# The Gastric Cancer Treatment Guideline

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## Introduction

The Japan Gastric Cancer Association issued the first edition of the *Gastric Cancer Treatment Guideline* in March 2001 [1]. Based on new evidence, the second edition was issued in April 2004 [2]. In this chapter, the content of this guideline is introduced.

## Background of the Japanese Guideline

Gastric cancer remains the most common cancer in Japan, although it surrendered first place of the high annual mortality rate to lung cancer. The mortality rate of gastric cancer is seven times higher in Japan than in the United States and three times higher than in the UK [3]. Consequently, gastric cancer patients are treated not only in cancer specialist hospitals but also in most university hospitals and general hospitals, even in rural areas. In more than 100 Japanese hospitals, more than 100 patients undergo gastrectomy for gastric cancer every year. Even in other hospitals, the hospital volume is much higher than in most European hospitals.

The second unique situation in Japan is that more than half the patients have T1 tumors, that is, early gastric cancer. This result is partly due to the mass screening system, which covers actually as little as 10% of the entire population over 40 years old [4]. On the whole, the knowledge of the high risk of gastric cancer among general practitioners and even among the common citizen seems more important for early detection of this disease. Most Japanese tend to undergo endoscopy when they have even minimum symptoms of the upper gastrointestinal tract. We have accumulated an enormous database using the common rule, The General Rules for the Gastric Cancer Study issued by the Japanese Research Society for Gastric Cancer in 1962. According to the large database, the incidence of lymph node metastasis increases by

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tumor depth, and the deeper the tumor invasion, the more distant regional lymph nodes become metastatic. The incidence of nodal metastasis was just 2%–3% in T1 mucosal cancer and 15%–20% in T1 submucosal cancer [5]. Using this database, it was possible to select patients with T1 tumors who have negligible risk of lymph node metastasis. Together with the development of the instruments and technique of endoscopic mucosal resection (EMR), many of these mucosal cancers with minimal risk of nodal metastasis are now treated endoscopically [6]. In the year 2003, approximately 350 patients with T1 tumor underwent an EMR as definitive treatment, whereas about 300 underwent open surgery at National Cancer Center Hospital, Tokyo.

One of the reasons for this high incidence of early gastric cancer (EGC) is that the diagnostic criteria of gastric carcinoma are slightly different in Japan from those in the West [7]. Many Western pathologists diagnose the lesions without definite invasion as dysplasia, whereas they are diagnosed as well-differentiated adenocarcinoma in Japan if they have cellular and structural atypia compatible with adenocarcinoma. As biopsy specimens are usually taken from the surface of the lesions, they cannot prove deeper invasion of the lesions. Therefore, many of these "dyplasia" actually invade into the submucosal layer or even deeper when they are resected and histologically examined [8].

The most common type of surgery for curable gastric cancer in Japan is a gastrectomy with D2 lymph node dissection. In many Western countries, surgeons refrain from this procedure due to higher mortality than limited surgery (D0/1) and uncertain efficacy [9]. This contrast is partly explained by the high incidence of the disease and subsequent high hospital and surgeon volume in Japan, but also by the relatively low body mass index of the average Japanese. Difficulty and efficacy of abdominal surgery are somewhat affected by the volume of intraabdominal adipose tissue. In obese patients, generally speaking, a complicated surgery is much more difficult than in slim patients. Less than 1% of patients have body mass index over 30 in Japan, whereas more than 20% are obese in the United States. This fact makes surgeons more conservative in use of an aggressive type of surgery in the West.

## Principles: Basic Structure of the Guideline

This guideline shows the standard treatments and reasonable options for each stage. They are clearly separated into two groups, the standard treatments or the treatments under investigation (Tables 1, 2). As treatment strategy varies widely in EGCs, the standard treatment is indicated with detailed conditions in stage Ia and Ib tumors. Unlike many other guidelines, the algorithm system is not used.

## Treatment of Early Gastric Cancer

A wide resection with lymphadenectomy remains the gold standard treatment for gastric cancer, even for T1 gastric cancers, 10% of which have lymph node metastasis. In the guideline, standard radical gastrectomy is defined as a gastrectomy of more than two-thirds of the stomach with D2 lymph node dissection. However, patients with negligible risk of having nodal metastasis can be treated by a mere wide resection, avoiding a gastrectomy, which makes a serious change of eating habits obligatory.

TABLE 1. Stage-specific standards of care by the Japanese Guideline

| | N0 | N1 | N2 | N3 |
|---|---|---|---|---|
| T1(M) | EMR, ModA | ModB | STD | Ext<br>Palliative surgery<br>CTX |
| T1(SM) | ModA<br>ModB | STD | | |
| T2 | STD | STD | STD | Radiation therapy |
| T3 | STD | STD | STD | Palliative care |
| T4 | Ext (C.R) | Ext (C.R) | | |
| M1 | | | | |

MER, endoscopic mucosal resection; ModA, modified gastrectomy A; ModB, modified gastrectomy B; STD, standard gastrectomy; Ext (C.R), extended gastrectomy with combined resection of involved organs; EXT, extended gastrectomy including extended lymphadenectomy, combined organ resection for lymphadenectomy; CTX, chemotherapy

