- group 10: lymph nodes of the splenic hilum (only in case of splenectomy);
- group 11p and d: lymph nodes along the proximal and distal splenic artery;
- group 12 a + b: lymph nodes in the hepato-duodenal ligament, along the proper hepatic artery and the common bile duct.

☐ Reconstruction of the alimentary tract

The alimentary tract is reconstructed preferably through a stapled Roux-en-Y oesophago-jejunal anastomosis (Figs. 16.29-16.31). Usually the Roux limb (jejunum) should be placed through a slit of mesocolon just to the right of the middle colic vessels. The length of jejunum above the mesocolon should be not too long (as short as 10 cm) and streight, in order to avoid kinking and adhesion to the dissected surface. Usually we prefer and end-to-side esophago-jejunal anastomosis for safety, being careful to leave a very short jejunal stump to avoid a blind loop and stasis of food. The Roux limb is fixed to the transverse mesocolon with closure of the slit.

☐ Pancreas preserving D2 total gastrectomy (Maruyama technique)

Maruyama's technique represents the standard D2 gastrectomy with splenectomy and preservation of the pancreas for proximal cancer of the stomach.

Since the '60s Japanese reference centres for gastric surgery had been performing D2 total gastrectomy with splenectomy and distal pancreatectomy for proximal and middle third gastric cancer; this procedure entailed the complete removal of loco-regional lymph node stations, including peri-pancreatic (lymph nodes along the upper border of the pancreas) and splenic hilum lymph

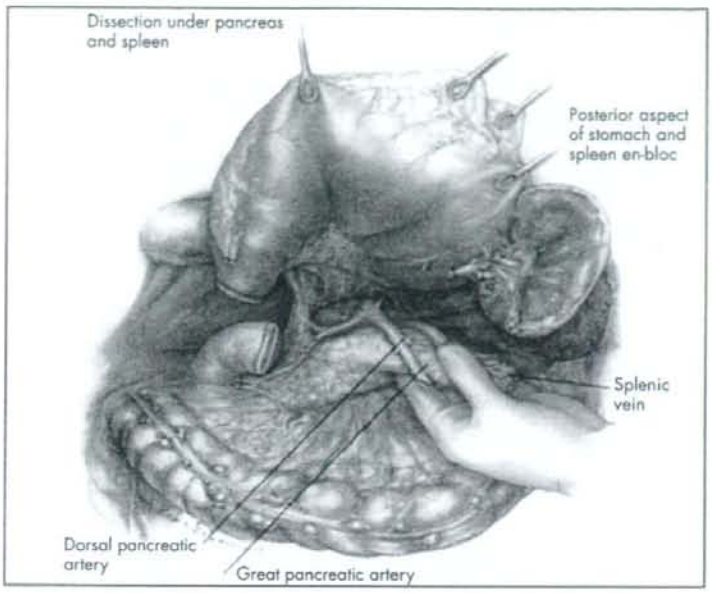

Fig. 16.28 – Vascular dissection at the body of the pancreas. (Reproduced with permission of the author from Sasako[11]).

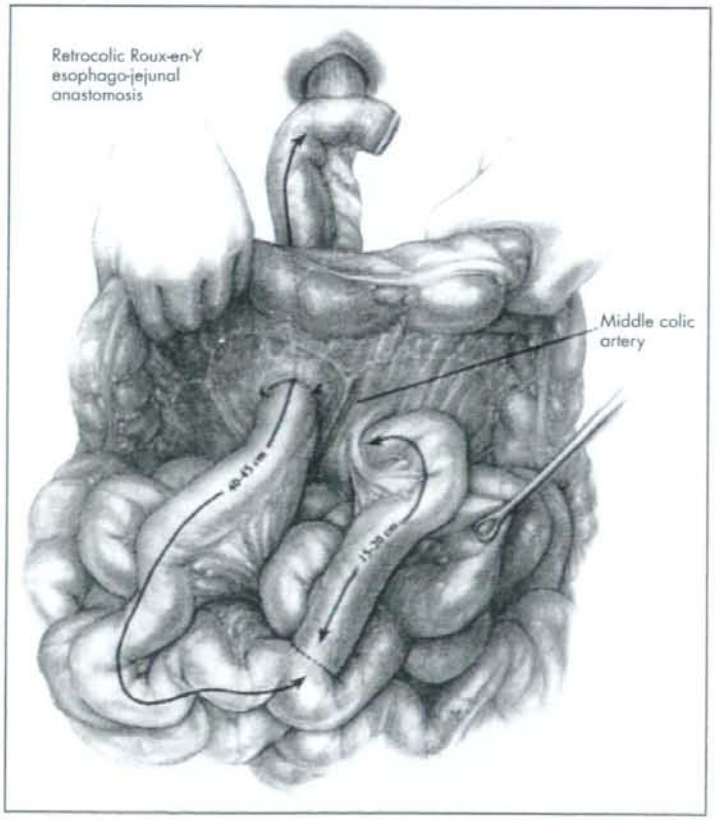

Fig. 16.29 – Reconstruction of the alimentary tract. (Reproduced with permission of the author from Sasako[11]).

Fig. 16.30 – Cardio-esophageal branch of the inferior left phrenic artery.

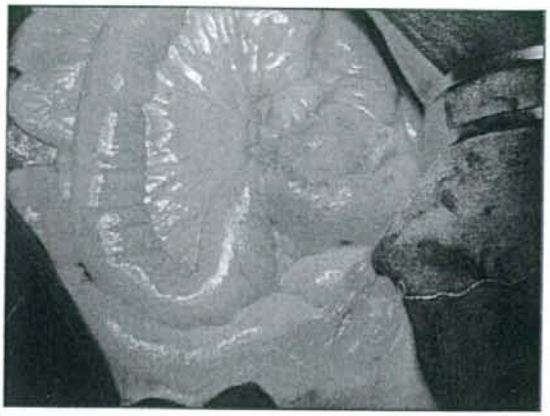

Fig. 16.31 – Jejuno-jejunal end to side anastomosis (trans-mesocolic Roux-en-y).

nodes. This operation was followed by a high rate of complications such as pancreatic fistulas, left sub-phrenic abscesses, serious pancreatitis and postoperative diabetes[11]. Even in recent studies, the mortality rate after splenectomy and distal pancreatectomy during total gastrectomy for proximal cancer was very high[12].

