classifica-*

tion of Gastric Carcinoma[23]; thus, some lymph nodes currently classified as N2 or N3 were recorded as N3 or N4 in this study. Stage T2 was subdivided into stages T2a and T2b, as specified by the UICC TNM classification.[16] The rates of hospital death, defined as death during the period of hospitalization for the operation or death from any cause within 30 days after surgery, and surgery-related complications were calculated by dividing the number of patients in whom an event occurred by the total number of enrolled patients. Patients were followed every 3 months until April 2006, which was 5 years after the last patient had been enrolled. Adjuvant therapy was not allowed before the recurrence of cancer.

STATISTICAL ANALYSIS

The primary end point of this study was overall survival, defined as the time from randomization to death. The secondary end points were recurrence-free survival, surgery-related complications, and hospital death. Recurrence-free survival was defined as the time from randomization to the first recurrence of cancer or death from any cause.

The expected 5-year survival rate of the group assigned to D2 lymphadenectomy alone was 50%. We initially planned to recruit 412 patients (206 in each group), a number that would allow the detection of a 12% increase in survival in the group assigned to D2 lymphadenectomy plus

Table 1. **Characteristics of the Patients.***

Characteristic	D2 Lymphadenectomy Alone (N=263)	D2 Lymphadenectomy plus PAND (N=260)	P Value†
Age — yr			0.34
Median	60	61	
Range	25–75	27–75	
Sex — no. (%)			0.40
Male	176 (66.9)	183 (70.4)	
Female	87 (33.1)	77 (29.6)	
Body-mass index — no. (%)‡			0.64
<22.0	138 (52.5)	126 (48.5)	
22.0–24.9	87 (33.1)	95 (36.5)	
≥25.0	38 (14.4)	39 (15.0)	
Tumor location — no. (%)			0.83
Upper third of stomach	53 (20.2)	47 (18.1)	
Middle third of stomach	103 (39.2)	103 (39.6)	
Lower third of stomach	107 (40.7)	110 (42.3)	
Tumor size — cm			0.71
Median	5.5	5.5	
Range	2.0–17.0	2.0–15.2	
Histologic type — no. (%)			0.33
Differentiated	97 (36.9)	107 (41.2)	
Undifferentiated§	166 (63.1)	153 (58.8)	
Borrmann macroscopic type — no. (%)			0.86
0, 1, or 2	109 (41.4)	110 (42.3)	
3 or 5	154 (58.6)	150 (57.7)	
Clinical T stage — no. (%)¶			1.00
T2b	99 (37.6)	98 (37.7)	
T3 or T4	164 (62.4)	162 (62.3)	

Table 1. (Continued).*

Characteristic	D2 Lymphadenectomy Alone (N=263)	D2 Lymphadenectomy plus PAND (N=260)	P Value†
Clinical node status — no. (%)			1.00
Negative	43 (16.3)	42 (16.2)	
Positive	220 (83.7)	218 (83.8)	
Pathological T stage — no. (%)¶			0.31
pT1	9 (3.4)	14 (5.4)	
pT2a	46 (17.5)	37 (14.2)	
pT2b	79 (30.0)	95 (36.5)	
pT3	121 (46.0)	109 (41.9)	
pT4	8 (3.0)	5 (1.9)	
Pathological node status — no. (%)			0.10
Negative	79 (30.0)	96 (36.9)	
Positive	184 (70.0)	164 (63.1)	
No. of positive nodes			0.30
Median	3	2	
Range	0–47	0–112	
Residual tumor — no. (%)			0.50
R0	261 (99.2)	260 (100)	
R1	2 (0.8)	0	

* PAND denotes para-aortic nodal dissection.
† P values were calculated with the use of Fisher's exact test except for comparisons of age, tumor size, and number of positive nodes, for which the Wilcoxon test was used.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ The undifferentiated type included two cases of adenosquamous carcinoma in the group assigned to D2 lymphadenectomy alone and one case of malignant lymphoma in the group assigned to D2 lymphadenectomy plus PAND.
¶ The T stage was determined according to the first English edition of the *Japanese Classification of Gastric Carcinoma*.[23] Stage T2 was subdivided into T2a (invasion confined to the muscularis propria) and T2b (subserosal invasion) according to the 6th edition of the International Union Against Cancer tumor–node–metastasis classification.[16]

PAND, with a one-sided alpha level of 0.05 and a power of 80%. We planned this study with a one-sided test because D2 lymphadenectomy plus PAND is more invasive than D2 lymphadenectomy alone and should in principle result in better survival than D2 lymphadenectomy alone. Because differences smaller than 12% would be clinically meaningful, the protocol was amended to increase the sample size to 520 (260 in each group) to detect an 8% increase in survival in the group assigned to D2 lymphadenectomy plus PAND (hazard ratio, 0.73), with a total accrual period of 5.5 years and an additional 5 years of follow-up. The data and safety monitoring committee approved this change in July 2000 without knowledge of any survival data.