TABLE 2. Treatments in clinical research by the Japanese Guideline

| | N0 | N1 | N2 | N3 |
|---|---|---|---|---|
| T1(M) | EMR* | LADG | | Ext<br>Reduction surgery<br>CTX<br>HTCTX |
| T1(SM) | LADG<br>LR, SG | | | |
| T2 | LADG | ACTX | ACTX | |
| T3 | ACTX | D3<br>ACTX | D3<br>ACTX | |
| T4 | CTX, ACTX<br><br>Rad | Ext<br>CTX<br>ACTX | | |
| M1 | | | | |

EMR*, extended indication for EMR; LADG, laparoscopy-assisted distal gastrectomy; LR, local resection wedge resection; SG, segmental gastrectomy; ACTX, adjuvant chemotherapy; D3, D3 lymphadenectomy; HTCTX, hyperthermochemotherapy

The endoscopic mucosal resection (EMR) is the most beneficial method for patients because they do not have to undergo laparotomy or general anesthesia [6]. Theoretically, several groups of patients have very limited probability of nodal metastasis [10]. If the lesion is a mucosal cancer of differentiated histology without either lymphatic or vascular involvement, and without ulcerative change, the probability of lymph nodal metastasis is less than 0.3%. If the lesions fulfill the criteria, except that there is ulcerative change inside the lesion, only those that are 3 cm or less in size can be regarded as node negative (less than 0.8%). For lesions showing minimal submucosal invasion, less than 500 μm in depth, without lymphatic or vascular involvement, with

size 3 cm or less, the upper limit of 95% confidence interval of the probability of nodal metastasis is 2.5%.

However, EMR for a large lesion is technically demanding and it is not easy to remove lesions larger than 2 cm in one piece by the strip biopsy method. In this regard, EMR using a specially invented knife or hook to dissect the entire submucosal layer from the surface of the proper muscle layer is becoming more and more popular because it enables one-piece resection with full mucosal and submucosal layers of large size, up to even 10 cm. The term endoscopic submucosal dissection (ESD) is recently being used for this technique with the intention of discriminating it from EMR by strip biopsy technique using a snare [6]. At the moment, ESD is not for every gastroenterologist or surgeon. Therefore, the indication for EMR is described as follows in the Japanese Guideline: mucosal cancer, differentiated-type histology, smaller than 2 cm, without ulcer or ulcer scar in the lesion. These criteria should be confirmed by histological evaluation of the endoscopically resected specimen. To be accurate in evaluating the whole specimen, it is strongly advised to carry out a one-piece resection. For this meaning, EMR for T1 tumors other than those described in the guideline are regarded as treatment under investigation.

T1 tumors that do not meet the criteria for EMR or ESD should be treated by surgery. Two types of modification of D2 gastrectomy are recommended in the Japanese Guideline, because of low incidence of lymph node metastasis to the second tier nodal stations [11]. The area of resection is the same as the standard gastrectomy, but with D1 (including all perigastric lymph nodes of the relevant part of the stomach) plus the left gastric artery nodes is one option for clinically T1 (mucosal) and pN0 cancer of differentiated type larger than 2 cm or of undifferentiated histology of any size. For clinically T1 (submucosal) and pN0 cancer or clinically T1 (mucosal) and pN1 cancer, two-thirds or wider gastrectomy with D1 plus the left gastric, the common hepatic, and the celiac artery nodes is the recommended option. The indication of the modified procedures is based on the clinical and surgical diagnosis and therefore contains some risk of underestimation. The guideline gives caution of this risk. Other T1 tumors should be treated by the standard D2 gastrectomy. Laparoscopic gastrectomy with D1 or D2 lymph node dissection is nominated as a treatment under investigation.

## Treatment of Curable Advanced Gastric Cancer

For sT2 and sN0–2 tumors and sT3 and sN0–2 tumors, the standard D2 gastrectomy is the gold standard in the Japanese Guideline. For sT4 and sN0–2 tumors, the standard D2 gastrectomy with additional resection of the involved organ is regarded as the standard [13]. If published results of clinical studies evaluating the efficacy of D2 dissection are reviewed, the majority of them showed negative results [12–14]. However, all these negative studies were heavily criticized regarding the quality of surgery given in the D2 arm [15,16]. These results were understandable if the concepts of hospital volume and learning curve are incorporated.

The clinical trial (phase III) carried out by the Japan Clinical Oncology Group (JCOG) to evaluate the efficacy of paraaortic lymph node dissection has been closed and the survival results are awaited [17].

Another JCOG clinical trial on gastric cancer invading the lower esophagus proved that the abdominal-only approach should be used for these tumors whose esophageal invasion is 3 cm or less. Therefore, the majority of patients with type II or III tumors of the Siewert classification should be treated through laparotomy and the transdiaphragmatic approach [18]. Thorough mediastinal node dissection by thoracotomy is not needed to treat these tumors.

Just as in Europe, any kind of adjuvant treatment is regarded as a treatment under investigation. Although many meta-analyses of adjuvant chemotherapy show a small but significant benefit of adjuvant chemotherapy over surgery alone, treatment regimens of these analyses are widely heterogeneous. Similar to the conclusions of all these meta-analyses, adjuvant chemotherapy after curative surgery is regarded as under investigation and should be evaluated exclusively in clinical trials with surgery alone as the control [19–21]. Also, the guideline advocates RCT on adjuvant chemotherapy for curable gastric cancer, both pre- and postoperatively.