To avoid the increase of mortality and morbidity related to this procedure, Japanese Authors studied how to preserve the pancreas in proximal and middle third cancers; lymphatic channels from the stomach, lymph node metastasis around the pancreas, blood supply of the pancreas and technique of mobilization of the spleen and distal pancreas were studied. Endoscopic and intraoperative lymphography documented that lymphatic channels were located only in the subserosal space of the pancreas but never inside the parenchyma; this demonstration could theoretically support D2 total gastrectomy with pancreas preservation as a curative procedure for cancer[13,14].

In addition, histopathological studies[12] using resected and autopsy materials from gastric cancer patients revealed that lymph nodes are observed only in subserosal fatty connective tissue of the pancreas, particularly along the splenic artery and at the splenic hilum. This result supported data from lymphography, confirming that lymph node metastasis does not occur in pancreas parenchyma and that survival results should not be negatively affect by preservation of the pancreas (Fig. 16.32).

As lymph node metastasis are located along the splenic artery and this artery should be removed during D2 pancreas preserving total gastrectomy with splenectomy, the blood supply of the preserved pancreas has been indagated. Anatomical studies

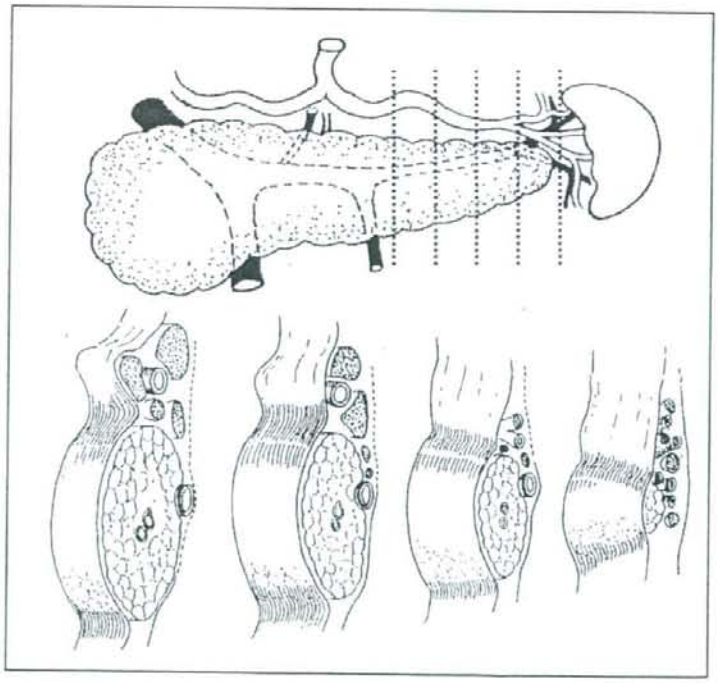

Fig. 16.32 – Lymphatic nodes and pancreas parenchyma (reproduced with permission from Maruyama[12]).

Fig. 16.33 – Peripancreatic dissection and removal of lymph nodes along the origin of the superior mesenteric vessels.

and celiac angiographies have clearly demonstrated that the distal pancreas receives blood supply through the transverse pancreatic artery (along the pancreatic duct) branching off from the dorsal pancreatic artery and that the dorsal pancreatic artery branches off 2 cm from the origin of the splenic artery from the celiac trunk. Therefore the division of the splenic artery distal to the origin of the dorsal pancreatic artery can preserve blood supply to the body and tail of the pancreas, as documented by celiac angiographies[12] of patients submitted to D2 pancreas preserving total gastrectomy with splenectomy. The splenic vein is adherent to the pancreas and is not surrounded by any lymphatic tissue. It can be preserved all along the pancreas parenchyma and divided at the tip of the tail of the pancreas, without negatively affect the curativity of the operation and the venous blood drainage of the pancreas.

Surgical technique

The aim of pancreas preservation technique is to completely remove the serosal membrane and all the fatty connective tissue containig lymphatic channels and lymph nodes from pancreatic parenchyma (Fig. 16.33).

After the completion of all the standard surgical procedure such as removal of the serosa from the pancreas head surface and lymph node dissection along the common hepatic artery, left gastric artery and celiac artery, the pancreas preserving procedure is started. The serosal membrane is carefully pealed off from the distal pancreas and all the fatty connective tissue including splenic artery lymph node is also completely removed from the slenic artery. Then the splenic artery is ligated and divided at about 2 cm from its origin from the celiac trunk paying attention to preserve the dorsal pancreatic artery whenever it branches off from the splenic artery and not from the celiac or the superior mesenteric vein as usual (Fig. 16.34).

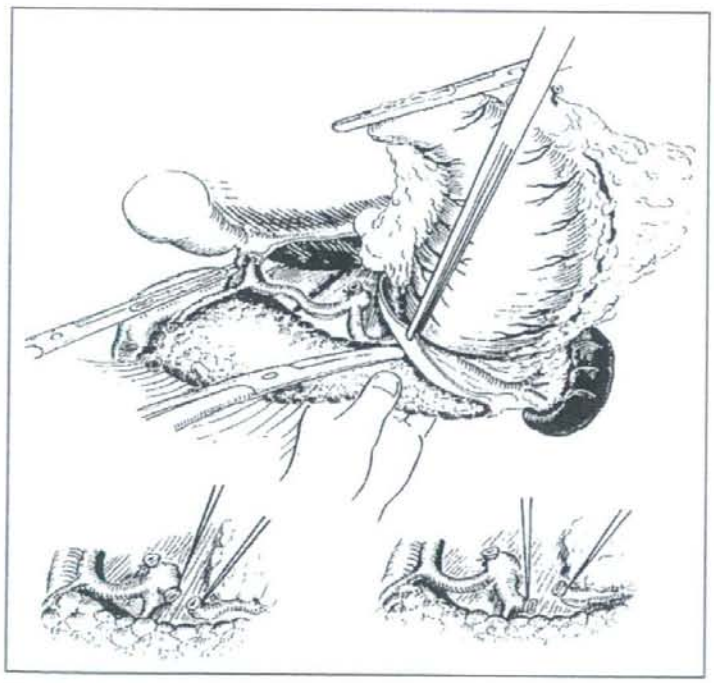

Fig. 16.34 – Preservation of dorsal pancreatic artery (reproduced with permission from Maruyama[12]).