Two interim analyses were planned, with adjustments for repeated comparisons taken into account by the O'Brien–Fleming alpha-spending function.[24] At the first and second interim analyses in March 2002 and March 2004, the data and safety monitoring committee reviewed the results and approved continuation of the planned follow-up.

Data from all eligible patients were analyzed for overall survival and recurrence-free survival on an intention-to-treat basis. Survival curves were estimated by the Kaplan–Meier method and compared with the use of the log-rank test, with stratification according to the factors used in the randomization, except for the institution where the surgery was performed. Hazard ratios were calculated by Cox regression analysis after adjustment for baseline stratification factors except for

institution. Analyses of two prespecified subgroups (Borrmann macroscopic type and clinical T stage) and nine post hoc subgroups were also conducted to evaluate interactions between treatment and subgroup with the use of Cox regression; we report the result of all these analyses. No more than one significant interaction test result ($P<0.05$) would be expected on the basis of chance alone as a result of multiple testing.

Two-sided P values were calculated for all tests and are reported here. Because the study was planned to use a one-sided test, we also present one-sided P values for the results of the survival analyses. P values less than 0.05 were considered to indicate statistical significance. Analyses were performed with the use of SAS software, version 9.13.

RESULTS

PATIENTS

Between July 1995 and April 2001, 523 patients were randomly assigned to D2 lymphadenectomy alone (263 patients) or D2 lymphadenectomy plus PAND (260 patients). One patient was deemed ineligible after enrollment because of a change in the histologic diagnosis to malignant lymphoma. Protocol violations occurred in 12 patients. In one patient, an intraoperative biopsy of a frozen section of a para-aortic node was performed. Another patient assigned to D2 lymphadenectomy alone underwent D2 lymphadenectomy plus PAND. The remaining 10 patients did not undergo all aspects of the lymph-node dissection required in the protocol. At the time of final analysis in April 2006, two patients had been lost to follow-up for more than 1 year, but they had already been followed for more than 5 years after surgery. Figure 1 shows the disposition of the patients.

The characteristics of the two groups were well balanced (Table 1). Total gastrectomy was performed in 102 patients assigned to D2 lymphadenectomy alone (38.8%) and in 97 patients assigned to D2 lymphadenectomy plus PAND (37.3%); 98 patients assigned to D2 lymphadenectomy alone (37.3%) and 93 assigned to D2 lymphadenectomy plus PAND (35.8%) also underwent splenectomy. Only 9 patients assigned to D2 lymphadenectomy alone (3.4%) and 12 assigned to D2 lymphadenectomy plus PAND (4.6%) underwent distal pancreatectomy. The median operation time for gastrectomy with D2 lymphadenectomy plus PAND was 300 minutes, which was 63 minutes longer than that for gastrectomy with D2 lymphadenectomy alone ($P<0.001$). The median blood loss was 230 ml greater (660 ml vs. 430 ml, $P<0.001$) and blood transfusions were more frequent (30.0% vs. 14.1%, $P<0.001$) in patients undergoing D2 lymphadenectomy plus PAND than in those undergoing D2 lymphadenectomy alone.

OPERATIVE COMPLICATIONS AND DEATHS

As reported previously,[21] the overall incidence of surgery-related complications was 20.9% (55 of 263 patients) in the group assigned to D2 lymphadenectomy alone and 28.1% (73 of 260 patients) in the group assigned to D2 lymphadenectomy plus PAND ($P=0.07$). The incidence rates of the four major surgery-related complications in the group assigned to D2 lymphadenectomy alone and the group assigned to D2 lymphadenectomy plus PAND were 2.3% and 1.9%, respectively, for anastomotic leakage, 5.3% and 6.2% for pancreatic fistula, 5.3% and 5.8% for abdominal abscess, and 4.6% and 1.5% for pneumonia. None of these differences were statistically significant. The frequency of minor complications, such as ileus, lymphorrhea, left pleural effusion, and severe diarrhea, was significantly higher in the group assigned to undergo D2 lymphadenectomy plus PAND than in the group assigned to undergo D2 lymphadenectomy alone (20.0% vs. 9.1%, $P<0.001$). The rate of hospital death was 0.8% (two deaths in each group).

OVERALL AND RECURRENCE-FREE SURVIVAL

After median follow-up periods of 5.6 years in the group assigned to D2 lymphadenectomy alone and 5.7 years in the group assigned to D2 lymphadenectomy plus PAND, 96 patients assigned to D2 lymphadenectomy alone and 95 assigned to D2 lymphadenectomy plus PAND had died, and 100 patients assigned to D2 lymphadenectomy alone and 98 assigned to D2 lymphadenectomy plus PAND had had recurrences of cancer. Table 2 lists the site of first tumor recurrence for the two groups. The most frequent site was the peritoneum (38.1% of all recurrences), and the pattern of recurrence was similar in the two groups. The 5-year overall survival rate for 22 of 260 patients (8.5%) who had histologically detected metastases in the para-aortic lymph nodes after undergoing D2 lymphadenectomy plus PAND was 18.2% (95% confidence interval [CI], 5.7 to 36.3).