In the United States, an adjuvant chemoradiotherapy (CRT) after curative surgery is now regarded as the standard treatment [22]. However, in the clinical trial that proved the benefit of CRT over surgery alone, the type of lymph node dissection was just D0 (almost without nodal dissection) for 54% of patients, D1 for 36%, and D2 dissection for 10% of the patients. This finding means that 90% of the patients underwent surgery with insufficient local control in terms of lymph node dissection. Together with the fact that adjuvant chemotherapy alone could not prove a benefit over surgery alone, this trial proved the efficacy and importance of local control for the treatment of gastric cancer. Because the standard surgery for curable tumors in Japan includes much wider lymph node dissection and the stage-specific survival results of this trial were still worse than those of Japanese data, these results supporting the efficacy of CRT cannot be applied to Japanese patients. The effect of CRT after D2 dissection remains uncertain. In the Japanese guideline, the standard treatment for curable advanced gastric cancer is still D2 gastrectomy alone. Any kind of adjuvant treatment is regarded as investigational.

## Treatment of Incurable Gastric Cancer

Only those who can undergo R0 resection have a possibility of cure depending on the tumor stage, that is, T factor and N factor. Patients with nonresectable disease or with distant metastasis are incurable and are primarily treated by chemotherapy if they do not have serious symptoms such as massive bleeding or stenosis hindering oral intake. In the guideline, resection of primary gastric tumor in patients with distant metastasis is defined as reduction surgery and is regarded as investigational treatment. This reduction surgery has often been carried out in Japan without any evidence of advantage for the patients.

Similarly, the majority of recurrences are nonresectable and are treated by chemotherapy. However, at the moment, there is no standard chemotherapy regimen for nonresectable or recurrent gastric cancer. In the United States, the combination chemotherapy using fluorouracil and cisplatin plus docetaxel (5-FU + CDDP + docetaxel) is now regarded as the standard [23]. In Europe, on the other hand, epirubicin

+ CDDP + 5FU is recommended as the standard regimen [24]. These two newly developed regimens are highly toxic, and their efficacy and safety are not yet confirmed in Japanese patients. Actually, combination chemotherapy including TS-1, CPT-11, paclitaxel, 5-Fu, or CDDP is under investigation with the expectation of a longer survival period than with 5-FU alone.

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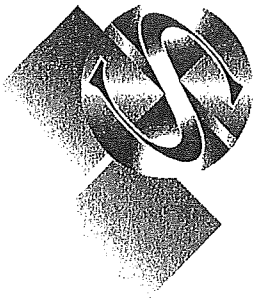

# Surgical Resection of the Stomach with Lymph Node Dissection

Mitsuru Sasako, Takeo Fukagawa, Hitoshi Katai and Kateshi Sano

## Aims

- To describe the techniques of radical lymph node clearance in gastric cancer surgery.
- To identify the aspects of surgery associated with significant morbidity.
- To define the use of pancreatic and splenic resection in gastric cancer surgery.

## Type of Gastric Resection

### Commonly Used Types of Resection

As gastrectomy is now rarely indicated for benign disease of the stomach, this chapter focusses on gastrectomy for gastric malignancies. For gastric cancers, several types of resection are commonly used. For proximal advanced tumours or large tumours, a total gastrectomy (TG) is usually used. For a distally located tumour which does not involve the proximal third of the stomach, a distal (DG) or distal subtotal gastrectomy (DSG) is the preferred type of gastric resection. In the 1980s, proximal gastrectomy (PG) was for a while abandoned because of the high incidence of reflux oesophagitis and in pursuit of radical surgery. However, with the identification of an increasing number of small T1/2 tumours located near the cardia, interest in the role of proximal gastrectomy has been renewed. For similar tumours in the middle of the stomach, pylorus preserving distal gastrectomy (PPG) is being undertaken in an attempt to improve quality of life after surgery [1].

### Total Versus Subtotal Gastrectomy

The concept of total gastrectomy as the appropriate radical surgical management of gastric cancer was promoted by some enthusiasts in the West during the 1970s. This concept has been described as "gastrectomie totale en principe". In Japan, however, TG was carried out only when it was required to allow an R0 resection to be achieved while DG was carried out for many antral tumours, with satisfactory results. To establish the role of the extent of gastric resection, several trials have been carried out to evaluate TG in principle.

There have been two randomised controlled trials comparing TG with DG for antral tumours. In France between 1980 and 1985, 201 patients were randomized between TG and DSG to test if TG could increase 5-year survival rate from 30% after DSG to 50%. After excluding 32 ineligible cases, 84% of randomised patients were included in the analysis; no differences in postoperative morbidity and mortality or in 5-year survival rates were demonstrated [2]. A

similar trial was carried out in Italy enrolling 648 patients between 1982 and 1993 [3]. This trial was set up to test the equivalence of DSG and TG, i.e. DSG should show 5-year survival rates no worse than −10% of the results of TG (50%). There was no significant difference in postoperative death (1.2% after DSG and 2.3% after TG) and 5-year survival rate after DSG was better than after TG (65% versus 62%), confirming the equivalence of the two methods for antral tumours. A further trial has compared DSG with D1 nodal dissection versus TG with D3 dissection [4]. The sample size was small (55 patients) and hypothesis tested included both the extent of gastric resection and extent of lymphadenectomy; as a result the trial is difficult to evaluate. The results demonstrated no significant differences in outcome though the survival curve after DSG was better than after TG.