Afterwards, it is necessary to completely mobilize the spleen and the distal pancreas (Fig. 16.35); in fact, embryologically, the spleen and the pancreas are located in the dorsal mesogastrium which has no vascular connection with the retro-peritoneum. The spleen and the pancreas can therefore be easily mobilised with safety and without bleeding following the ideal layer between the posterior surface of the pancreas and the anterior surface of the retro peritoneum, ligating and dividing only a couple of small vessels at the surface of left adrenal gland.

The mobilization goes on following the posterior surface of the splenic vein. The spleen is pulled up,

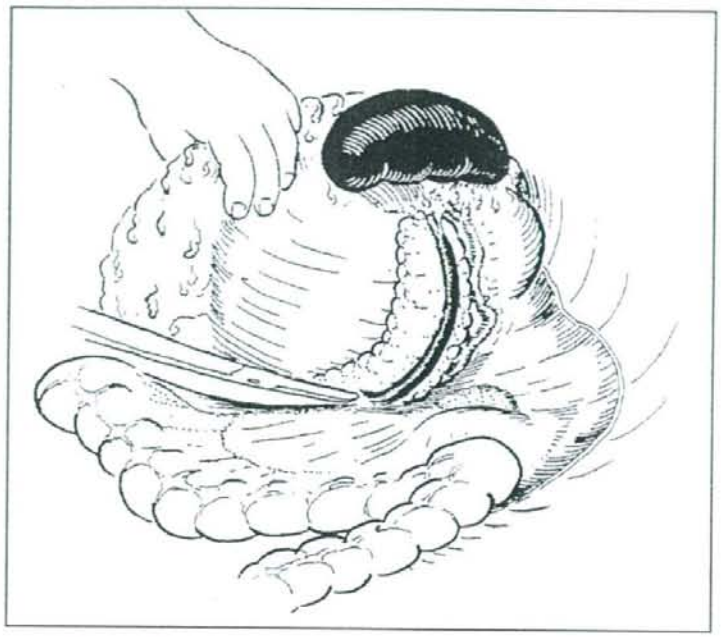

Fig. 16.35 – Mobilization of spleen and pancreas (reproduced with permission from Maruyama[12]).

the serosal membrane is removed from the posterior surface of distal pancreas and the tail of the pancreas is carefully exposed by removing the connective tissue from the gland. A couple of small pancreatic caudal arteries can be divided; the splenic vein is double ligated and divided at the tip of the tail of the pancreas (Figs. 16.36, 16.37). Fatty connective tissue is carefully removed from the pancreas upper border, together with the distal part of the splenic artery, by ligating and dividing a couple of small branches to the parenchyma.

The spleen, the splenic artery and all the fatty connective tissue containing lymph nodes around the pancreas are removed, while the pancreatic parenchyma and splenic vein are preserved.

COMMENTS

Maruyama *et al.* demonstrated that pancreas preserving D2 total gastrectomy with splenectomy reduces complications related to pancreas resection such as pancreatic juice leakage, left subphrenic abscesses, severe pancreatitis and postoperative diabetes, without negatively affect the curativity of the procedure[12].

The procedure is indicated for patients with cancer of the proximal and middle third of the somach without direct involvement of the pancreas and/or large macroscopic metastasis along the upper border of the pancreas.

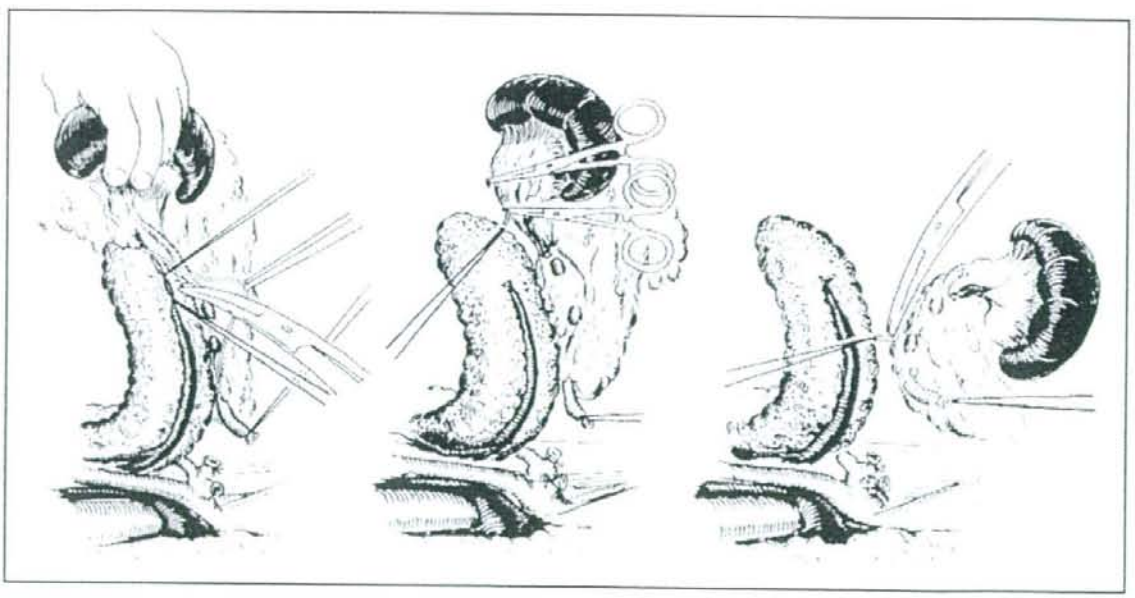

Fig. 16.36 – Splenectomy with splenic vein preservation (reproduced with permission from Maruyama[12]).