Figures 2A and 2B show the overall and recur-

rence-free survival rates for all eligible patients. The 5-year overall survival rate was 69.2% (95% CI, 63.2 to 74.4) for the group assigned to D2 lymphadenectomy alone and 70.3% (95% CI, 64.3 to 75.4) for the group assigned to D2 lymphadenectomy plus PAND. The hazard ratio for death was 1.03 (95% CI, 0.77 to 1.37) in the group assigned to D2 lymphadenectomy plus PAND, and the stratified log-rank test showed no significant difference between the groups (one-sided P=0.57, two-sided P=0.85). After adjustment of eight baseline variables (age, sex, body-mass index, tumor location, tumor size, Borrmann macroscopic type, clinical T stage, and clinical N stage) with the use of Cox regression analysis, the hazard ratio was essentially unchanged (hazard ratio, 1.03; 95% CI, 0.78 to 1.38; P=0.83).

The 5-year recurrence-free survival rate was 62.6% (95% CI, 56.4 to 68.2) in the group assigned to D2 lymphadenectomy alone and 61.7% (95% CI, 55.4 to 67.3) in the group assigned to D2 lymphadenectomy plus PAND. The hazard ratio for recurrence in the group assigned to D2 lymphadenectomy plus PAND was 1.08 (95% CI, 0.83 to 1.42; one-sided P=0.72; two-sided P=0.56).

Although there were no significant interactions between treatment effect and any baseline clinical findings, there were significant interactions between treatment effect and pathologic T stage and nodal status (Fig. 3). Among the 174 node-negative patients, the 5-year overall survival rate was 78.4% (95% CI, 67.6 to 86.0) in the group assigned to D2 lymphadenectomy alone and 96.8% (95% CI, 90.5 to 99.0) in the group assigned to D2 lymphadenectomy plus PAND. Conversely, among the 348 node-positive patients, the 5-year overall survival rate was 65.2% (95% CI, 57.9 to 71.6) in the group assigned to D2 lymphadenectomy alone and 54.9% (95% CI, 46.9 to 62.1) in the group assigned to D2 lymphadenectomy plus PAND. The hazard ratios for death in the group assigned to D2 lymphadenectomy plus PAND were 0.39 (95% CI, 0.18 to 0.84; P=0.009) for node-negative patients and 1.39 (95% CI, 1.02 to 1.89; P=0.04) for node-positive patients.

Table 2. **Site of First Tumor Recurrence.***

Site	D2 Lymphadenectomy Alone (N=109)	D2 Lymphadenectomy plus PAND (N=106)
	no. (%)	
Peritoneum	43 (39.4)	39 (36.8)
Lymph nodes	24 (22.0)	23 (21.7)
Liver	21 (19.3)	24 (22.6)
Others	21 (19.3)	20 (18.9)

* In nine patients in the group assigned to D2 lymphadenectomy alone and seven patients in the group assigned to D2 lymphadenectomy plus para-aortic nodal dissection (PAND), more than one site was involved at the time of first recurrence.

DISCUSSION

The clinical value of systematic PAND in addition to D2 gastrectomy in curable gastric cancer has been controversial. In this randomized trial, we found no improvement in overall or recurrence-free survival with D2 lymphadenectomy plus PAND gastrectomy as compared with D2 lymphadenectomy alone. The pattern of recurrence was similar in the two groups, and D2 lymphadenectomy plus PAND did not reduce the rate of recurrence of cancer in the lymph nodes. There were no significant differences between the two groups in the rates of surgery-related complications. D2 lymphadenectomy plus PAND, however, was associated with a longer operation time, greater blood loss, and a significant increase in minor complications. For all these reasons, we cannot recommend D2 lymphadenectomy plus PAND for patients with curable gastric cancer.

Multiple studies have reported a close relation between the number of cases treated in a hospital and outcomes in the surgical treatment of cancer.[25-29] In two European randomized trials comparing D1 with D2 gastrectomy, the mortality rates in patients treated with D2 gastrectomy reached 10% or higher.[30,31] The excessive number of early deaths in these studies may have obscured any potential difference in long-term survival between patients undergoing D1 and D2 gastrectomy. The Dutch trial was conducted in 80 hospitals, including small community hospitals, by 11 surgeons who had little experience with D2 gastrectomy before the study. The limited experience of the surgeons made it difficult for them to learn how to perform the procedure safely and effectively, and the small volume of cases limited the ability of the hospitals to manage major surgical complications. By contrast, in a Taiwanese single-institution trial comparing D1 gastrectomy with D2 or more extensive gastrectomy, all the surgeons had performed at least 80 D2 procedures before