Theoretically, the oncological gain provided by TG over DSG lies in the reduction in the risk of positive resection margins, the removal of missed second primaries and increasing the extent of lymphatic clearance. The extent of nodal dissection increases the dissection of the left cardiac nodes, short gastric artery nodes, splenic hilum nodes and distal splenic artery nodes. The pattern of lymphatic spread in antral cancers would indicate that removal of these node groups is unlikely to improve outcome. The problem of positive margins is mainly due to inaccurate diagnosis of proximal extension of tumours. For cancers in the mid body on the greater curve, the risk of lymphatic involvement of the splenic hilar and distal splenic artery nodes might support a need for total gastrectomy. For such cases, negative sampling of the nodes at the root of the left gastroepiploic artery or the sentinel nodes may safely allow surgeons to avoid TG.

## Indications for Proximal Gastrectomy (PG)

In 1970s, PG was abandoned for two reasons: a high incidence of local failure in the remnant stomach and frequent and severe reflux oesophagitis due to bile reflux when reconstruction was by oesophagogastrostomy. A dramatic increase in junctional tumours small cancers at the cardia, has been observed in the West. For small tumours located at the cardia as well as T1 tumours in the proximal third of the stomach, PG has been revived in both hemispheres during the 1990s. For T1 tumours of the proximal stomach, PG with extended D1 (D1 plus proximal splenic, coeliac and common hepatic artery nodes) is carried out, followed by a reconstruction with short segment jejunal interposition (modified Merendino's operation: Figure 25.1). For large tumours involving the cardia, because of intramural distal extension to the antrum and the significant incidence of nodal metastasis to the lower lesser curvature and infrapyloric nodes, a TG should be carried out. Harrison et al [5] claimed that TG is not necessary for proximal gastric cancer but the average size of the tumours treated by PG in their series was just 4 cm, much smaller than those treated by TG. Their method of reconstruction was traditional oesophagogastrostomy. As they did not evaluate the quality of life (QOL) of patients, especially in terms of reflux oesophagitis, their technique cannot be justified.

## Pylorus Preserving Gastrectomy (PPG)

Due to the increasing recognition of early gastric cancer in Japan, several surgical techniques have been recently tested to reduce

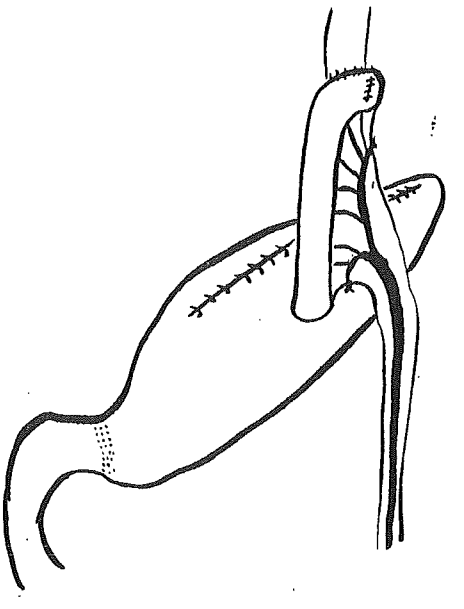

**Figure 25.1.** Modified Merendino's operation of proximal partial gastrectomy with jejunal interposition.

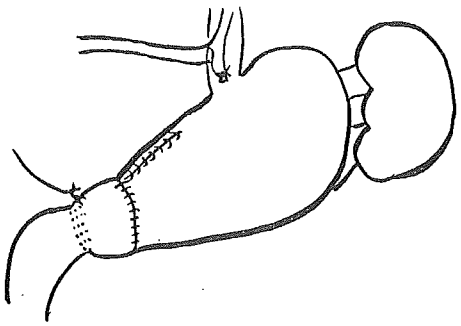

Figure 25.2. Pylorus preserving distal partial gastrectomy.

the incidence of postgastrectomy symptoms. Pylorus preserving gastrectomy is one of these options. This procedure was originally described by Maki as a surgical treatment for benign gastric ulcer [6]. By preserving the pylorus with a small part of the gastric antrum, rapid emptying of the stomach, causing the dumping syndrome, should be reduced. In the 1990s, this technique was introduced in patients with early gastric cancer of the middle part of the stomach [1]. There is now experience with hundreds of patients who have undergone this operation with satisfactory results, in terms of QOL and survival. The original method preserved 1.5 cm of the distal antrum but the preference now is to preserve at least 3 cm of the antrum for better gastric emptying (Figure 25.2).