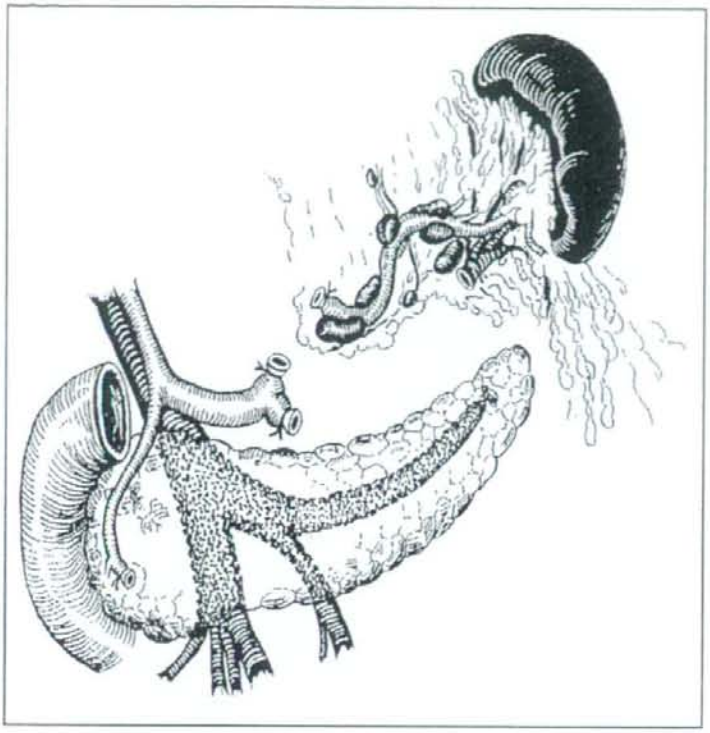

Fig. 16.37 – Splenectomy with removal of splenic artery (reproduced with permission from Maruyama[12]).

D2 DISTAL GASTRECTOMY

The surgical steps of total gastrectomy are reproduced for a partial gastrectomy: careful exploration of the abdominal cavity, peritoneal washing for intraoperative cytology, removal of the lymph nodes of the group 16B1 for intraoperative frozen section.

Lymph node dissection is continued until the removal of lymph node stations of the proximal part of the splenic artery (group 11p). A particular attention must be paid in order not to damage the splenic artery during this dissection in order to absolutely preserve the spleen and the pancreas. The posterior gastric artery must be preserved as well in order to guarantee a good blood supply of the gastric remnant together with the short gastric vessels.

The right paracardial lymph nodes (group 1) should be removed (Fig. 16.38) even if the proximal third of the stomach will be preserved; on the opposite, left paracardial nodes (group 2) should not be resected.

In order to remove the right paracardial lymph nodes all the branches towards the gastric wall departing from the superior gastro-oesophageal branch of the left gastric artery should be ligated and divided (Fig. 16.38); this will entail the removal of the fatty tissue of the lesser curvature containing lymph nodes group 1, from the origin of the superior gastro-oesophageal artery to the cardia. Lymph node stations No 3 (lesser curvature) and No 5 (right gastric artery) will be removed together with the specimen.

On the greater curvature the lymph node dissection should preserve the short gastric vessels, in order to guarantee a good blood supply of the gastric proximal third together with the posterior gastric artery.

As for total gastrectomy, lymphadenectomy will entail also lymph nodes of the hepatoduodenal ligament, common hepatic artery, coeliac trunk, left gastric artery, as well as the splenic artery until the origin of the posterior gastric artery.

For a complete D2 distal gastrectomy the removal of the lymph nodes of the superior mesenteric vein at the inferior pancreatic border (Fig. 16.33, LN group 14v) is required as well. For this procedure all the fatty tissue above the anterior face of the superior mesenteric vein, from the inferior

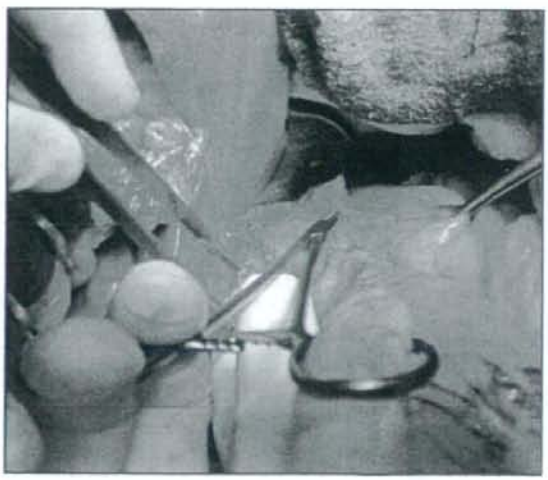

Fig. 16.38 – Dissection of right paracardial lymph nodes.

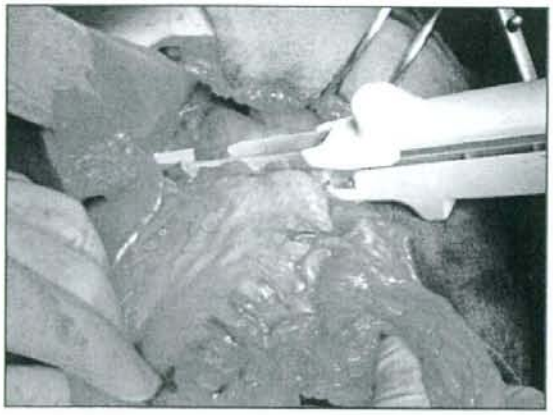

Fig. 16.39 – Division of the stomach between its proximal and middle third.

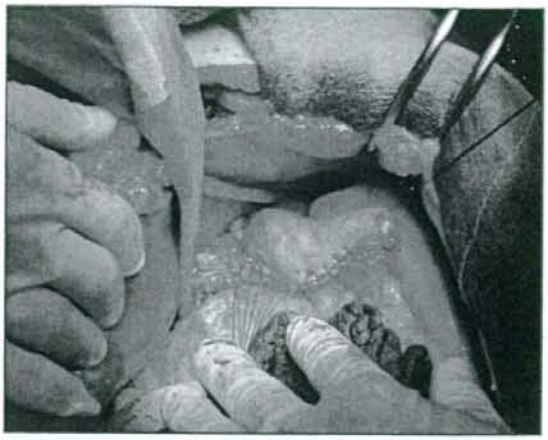

Fig. 16.40 – Manual seromuscolar reinforcement of stapled suture of gastric stump.

margin of the pancreas until its first branch of division should be dissected and removed.