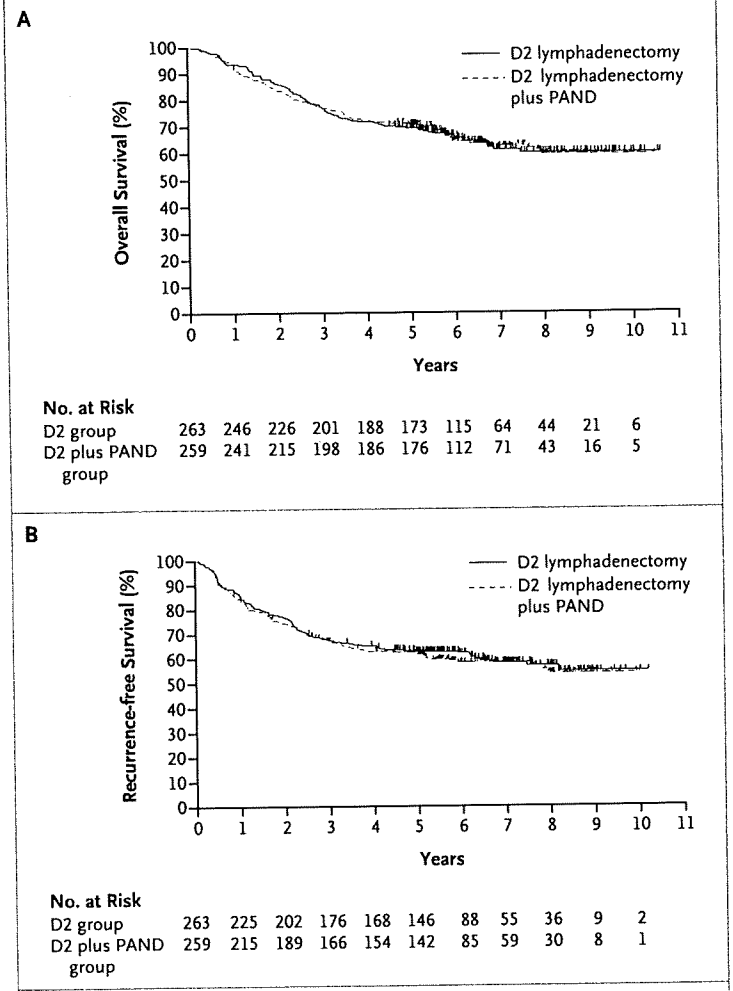

Figure 2. **Kaplan–Meier Estimates of Overall Survival (Panel A) and Recurrence-free Survival (Panel B).**

PAND denotes para-aortic nodal dissection.

participating in the study, and there were no deaths in either group. The procedures in our study either were performed by experienced surgeons or took place in 24 specialized hospitals with a high volume of cases, and our patients had no major coexisting conditions. These two features accounted for very low mortality rates (0.8%) and good long-term survival in both groups.

There were no significant interactions between treatment effect and any baseline clinical findings. We also conducted a post hoc subgroup analysis based on pathologic T stage and node status, variables that were determined after randomization. Surprisingly, among patients with pathologically negative nodes, survival rates were better in those assigned to D2 lymphadenectomy plus PAND than in those assigned to D2 lymphadenectomy alone, whereas in patients with any metastatic nodes, survival rates in the group assigned to D2 lymphadenectomy plus PAND were worse than those in the group assigned to D2 lymphadenectomy alone. This paradoxical interaction with nodal pathologic findings needs cautious interpretation, because it was detected in a post hoc subgroup analysis and was thus subject to biases and errors resulting from multiple testing; moreover, this finding should not influence clinical decisions, since we have no accurate method of assessing lymph-node metastases before surgery, and intraoperative frozen-section diagnosis of all dissected lymph nodes (of which the median number is >50) is not feasible. In fact, the proportion of patients with pathologically negative nodes (33.5%) was twice as high as that determined from clinical findings (16.3%). Within the range of the first- and second-tier nodal stations, a high probability of residual nodal metastasis, as calculated by a computer program based on the large database at the National Cancer Center Tokyo, was associated with a poor prognosis. This finding was confirmed in two randomized trials of surgery for gastric cancer conducted in Europe and the United States.[32,33] Our results are contradictory, since treatment with D2 lymphadenectomy plus PAND should reduce the probability of residual metastases in node-positive patients but not in node-negative patients, in whom there is no possibility of nodal metastases in the para-aortic area. Since this result from a post hoc subgroup might be a false positive owing to multiple testing, the possible survival benefit of D2 lymphadenectomy plus PAND in node-negative patients will need to be clarified in further studies.