# Concept, Classification and Efficacy of Lymph Node Dissection for Gastric Carcinoma

## Concept

The initial description of lymph node dissection for cancer treatment was in breast cancer by Halsted and the work was developed by Haagensen. The primary aim of this procedure is to avoid local failure in axillary lymph nodes. Originally all systemic metastasis was thought to occur via lymphatic spread. In this theory, called the Halstedian cancer model, cancer cells spread initially to the nearest nodes and then to farther nodes step by step, and eventually to various distant sites. Therefore the wider the nodal dissection, the better the survival that should be achieved. Local recurrence should be rare after adequate nodal dissection. However, cancer metastases occur not only via lymph stream but also primarily via the bloodstream and sometimes directly through the pleural or peritoneal cavity. In breast cancer, 20–30% of node-negative patients develop systemic recurrence [7]. Local recurrence sometimes occurs as a part of systemic recurrence in high grade tumours. Prognosis of patients with multiple nodal metastases worsens steeply as the number of metastatic nodes increases [8]. All these facts demonstrate that regional lymph nodes do not form an effective barrier to cancer dissemination. Several clinical trials have shown nodal dissection does not contribute to better survival for breast cancer and nodal metastasis is an indicator of poor prognosis. Nodal disease is indicative of a high risk of the presence of systemic disease (systemic disease model).

Unlike breast cancer, gastric cancer more closely follows the requisites for the original Halstedian model. Those having no or limited spread of nodal metastasis have a good prognosis if peritoneal seeding does not occur. Five-year survival rates of those having 4, 6, 8, 10 nodal metastases are 52.3%, 43.5%, 37.7%, 29.9%, respectively (unpublished data from National Cancer Center Hospital Tokyo). Systemic/distant metastases are quite rare in T1 and T2 tumours, whereas lymph node metastases are already frequent in these stages (Table 25.1) [9]. Thus in gastric cancer, nodal metastasis is the primary site of metastatic spread in most cases and systemic recurrence after curative operation in node-negative patients is rare. The commonest type of recurrence of advanced tumours is peritoneal seeding after formal nodal dissection [10]. However, recurrence after limited surgery occurs most frequently in the gastric bed and, with regional peritoneal seeding, accounts for over 90% of recurrences [11]. These differences between breast and gastric cancers might be explained by the following. First, the stomach is located in the portal venous system, with bloodborne metastases occurring most frequently via the portal vein to the liver rather than through the lympho-venous connection in the neck. Second,

the high intraluminal bacteria count is associated with an abundant lymphatic system including mucosa associated lymphoid tissue.

Most of the reported adjuvant chemotherapy trials have failed to prove any efficacy over surgery alone [12]. Recently a clinical trial comparing surgery plus radiochemotherapy versus surgery alone showed significantly better survival for the radiochemotherapy group [13]. In this study, 90% of the patients underwent either D0 or D1 lymph node dissection. This could be interpreted as showing that adjuvant chemotherapy may be effective when the local regional lymph node metastases are well controlled by radiotherapy. However, the survival results of the radiochemotherapy group in this study could not reach the level of the results achieved by D2 dissection alone. Therefore it is still uncertain whether D0/1 surgery plus radiochemotherapy can replace D2 dissection or not. In fact, retrospective analysis of the patients in this trial suggests that surgical undertreatment undermined survival [14].

## Classification

Of the two commonly used classifications for gastric cancer, the Japanese classification [15] and the Union Internacional Contra la Cancrum (UICC) TNM classification, only the former includes a method for classification of the extent of lymph node dissection. The regional lymph nodes are topographically classified from the first to third tier nodes, according to the tumour location in the stomach. In general terms, perigastric nodes are usually classified as the first tier and lymph nodes in the suprapancreatic area with splenic hilum nodes comprise the second tier; nodes in the hepatoduodenal ligament, retropancreatic and para-aortic nodes are the third tier. Nodal dissection is defined as D1, D2 and D3. D0 is defined as excision which fails to remove all of the first tier nodes. D1 includes all first tier stations but not all of the second tier stations. D2 dissection includes all first and second tier stations but not all the third tier nodes. D3 means dissection including all first, second and third tier stations.

## Efficacy

Many retrospective comparisons of lymph node dissection, D1 versus D2, have shown better survival for D2 (Table 25.2). The results of D1 have never reached the level of D2 dissection in terms of long-term survival according to stage. When the results of surgery are compared according to TNM stage, stage migration confounds comparisons. The wider the dissection, the more accurate the stage diagnosis, thus resulting in an increase in the number of cases at advanced stages and improvement of the results by stage in each category, stage migration. Therefore, for gastric cancer, the results of two groups who underwent different nodal dissection should be compared by T stage, which is not influenced by type of nodal dissection. Even in such comparisons, D2 always shows better results than D1. However, randomised controlled trials (RCTs) have never proven the superiority of D2 dissection over D1. Table 25.2 shows the results of these RCTs. Furthermore the two large-scale RCTs, the MRC trial [16] and the Dutch trial [17], showed significantly higher postoperative hospital mortality after D2 than D1. Initially these results we interpreted as pointing to an