The following lymph node stations (according to the Japanese Gastric Cancer Association) should be removed:

- group 1: right paracardial lymph nodes;
- group 3: lymph nodes along the lesser curvature;
- group 4sb, d: lymph nodes along the greater curvature (along the left gastro-epiploic vessels, along the right gastro-epiploic vessels);
- group 5: suprapyloric lymph nodes;
- group 6: infrapyloric lymph nodes;
- group 7: lymph nodes along the left gastric artery;
- group 8a: lymph nodes along the common hepatic artery, anterosuperior group;
- group 9: lymph nodes around the celiac artery;
- group 11p: lymph node along the proximal splenic artery, until the branching off of the posterior gastric artery;
- group 12a: lymph nodes in the hepatoduodenal ligament (along the proper hepatic artery);
- group 14v: lymph nodes along the superior mesenteric vein.

The stomach is resected with a linear stapler (Fig. 16.39). A continous suture is performed in order to guarantee the complete blood control of the suture line.

The reconstruction technique usually perfomed by the IGCSG surgical team is a trans-mesocolic end-to-side Roux-en-Y gastro-jejunostomy, performed with a mechanical stapler (Figs. 16.40-16.42).

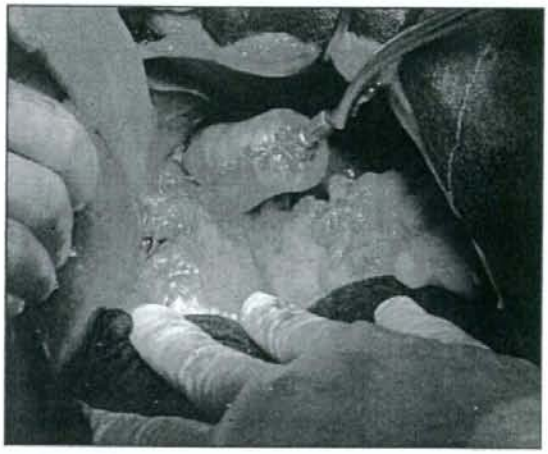

Fig. 16.41 – Introduction of the envil into gastric stump.

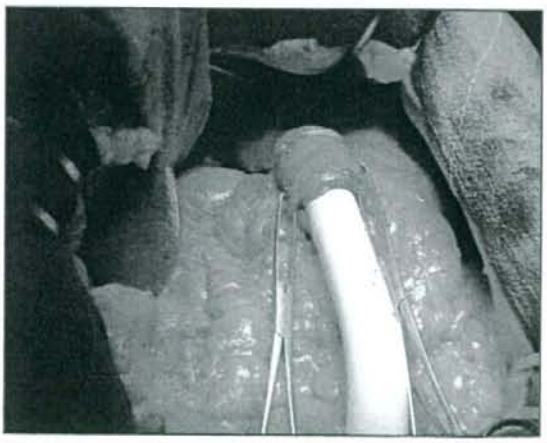

Fig. 16.42 – End-to-side stapled gastro-jejunal anastomosis with CEEA.

DIFFUSE CANCERS

Total D2 gastrectomy is the treatment of choice for diffuse tumours. In these cases, lymphadenectomy entails the removal of the following stations:

- group 1: right paracardial lymph nodes;
- group 2: left paracardial lymph nodes;
- group 3: lymph nodes along the lesser curvature;
- group 4 sa, sb, d: lymph nodes along the greater curvature (along the short gastric vessels, along the left gastro-epiploic vessels, along the right gastro-epiploic vessels);
- group 5: suprapyloric lymph nodes;
- group 6: infrapyloric lymph nodes;
- group 7: lymph nodes along the left gastric artery;
- group 8a: lymph nodes along the common hepatic artery, anterosuperior group;
- group 9: lymph nodes around the celiac artery;
- group 10: lymph nodes at the splenic hilum;
- group 11p: lymph node along the proximal splenic artery, until the branching off of the posterior gastric artery;
- group 12a: lymph nodes in the hepatoduodenal ligament (along the proper hepatic artery);
- group 14v: lymph nodes along the superior mesenteric vein.

POSTOPERATIVE CARE

A good postoperative care enables an early recovery of patient's functions and a rapid mobilization, in order to prevent complications linked to hospitalization.

Nutrition

Patients submitted to total or distal gastrectomy receive artificial nutrition (parenteral or enteral nutrition) in order to enable a rapid consolidation of the surgical sutures and prevent the peritoneal spreading in case of anastomotic leakage.

Seven days after surgery, an upper GI series with a water-soluble contrast medium is requested to verify the healing of the anastomosis; only after the regularity of the suture has been documented patients can restart oral intake.

Hence, artificial nutrition plays a main role in these patients. At this purpose, as it is demonstrated that the enteral feeding can reproduce the physiological oral intake also in the early postoperative period, after total gastrectomy patients receive total parenteral nutrition together with enteral nutrition, which is administered through a catheter jejunostomy performed during the main procedure, following the technique described by Delaney[15,16] (Fig. 16.43).

The TPN is calibrated according to patient's demands. Total parenteral and enteral nutrition are managed by a multidisciplinary board of surgeons, nutritionists and dieticians; patient's nutritional schedule is revalued every single day from medical board and eventually modified depending on patient's specific demands during his postoperative course.

Enteral nutrition can be started on the first postoperative day; during the first 24-48 hours 5% glucose solutions, than nutritional solutions with high osmolarity are used.

Sometimes enteral nutrition through catheter jejunostomy can cause significant diarrhoea syndromes; in these cases enteral nutrition is stopped and TPN will be the sole artificial nutrition administered.