One limitation of this study is that the incidence of metastases in the para-aortic nodes (8.5%) was lower than expected. A previous report showed that the most reliable predictor of metastases in the para-aortic nodes was the pathologic status of nodes at station 7.[34] In our 76 patients with metastases at this station, however, 5-year overall survival rates after D2 lymphadenectomy plus PAND (36.4%; 95% CI, 20.6 to 52.3) were not significantly better than those after D2 lymphadenectomy alone (44.2%; 95% CI, 29.2 to 58.2; hazard ratio, 1.09; 95% CI, 0.62 to 1.93; P=0.76). D2 lymphadenectomy plus PAND in node-positive patients results in worse survival rates; it is un-

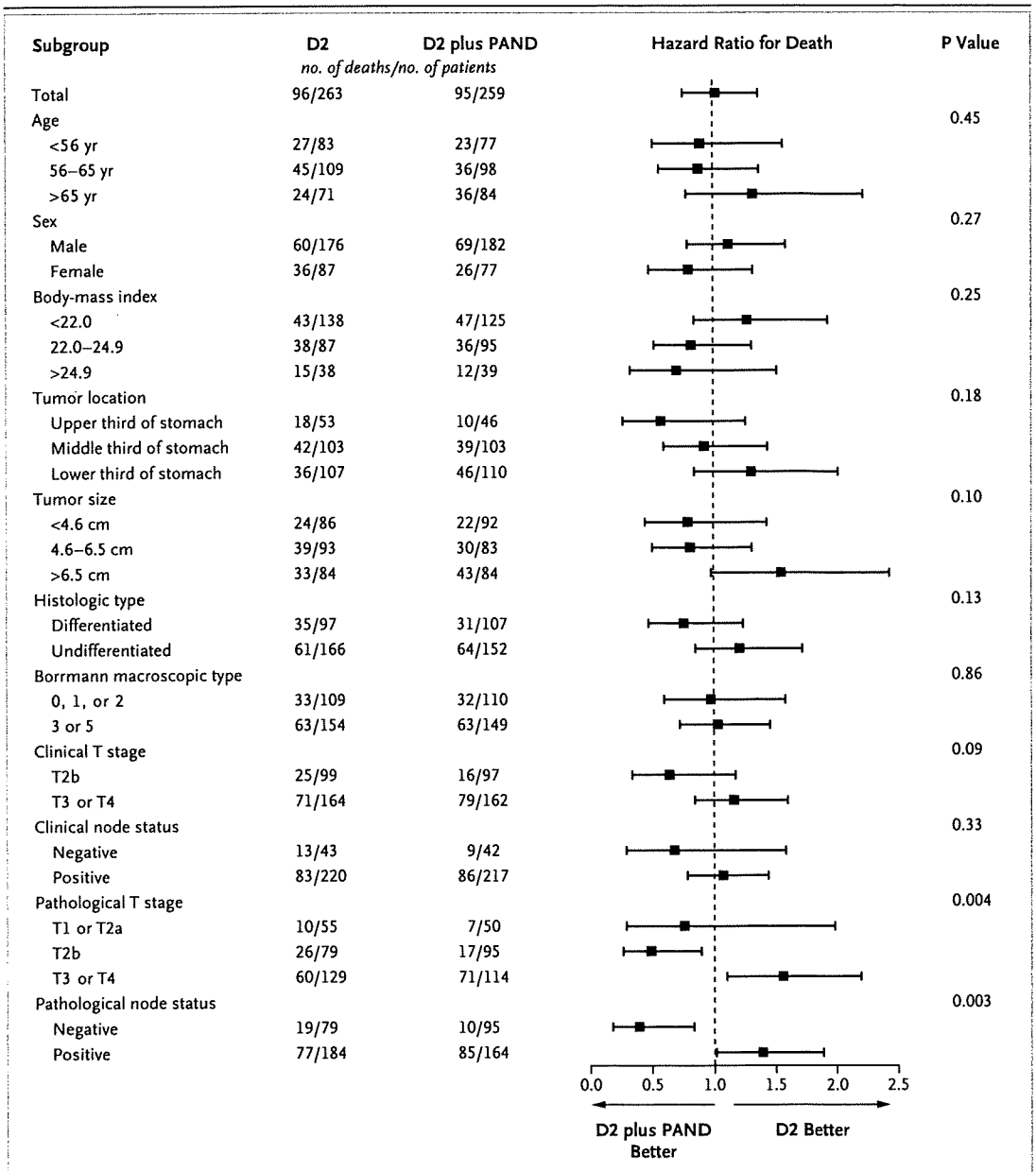

Figure 3. **Tests for Heterogeneity of Treatment Effect According to the Clinicopathological Characteristics of the Patients.**

D2 denotes D2 lymphadenectomy, and PAND para-aortic nodal dissection. The figure shows P values for interactions and hazard ratios for death in the group assigned to D2 lymphadenectomy plus PAND, with 95% confidence intervals. The body-mass index is the weight in kilograms divided by the square of the height in meters.

likely that D2 lymphadenectomy plus PAND would have resulted in better survival rates if we had had more patients with para-aortic node metastases.

A large phase 3 trial recently demonstrated that adjuvant therapy with S-1, an orally active fluoropyrimidine, significantly improved survival in Japanese patients with stage II or III gastric cancer.[35] As was suggested in the case of chemoradiation,[10] there may be some interaction between surgery and adjuvant treatment. In our study, which was performed before the S-1 trial, no patients received any adjuvant treatment.