**Table 25.1.** Metastases at the time of operation, 5-year survival, and haematogenous recurrence after resection in 4683 patients at National Cancer Center Hospital Tokyo, 1972–1991

| Tumour depth | *n* | LN | Liver | Peritoneum | 5Y SR (%) | Haematogenous rec. |
|---|---|---|---|---|---|---|
| pT1(m) | 1063 | 3.3 | 0 | 0 | 93.3 | 2 (0.2%) |
| pT1(sm) | 881 | 17.4 | 0.1 | 0 | 88.9 | 9 (1.0%) |
| pT2(mp) | 436 | 46.7 | 1.1 | 0.5 | 81.3 | 26 (5.9%) |
| pT2(ss) | 325 | 63.6 | 3.4 | 2.2 | 65.8 | 31 (9.5%) |
| pT3 | 1232 | 79.9 | 6.3 | 17.8 | 35.5 | 149 (12.1%) |
| pT4 | 724 | 89.7 | 15.5 | 41.6 | 10.1 | 106 (14.6%) |
| All | 4683 | 47.8 | 4.5 | 11.5 | 60.3 | 318 (6.8%) |

*n*. number: LN. lymph node: 5Y SR. 5-year survival rate, Rec, recurrence

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inherently greater risk in D2 dissection. However, precise analyses of these trials and other reports elucidated surgical inexperience in those undertaking D2 dissection in these trials. Moreover, the only single arm study to assess the safety and effectiveness of D2 dissection, which was started after the publication of the results of MRC and Dutch trials, has demonstrated the safety of D2 dissection if done in high volume hospitals in the West. These trials provide important lessons around the importance of quality assurance in phase trials in surgery. The issue of timing of trial initiation has been raised, with suggestions that this should be determined on the basis of demonstration that individuals are near to the plateau of their learning curve of a difficult technique. Inexperience can produce large biases when comparing technically demanding surgical procedures.

Survival results of these trials in comparison to other studies are shown in Table 25.3. This table compares exclusively the results of D2 surgery, to avoid the stage migration effect. Sometimes, the results of the Dutch trial and MRC trials are interpreted as real evidence of non-superiority of the D2 dissection for gastric cancer. However, these are not trials set up to show the equality of D1 and D2 and with the factors pointed out above, the question is still unsolved. However, from the experience in these trials, it is obvious that D2 dissection should not be carried out by surgeons with insufficient experience of this technique and inexperienced surgeons should carry out this procedure strictly under the supervision of experienced surgeons.

# Indications for Extended lymph Node Dissection (D2 Dissection)

## Tumour Factors

This procedure should not be undertaken in incurable patients because of the increased morbidity associated with the technique. For T1

**Table 25.2.** D1 versus D2 5-year survival rates

| Author | 5-year survival rate D1 | 5-year survival rate D2 | Reference |
|---|---|---|---|
| Pacelli F, et al | 50.1 | 65.4 | Br J Surg 1993;80:1153–6 |
| Onate-Ocana LF, et al | 35.1 | 64.0 | Ann Surg Oncol 2000;7:210–17 |
| De Manzoni G, et al | 28 | 63 | Br J Surg 1996;83:1604–7 |
| Lee WJ, et al | 34.8 | 41.5 | World J Surg 1995;19:707–13 |
| Sue-Ling H | 18 | 45 | Eur J Surg Oncol 1994;20:179–82 |
| Gall FP, et al | 43.6 | 51.8 | Eur J Surg Oncol 1985;11:219–25 |

**Table 25.3.** D2 Surgery: trial results

| Author | No. of patients | # patients/y/h | PO mortality | 5-Year survival rates (%) Overall | IA | IB | II | IIIA | IIIB | IV |
|---|---|---|---|---|---|---|---|---|---|---|
| Siewert | 803 | 14 | 5.0 | NM | 84 | 68 | 57 | 32 | 14 | 13 |
| Pacelli | 157 | 16 | 3.8 | 65 | 86 | → | 66 | 49 | → | none |
| Sue-Ling | 207 | 10 | 6 | 54 | 87 | → | 65 | 24 | → | NM |
| Cuschieri | 200 | 1 | 13.0 | 33 | 58 | → | 31 | 11 | → | none |
| Bonenkamp | 331 | 1 | 9.7 | 47 | 81 | 61 | 42 | 28 | 13 | 28 |
| Sasako | 2541 | 254 | 0.3 | 66 | 92 | 90 | 76 | 59 | 37 | 8 |
| Jatzko | 345 | 33 | 4.9 | 58 | 98 | 84 | 56 | 49 | 8 | 11 |
| Hundahl* | 32532 | NM | NM | 28 | 78 | 58 | 34 | 20 | 8 | 7 |

* Results of National Data Base, most cases are treated by D0/1, NM, not mentioned; none, no patient included; →, stage IB is included in stage IA and stage IIIB is included in stage IIIA; # patients/y/h, number of patients treated per year per hospital; PO mortality, postoperative mortality.

tumours, the risk of second tier node involvement is 5% and therefore in Western practice where the postoperative mortality is of the order of 5% in experienced centres, a D1 resection would be appropriate. This is dependent on the assumption that preoperative assessment of the depth of invasion is accurate.

For T4 tumours, a D2 dissection should be applied only when the entire tumour can be resected by the resection of neighbouring organs involved by the primary tumour. It remains unclear whether D2 dissection is of value in linitis plastica because of the frequency of recurrence in the peritoneal cavity despite an even higher incidence of nodal metastases in the second tiers than in other types. Indeed some authors claim that surgery is not indicated for this type of tumour. However, about 20% of cases of linitis plastica can be cured by D2 dissection combined with adjuvant chemotherapy when an R0 resection can be achieved. Although the recurrence rate in the peritoneum is high, cure without resection is not realistic and therefore D2 dissection remains an option in curable linitis plastica. As most tumours involve the greater curvature of the body and often the gastrosplenic ligament, splenectomy is usually required in addition.