Analgesia

The opioids have a significant role in postoperative analgesia; during the first stage of postoperative course, opioids are given by intravenous administration often through elastomeric pumps. After few days of treatment the opioids are usually replaced by other kinds of drugs (*i.e.* paracetamol, NSAID), with a good control of postoperative surgical pain and less negative effect on bowel voiding.

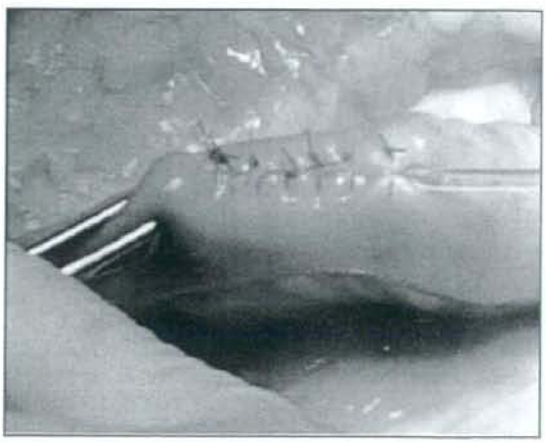

Fig. 16.43 – Nutritional catheter jejunostomy: Witzel's suture.

Recently, postoperative analgesia is obtained also through epidural infusion of analgesic and anaesthestic drugs administered through a catheter placed intraoperatively. The synergy between intravenous and spinal analgesia allows a complete control of surgical postoperative pain and a prompt recovery of patient's mobilization.

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Int J Clin Oncol (2008) 13:193–195
DOI 10.1007/s10147-008-0791-1

REVIEW ARTICLE

Mitsuru Sasako

Surgery and adjuvant chemotherapy

Received: April 8, 2008

Abstract It was clearly demonstrated that good local control by either radiotherapy or D2 surgery is essential to cure gastric cancer. D2 surgery can be carried out safely with a large volume of patients and can provide better survival than limited surgery. More extended surgery than D2 cannot provide better survival and causes greater morbidity; therefore, it should not be carried out as prophylactic lymphadenectomy. The effect of adjuvant treatment depends on the type of surgery. Neoadjuvant plus post-operative triplet chemotherapy, postoperative adjuvant chemoradiotherapy, and postoperative S-1 monotherapy now are the standards of care in Europe, the United States, and Japan, respectively.

Key words Gastric cancer · D2 dissection · Adjuvant chemotherapy

Principle of treatment aimed at curing patients with solid cancers

For the majority of solid cancers, treatment aimed at cure comprises good local control and systemic therapy to control occult metastasis. Actually, radiotherapy or surgery including endoscopic resection are the usual methods of local control.[1] For several decades, Western physicians have claimed that advanced gastric cancer was already a systemic disease and that surgery with extended lymphadenectomy could not cure it.[2] However, the results of the Intergroup study (INT0116/SWOG9002) to evaluate the efficacy of postoperative adjuvant chemoradiotherapy demonstrated clearly the necessity and efficacy of good local control to cure gastric cancer.[3] D1 was proven to be insufficient treatment for curable gastric cancer. Thus, either rather simple surgery such as D1 with additional radiotherapy or good D2 dissection is regarded as the basic local treatment for gastric cancer at the moment.

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D2 dissection: the gold standard

Dutch and British randomized controlled trials (RCT) failed to prove the survival benefit of D2 dissection over D1.[4,5] However, these studies are heavily criticized for poor quality control of surgery and postoperative care, unacceptably small hospital volume, high incidence of insufficient nodal dissection (noncompliance), and adoption of the more aggressive option of D2 dissection by routine use of pancreaticosplenectomy.[6] The number of patients treated in an institute each year, which is called hospital volume, showed clear negative correlation with hospital mortality.[7] A certain incidence of morbidity is expected in this surgery in case of a total gastrectomy, thus requiring the knowledge and experience of managing these complications. Mortality after major surgical complications in the Dutch trial and in the consecutive series at the National Cancer Center Hospital Tokyo (NCCH) in the 1980s provides a clear contrast. Mortality after anastomotic leakage was 41.3% and 14.3% in the Dutch trial and the NCCH series, respectively. Similarly, mortality after intraabdominal abscess was 20.9% and 2.7%, respectively.[7] These data suggest experience is mandatory to avoid treatment-related death after major adverse events of surgery.

Eventually, in 2006, a RCT comparing D1 versus D2 (including D3 in the first edition of the Japanese Classification of Gastric Carcinoma) showed for the first time superiority of D2 over D1 dissection in clinical trials.[8] Five-year overall survival was 60% and 54% in the D2 and D1 groups, respectively ($P = 0.041$). This study is a single institutional study with three participating surgeons; thus, generalizability remains uncertain, especially in low-volume hospitals. However, with their experience, D2 can be carried out with quite low hospital mortality (0%) and provide better survival than D1.

Recently, the results of an RCT comparing D2 with more extended surgery, i.e., D2 plus paraaortic lymph node dissection (PAND) was reported. The two survival curves were almost overlapping, while D2 + PAND showed longer operation time and more blood loss and higher morbidity than D2, with statistical significance. It was concluded that prophylactic D2 + PAND should not be carried out for curable advanced gastric cancer.[9]

These results led us to conclude that D2 surgery should be regarded as the standard treatment for curable gastric cancer, at least in Japan.

Adjuvant chemotherapy for curable gastric cancer

Macdonald et al. reported the results of the Intergroup 0116/SWOG 9008 study[3] in 2001 to evaluate the efficacy of adjuvant treatment comprising 45 Gy administration of radiotherapy and five courses of chemotherapy of fluorouracil (5-FU) and leucovorin. Postoperative adjuvant chemoradiotherapy (CRT) showed statistically significant improvement of relapse-free survival (RFS) and overall survival (OS) for patients with gastric cancer undergoing curative surgery, compared with surgery alone as control. Three-year OS after CRT was 50%, while that of the surgery alone group was 41% (HR = 1.35, 95% CI = 1.09–1.66, P = 0.005). Only 10% of patients underwent D2 dissection in spite of the recommendation of D2 dissection in the protocol, suggesting that poor local control by surgery was salvaged by radiotherapy. After these results were reported, the standard treatment after potentially curative surgery for node-positive patients is postoperative CRT in the United States.