In conclusion, extended D2 lymphadenectomy plus PAND should not be used to treat curable stage T2b, T3, or T4 gastric cancer. D2 gastrectomy is associated with low mortality and reasonable survival times when performed in selected institutions that have had sufficient experience with the operation and with postoperative management.

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Original article

Outcome of pylorus-preserving gastrectomy for early gastric cancer

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Background: Pylorus-preserving gastrectomy has been introduced as a function-preserving operation for early gastric cancer in Japan. The aim of this study was to investigate the safety and radicality of the procedure.

Methods: Between 1995 and 2004, 611 patients with apparent early gastric cancer in the middle third of the stomach had pylorus-preserving gastrectomy. The short-term surgical and long-term oncological outcomes of these operations were assessed.

Results: The accuracy of preoperative diagnosis of early gastric cancer was 94·3 per cent. Nodal involvement was seen in 62 patients (10·1 per cent). There were no postoperative deaths. Complications developed in 102 patients (16·7 per cent). Major complications, such as leakage and abscess, were observed in 19 (3·1 per cent). The most common complication was gastric stasis, occurring in 49 (8·0 per cent). The overall 5-year survival rate in patients with early gastric cancer was 96·3 per cent.

Conclusion: Pylorus-preserving gastrectomy is a safe operation with an excellent prognosis in patients with early gastric cancer. It is recommended as the standard procedure for early gastric cancer in the middle third of the stomach.

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Introduction

Since the 1950s, gastric cancer has been the most common cause of death among neoplasms of the digestive system in Japan. Gastrectomy with extended (D2) lymphadenectomy has become firmly established as the standard operation[1–4]. In recent years, early gastric cancer (EGC) has accounted for nearly 50 per cent of all gastric cancers in Japan[5]. EGC has an excellent prognosis after surgical treatment, with 5-year survival rates of more than 90 per cent being reported by both Western and Japanese investigators. Japanese surgeons have therefore revised their strategy of focusing on highly radical operations. This has led to function-preserving surgery to minimize postgastrectomy problems with the intention of creating a better quality of life, while maintaining a high level of radicality[6,7].

Pylorus-preserving gastrectomy (PPG) is a function-preserving procedure devised by Maki and colleagues[8] in 1967. Its purpose is to maintain the reservoir function of the stomach in order to relieve dumping syndrome and prevent bile reflux. Preservation of nerve supply and blood flow to the pyloric antrum is intended to maintain pyloric function. In 1995 the technique was first adopted at this institution to treat EGC in the middle or lower third of the stomach, with clear advantages over distal gastrectomy (Billroth I) in terms of long-term functional outcomes[9]. The aim of the present study was to focus on short-term surgical and long-term oncological outcomes, investigating the safety and radicality of PPG to determine whether it could be recommended as the standard operation for EGC in the middle third of the stomach.

Methods

Between 1995 and 2004, 611 patients with EGC diagnosed before surgery underwent PPG at the National Cancer Center Hospital, Tokyo. Short- and long-term outcomes were analysed. All tumours were adenocarcinomas in either the mucosal or submucosal layer. The study included all patients with EGC in the middle third of the stomach diagnosed before surgery, excluding those who were candidates for endoscopic mucosal resection (EMR)[10]. Current recommendations for EMR are tumours confined

to the mucosal layer, type I, IIa or depressed type IIc with no ulcer or ulcer scar (no fold convergence endoscopically), well or moderately differentiated adenocarcinomas, and tumours smaller than 2·0 cm (the distance between the distal transection line and the pyloric ring should be more than 2·5 cm because the remnant pyloric antrum must have a certain capacity for peristalsis to occur and move gastric contents into the duodenum[11]).

The surgical specimens were examined and scored according to the Japanese Classification of Gastric Carcinoma[12]. Postoperative follow-up included clinical and laboratory examinations every 6 months for the first 2 years, and annually thereafter at least until 6 years after operation. Information was obtained from follow-up records and the city registry office. The last follow-up date was 30 September 2006.

Surgical procedures

Fig. 1 shows the anatomy for PPG. The greater omentum was preserved and the gastrocolic ligament was cut at least 3 cm from the gastroepiploic vessels. The stomach was transected with a macroscopic margin at least 2 cm from the tumour border. Lymph nodes from stations 1 (right cardia), 3 (lesser curvature), 4sb (left gastroepiploic artery), 4d (right gastroepiploic artery), 6 (infrapyloric), and 7, 8a, 9 and 11p (suprapancreatic) were excised, but those at station 5 (suprapyloric) were left intact. Pyloroplasty was not performed. The hepatic and pyloric branches of the vagus nerves were routinely preserved, and the coeliac branch was routinely preserved from 2003. The root of the right gastric artery was preserved and transected just distally to the first branch. The left gastric artery was divided at its origin when the coeliac branch was sacrificed, and slightly more distally when the coeliac branch was preserved. Infrapyloric vessels were routinely preserved from 2003. The anastomosis was made using a sero-submucosal technique with absorbable sutures.