## Patient Factors

Postoperative hospital mortality after D2 dissection is over three times greater in aged patients and mortality after total gastrectomy is over five times greater in patients over 80 years old compared with those under 70. The results of the Dutch trial showed much higher mortality after D2 in aged patients. D2 total gastrectomy for aged patients should be carried out only in high volume hospitals by experienced surgeons.

As D2 dissection includes the meticulous dissection of lymph nodes in the suprapancreatic area, in obese patients the risks are increased as the pancreas is embedded in thick adipose tissue, hindering recognition of the border of the organ and increasing the risk of injury to either the parenchyma or the vessels to the pancreas.

Patients with impaired liver function are regarded as high risk for D2 dissection, especially cirrhotic patients. The development of massive and often uncontrollable ascites after D2 dissection occurs frequently and is often fatal. These patients have increased lymphatic flow surrounding the liver and D2 dissection disturbs the lymph circulation of these patients enormously.

After D2 dissection, fluid retention in both the abdominal and the retroperitoneal space is very great and maintenance of fluid balance following surgery can be difficult. Thus pneumonia or cardiac failure during the resorptive phase can occur and this phase requires intensive management. D2 should be undertaken with caution in those with impaired respiratory and cardiac function.

# Combined Organ Resection for Lymphadenectomy

In the history of radical resection of cancers, combined resection of organs surrounding the primary tumour is based on the idea of en-bloc resection, which means complete resection of all the tissues through which draining lymph vessels pass. In gastric cancer surgery, complete bursectomy and omentectomy, pancreaticosplenectomy were based on the same idea. In en-bloc resection of the gastric bed with vascular pedicle, Appleby's operation, three-quarters of the pancreas distal to the portal vein, spleen, coeliac artery with its branches are resected en bloc [18]. Until 1980, pancreaticosplenectomy was a standard part of the D2 radical total gastrectomy. However, comparison of the survival benefit against the increased morbidity and mortality and the high incidence of diabetes mellitus led many surgeons to abandon pancreas resection. As a result, pancreas-preserving total gastrectomy became the standard in Japan during the 1990s [19]. It is now recognised that good survival rates can be achieved in node-positive patients without en-bloc resection of these neighbouring organs.

Two large clinical trials comparing D1 versus D2 showed that combined resection of spleen and pancreas largely accounted for the increased morbidity and mortality in a D2 dissection [16,17]. The remaining question is whether splenectomy alone increases the risk of operative mortality and whether it contributes to improved survival. Although in these trials splenectomy was associated with a worse prognosis, the close correlation with tumour site and histology (more proximal tumour and more

diffuse type) confounds unbiased comparison. Therefore, this can be answered only by an RCT comparing D2 TG with or without splenectomy. The Japanese Clinical Oncology Group started such a trial in 2002 aiming to accrue 500 patients to demonstrate non-inferiority of splenic preservation.

Combined resection of the entire or a part of organs invaded by the primary tumour is accepted as the only way to achieve R0 resection for some cases. For these T4 tumours, radiotherapy has not yet been proven to be as effective as surgical resection.

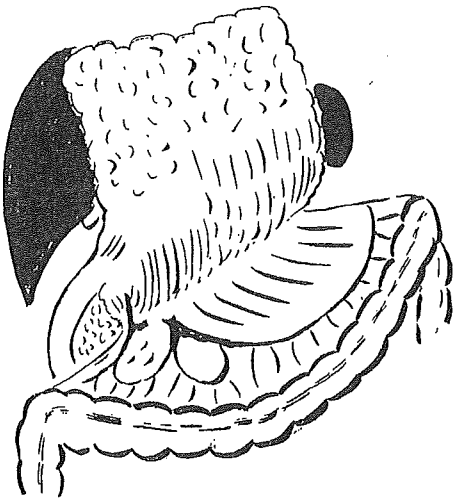

**Figure 25.3.** Elevation of greater omentum with anterior leaf of transverse mesocolon.

# Techniques of D2 Dissection

## Standard D2 TG: Pancreas Preserving TG

First an extensive mobilisation of the duodenum and the head of the pancreas is carried out to observe and palpate the para-aortic area. If there are nodes which are suspicious, sampling for frozen section should be carried out. If they are negative for cancer, radical D2 dissection is started. Complete omentectomy with resection of the anterior sheet of mesocolon is carried out (Figure 25.3). Many T3 tumours have lymphatic spread in the omentum, complete omentectomy remains a part of the standard D2 dissection. Similarly, T3 tumours adhering to the anterior sheet of the mesocolon and/or the pancreatic capsule may necessitate the resection of these structures and frequently turn out to be invading them. Complete bursectomy avoids tumour exposure in such cases. By carrying out this procedure, the accessory right colic vein is identified and followed proximally. It joins with the right gastroepiploic vein, forming Henle's surgical trunk which flows into the superior mesenteric vein (Figure 25.4). The right gastroepiploic vein is ligated and divided at its origin. For antral tumours, nodes on the superior mesenteric vein are also dissected. As the layer exposed by the bursectomy continues to the posterior aspect of the pancreas, the layer of the dissection should be changed to the anterior surface of the pancreas. Several vessels coming from behind the pancreas towards the anterior