Cunningham et al. reported the results of the MAGIC trial to evaluate the efficacy of perioperative chemotherapy (three cycles each before and after surgery).[10] The chemotherapy used for this trial was a combination of epirubicin (50 mg/m^2, day 1), cisplatin (60 mg/m^2, day 1), and 5-FU (200 mg/m^2/day, continuous i.v., day 1–21) (ECF). This treatment showed statistically significant improvement of both PFS and OS compared with surgery alone as control; 5-year OS was 36.3% and 23.0% in the perioperative chemotherapy and surgery alone groups, respectively. These results are highly appreciated in Europe and Great Britain, where at least neoadjuvant chemotherapy is regarded as the standard of care. However, several points can be criticized in this study. There are 100 participating hospitals with no active quality control of surgery. Therefore, only about 56% of curable patients underwent D2 dissection. Second, more than 14% of patients had adenocarcinoma of the esophagus, requiring a different type of surgery. Third, shortly after randomization, 9 of 253 patients allocated to surgery alone either did not undergo surgery or no information about surgery was available for them. If the quality of eligibility assessment is reasonable, it is impossible that so many of the randomized patients did not undergo surgery. Fourth, among 198 patients who underwent surgical resection, the pathological T stage was unknown in 5 patients and pathological nodal stage was unknown in 42 patients. These facts suggest strongly that the quality of this trial was much poorer than that of the INT 0116 study and JCOG studies. As they did not report the OS of curable patients separately in the surgery alone group, comparison with other clinical trials that included exclusively curable patients is almost impossible. However, the tumors resected in the control group were not more advanced than those included in the INT 0116 or JCOG studies.

In this century, six other articles reporting the results of RCTs on adjuvant chemotherapy with surgery alone as control could be found in the Western world.[11–16] Only one of these, with a small sample size, showed a statistically significant difference of OS between adjuvant chemotherapy and surgery alone.

There have been five articles reporting the results of RCTs in Japan, having surgery alone as the control arm, after 2000.[17–21] The first three failed to prove the efficacy of adjuvant chemotherapy. One of them, JCOG9206-1, showed some difference that might have been significant if the sample size had been large enough. Nakajima et al. reported the results of the N-SAS-GC study to evaluate the efficacy of UFT for pT2 pN1-2 patients.[20] Although this study was positive to show the efficacy of high-dose UFT for patients with T2N1–2, the number of enrolled patients was just 38% of the projected sample size, and the OS and RFS of the control arm was about 10% worse than the other Japanese study, JCOG9206-1, for the same population in the same decade.[18] Therefore, confirmation is needed to apply this result to clinical practice. The most recent study, ACTS-GC, showed clearly the benefit of S-1 monotherapy as postoperative adjuvant chemotherapy for stage II/III patients who underwent D2 dissection.[21] In the subgroup analysis, all the subpopulations showed the same tendency (HR < 1), showing applicability for all stage II/III patients. Grade 3/4 adverse events were less than 7%; 6 months compliance was about 80% and that at 1 year was 65%. S-1 monotherapy after curative surgery was therefore feasible and effective to improve the OS and RFS of patients with this stage. Now, this treatment is regarded as the standard of care of stage II/III gastric cancer patients in Japan.

The role of radiotherapy after D2 dissection is controversial. Theoretically, it means duplication of local control for possible lymph node metastasis. Subgroup analysis of the INT 0116 study showed no benefit of CRT in the patients who underwent D2 dissection, although the interaction was not statistically significant because the number of those undergoing D2 dissection was too small. One Korean institution is carrying out a RCT comparing D2 surgery alone versus D2 + CRT to evaluate the efficacy of CRT after D2 dissection. As the control arm of this study remains surgery alone, the results must be carefully interpreted. If the results of this study show a clear benefit of chemoradiotherapy after D2 dissection, we might consider some trials comparing D2 + CRT versus D2 + chemotherapy.

In conclusion, standard treatment for curable advanced gastric cancer in Japan is D2 surgery followed by adjuvant chemotherapy by S-1 for 1 year.

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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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N Engl J Med 2008;359:453-62.

Reprinted from THE NEW ENGLAND JOURNAL OF MEDICINE
(ISSN 0028-4793) Vol. 359:453-462 (July 31, 2008).

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.

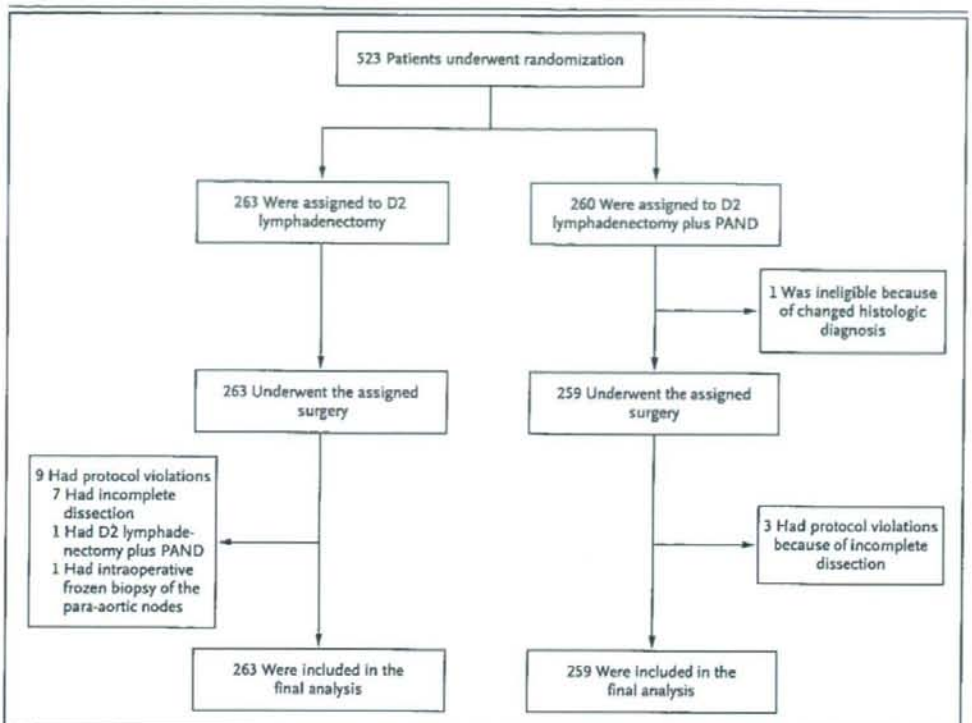

Figure 1. Disposition of the Patients.
PAND denotes para-aortic nodal dissection.