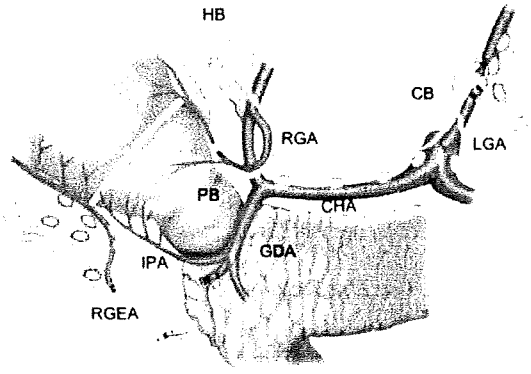

Fig. 1 Anatomy for pylorus-preserving gastrectomy. CB, coeliac branch; CHA, common hepatic artery; GDA, gastroduodenal artery; HB, hepatic branch; IPA, infrapyloric artery; LGA, left gastric artery; PB, pyloric branch; RGA, right gastric artery; RGEA, right gastroepiploic artery

Statistical analysis

All analyses were performed on an intention-to-treat basis. Survival rates were calculated by the Kaplan–Meier method. Statistical analyses were performed using SPSS® version 14.0 (SPSS, Chicago, Illinois, USA). $P < 0.050$ was considered significant.

Results

The mean age of the 611 patients was 58·1 (range 26–86) years; 376 were men and 235 were women (*Table 1*). Mean body mass index was 23·0 (range 14·9–33·3) kg/m^2. Tumours were in the middle third of the stomach in 532 patients. Before surgery, 248 tumours (40·6 per cent) were diagnosed as mucosal and 363 (59·4 per cent) as submucosal cancers.

EGC (343 in the mucosa, 233 in the submucosa) was confirmed in 576 (94·3 per cent) of the 611 patients and non-early cancer (23 in the muscularis propria, 11 in the subserosa, one in the serosa) in the other 35 (5·7 per cent). The accuracy of preoperative diagnosis of EGC by endoscopy and upper gastrointestinal series was 94·3 per cent. The incidence of nodal involvement was 10·1 per cent overall (62 of 611 patients), 3·8 per cent (13 patients) in mucosal cancers and 17·6 per cent (41 patients) in submucosal cancers (*Table 2*). Of the 13 patients with node-positive mucosal cancer, ten had pathological node stage (pN) 1 disease and the other three had pN2 disease.

Table 1 Characteristics of 611 patients included in the study

	No. of patients (n = 611)
Age (years)*	58·1(11·4) (26–86)
Sex ratio (M:F)	376:235
Body mass index (kg/m^2)*	23·0(3·0) (14·9–33·3)
Tumour location	
Upper third	7
Middle third	532
Lower third	72
Preoperative tumour stage	
Mucosa	248
Submucosa	363

*Values are mean(s.d.) (range).

Table 2 Nodal status by histological type and depth of invasion

Variables	N0	N1	N2	Total
Histological type*				
Differentiated type	208	22	2	232
Undifferentiated type	341	28	10	379
Depth of invasion				
Mucosa	330	10	3	343
Submucosa	192	36	5	233
Muscularis propria	18	3	2	23
Subserosa	9	1	1	11
Serosa	0	0	1	1
Total	549	50	12	611

*According to the Japanese Classification of Gastric Carcinoma. Differentiated type includes papillary adenocarcinoma and tubular adenocarcinoma. Undifferentiated type includes poorly differentiated adenocarcinoma, signet-ring cell carcinoma and mucinous adenocarcinoma.

Table 3 Postoperative morbidity

	No. of patients (n = 611)
Major complications	
Postoperative bleeding	4 (0·7)
Anastomotic leakage	2 (0·3)
Pancreas-related abscess	9 (1·5)
Other intra-abdominal abscess	4 (0·7)
Minor complications	
Gastric stasis	49 (8·0)
Thrombophlebitis	1 (0·2)
Atelectasis or pneumonia	20 (3·3)
Intestinal obstruction	2 (0·3)
Cholecystitis	1 (0·2)
Wound infection	10 (1·6)

Values in parentheses are percentages.

Of 41 patients with node-positive submucosal cancer, 36 had pN1 and five had pN2 disease.

All operations were carried out with curative intent. The coeliac branch of the vagus nerve was preserved in 400 patients (65·5 per cent). The mean(s.d.) length of the pyloric cuff was 3·3(1·1) cm. The median duration of operation was 200 (range 93–466) min, median blood loss was 260 (range 21–1989) ml and median postoperative hospital stay was 14 (range 5–83) days.

Postoperative complications developed in 102 (16·7 per cent) of 611 patients (*Table 3*). Major complications occurred in 19 (3·1 per cent): postoperative bleeding in four (0·7 per cent), anastomotic leakage in two (0·3 per cent), intra-abdominal abscess in four (0·7 per cent) and pancreas-related abscess in nine (1·5 per cent). Gastric stasis was the most frequent complication, occurring in 49 patients (8·0 per cent) who had severe symptoms requiring fasting and intravenous fluid support. Total parenteral nutrition was used in nine patients with delayed emptying. No other treatment for gastric stasis was used. Passage to the duodenum was examined by contrast radiology. The first study was performed on the fourth postoperative day in all patients. Further examinations were performed at least once a week for those with delayed emptying, until there was radiological evidence of adequate emptying. Reoperation was performed successfully in four patients (0·7 per cent) for postoperative bleeding.

Median follow-up was 50 (range 5–130) months. Five patients developed a second primary gastric carcinoma in the remnant stomach. In four, the tumour was located proximal to the anastomosis and in one it was distal. Three were treated by EMR and two by gastrectomy, all with curative intent.

Six patients developed recurrence and five died, three as a result of liver metastases and two from peritoneal metastases. One patient, who had recurrent non-early cancer (muscularis propria) with three positive nodes, developed nodal metastases along the hepatoduodenal ligament but was still alive at the time of writing. Another 19 patients died from other causes.

Overall 5- and 10-year survival rates were 96·1 and 89·1 per cent respectively. Overall 5- and 10-year survival rates in patients with EGC were 96·3 and 91·5 per cent respectively.

Discussion

PPG is a safe operation in patients with EGC, with an operative mortality rate of zero and an overall 5-year survival rate of 96·3 per cent. The rate of postoperative complications was 16·7 per cent, although these were major in only 3·1 per cent of patients. Gastric stasis was the most common complication, occurring in 8·0 per cent. PPG compares favourably with Billroth I or II reconstruction in reducing rapid gastric emptying and biliary reflux[13–15]. It has the major advantages of good weight recovery, and prevention of dumping syndrome and gallstones[9,13,15,16]. The real concerns raised by sparing the pyloric antrum are gastric stasis during the early postoperative period, secondary cancer in the remnant stomach and the implications for long-term survival.

The critical risk factors for gastric stasis after PPG remain unclear. The pathophysiological mechanism of stasis is commonly thought to be some combination of anastomotic oedema and nerve dysfunction caused by mechanical and chemical injury[17–19]. The overall incidence of gastric stasis in the present series of PPGs was 8·0 per cent. Other authors have reported gastric stasis

in 20–80 per cent of patients who had PPG with or without preservation of the pyloric branch of the vagus nerve[20–23]. Kodama and colleagues[13] reported that 23 per cent of patients who had PPG developed remnant gastric stasis and that 6 per cent had severe stasis that required intravenous therapy, consistent with the present results. Preserving the infrapyloric vessels as well as the first gastric branch of the right gastric artery to secure blood flow to the pyloric antrum and anastomosis, along with the nerve along the infrapyloric vessels, may maintain pyloric function and prevent gastric stasis. This surgical technique also seems to be useful for increasing the distance from the pyloric ring.

It is unclear how sparing the pyloric antrum influences the growth of second primary gastric cancers. Preventing bile reflux may decrease the incidence of second primary gastric cancers in the long term[24]. Intestinal metaplasia in the pyloric antrum has been considered the major cause of multicentric carcinogenesis of the stomach[25,26]. Follow-up endoscopy detected a secondary primary cancer in six patients (1·0 per cent) in the present series, and only one tumour was located distal to the anastomosis. Takeda and colleagues[27] reported an incidence of EGC in the remnant stomach after partial gastrectomy of 1·8 per cent and an incidence of second primary gastric cancer within 10 years of surgery of 0·86 per cent. The carcinogenesis induced by bile reflux usually occurs more than 20 years after the initial operation[28], so a longer follow-up may be necessary to prove benefit after PPG.

As the suprapyloric nodes have long been classified as N1 nodes, a major concern with PPG is the impact of not dissecting them on long-term survival. However, pathological studies in EGC have shown a very low incidence of metastasis to this station from cancers arising in the middle or lower thirds of the stomach: only 0·6 per cent (12 of 2089) for pathological tumour (T) stage 1 gastric cancers from 1980 to 1999 at the National Cancer Center Hospital (M. Saka, unpublished data). In the present study, the overall 5-year survival rate was 96·1 per cent in all patients and the overall recurrence rate was 1·0 per cent. Follow-up should be continued, as EGC may recur 5 years after treatment[29,30]. Although Katai and colleagues[31] reported local node recurrence soon after surgery, which may be increased after operation without suprapyloric node dissection, the excellent outcome of patients with EGC treated by PPG seems comparable to the outcome of conventional distal gastrectomy.

This study has confirmed the safety and radicality of PPG within the confines of the Japanese Classification of Gastric Carcinoma. It is recommended as the standard procedure for EGC in the middle third of the stomach.

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