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

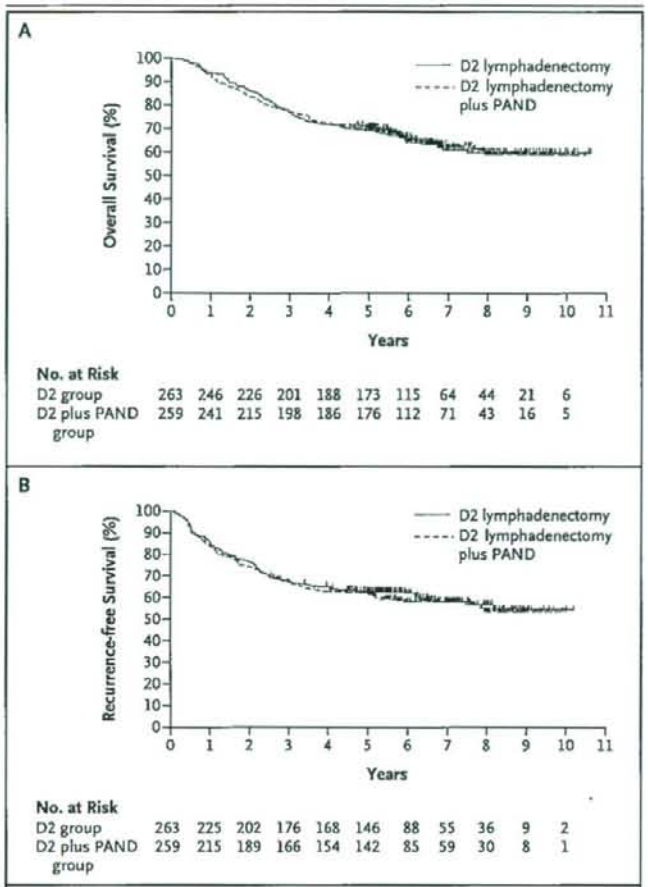

Figure 2. Kaplan–Meier Estimates of Overall Survival (Panel A) and Recurrence-free Survival (Panel B).

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-

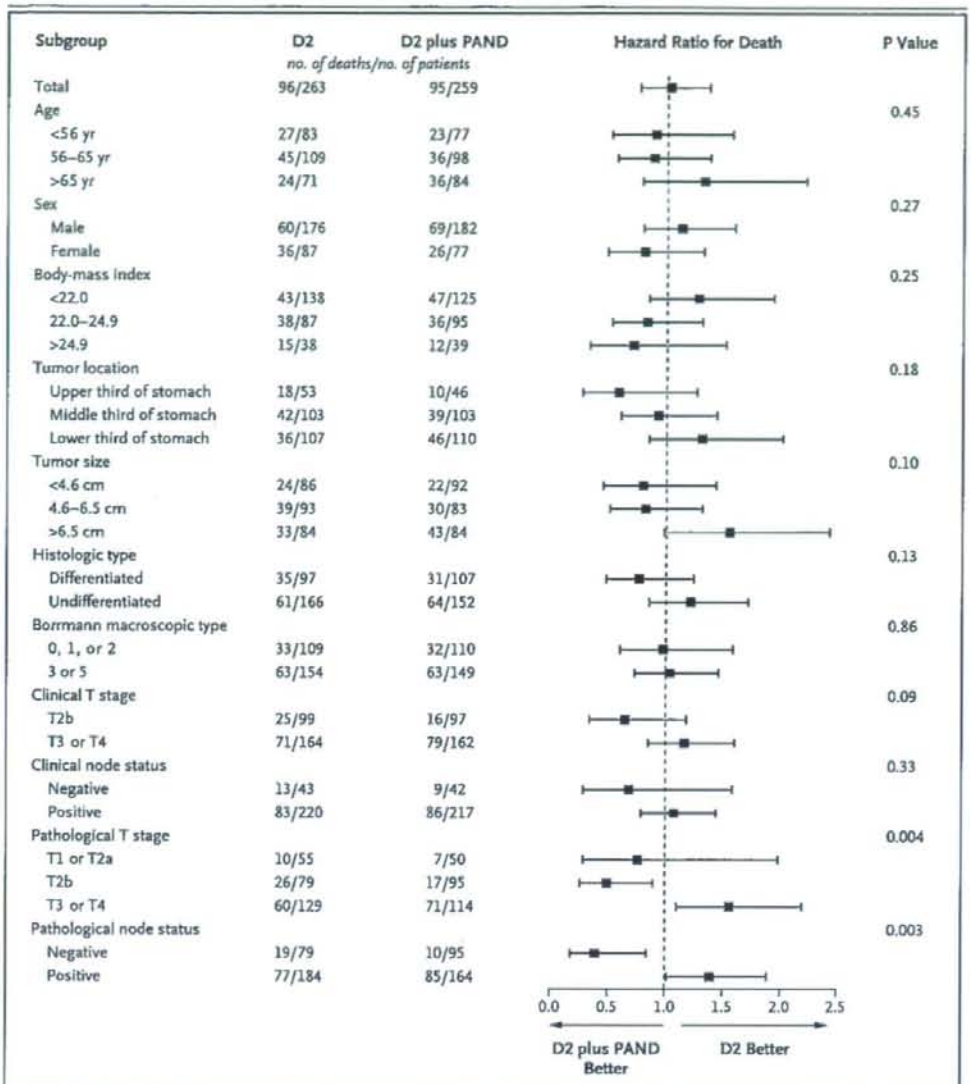

Figure 3. Tests for Heterogeneity of Treatment Effect According to the Clinicopathological Characteristics of the Patients.

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.