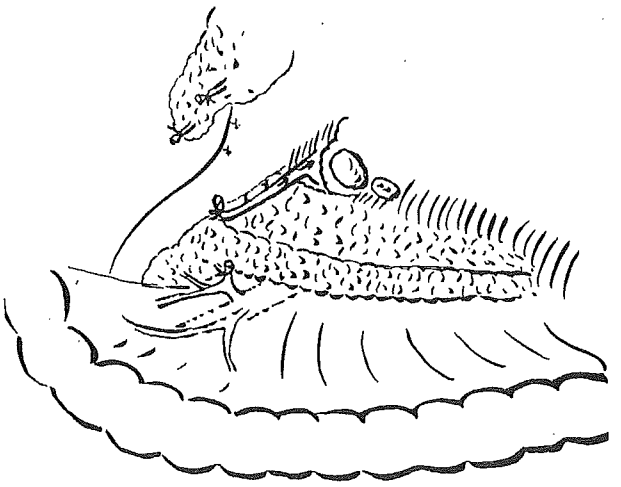

**Figure 25.4.** Division of right gastro-epiploic vein at Henley's trunk.

sheet of the mesocolon should be ligated at the inferior border of the pancreas.

The capsule of the pancreas is now dissected from the parenchyma in the middle part of the organ first, then toward the tail and the head, until the gastroduodenal artery is recognised. Following this artery, the root of the right gastroepiploic artery is found. After ligation and division of this artery at its origin, the stomach is lifted up to divide the back surface of the proximal duodenum from the pancreas and the gastroduodenal artery is followed cranially until the bifurcation of the common hepatic artery is recognized (Fig ure 25.4). The stomach

is laid back to the natural position and the lesser omentum is divided near the lateral segment of the liver from the left edge of the hepatoduodenal ligament to the oesophageal hiatus (Figure 25.5). This line is extended on the hepatoduodenal ligament to the left side of the common bile duct, where this incision is turned caudally towards the duodenum. Then the supraduodenal vessels, usually three or four in total, are ligated and divided close to the duodenal wall (Figure 25.6). This procedure makes a window above the duodenum, through which the gastroduodenal artery can be clearly seen. The connective tissue containing the lymph nodes in the hepatoduodenal ligament left of the common bile duct is dissected from right to left, from the duodenum towards the hepatic hilum along the gastroduodenal and then the hepatic artery. By doing so, the origin of the right gastric artery is easily identified, ligated and divided (Figure 25.6). Now the duodenum is divided a couple of centimetres from the pylorus by a linear type stapler. Pulling up the stomach from right to left and/or cranially, the suprapancreatic lymph nodes, common hepatic, coeliac, left gastric and splenic artery nodes are dissected, starting from the lymph nodes on the left side of the portal vein towards the nodes along the splenic artery. Downward traction of the pancreas by an assistant is extremely useful (Figure 25.7). During this procedure, the left gastric vein is encoun-

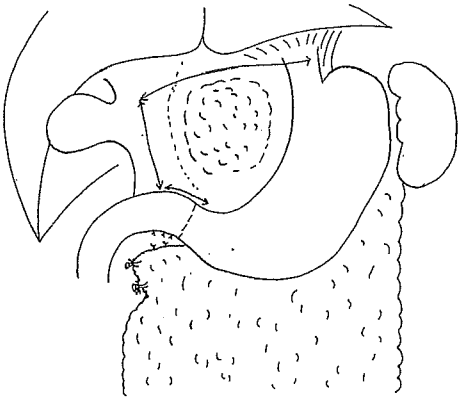

**Figure 25.5.** Line of division of the lesser omentum and duodenal clearance.

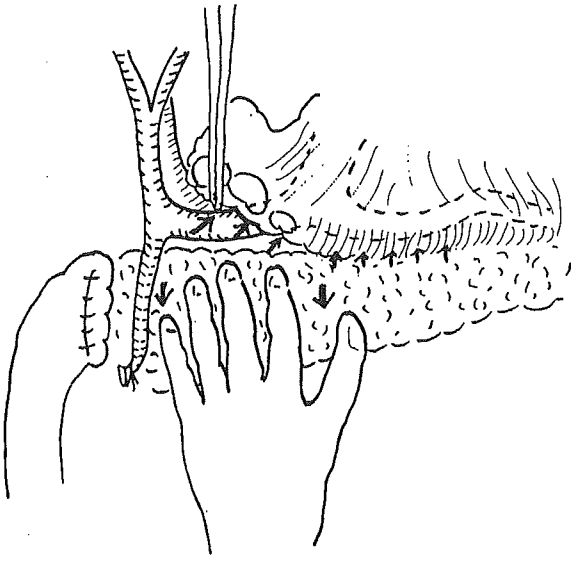

**Figure 25.7.** Clearance of suprapancreatic nodes along hepatic artery, celiac axis and splenic artery and peritoneum over pancreas. Note downward tension provided by assistant.

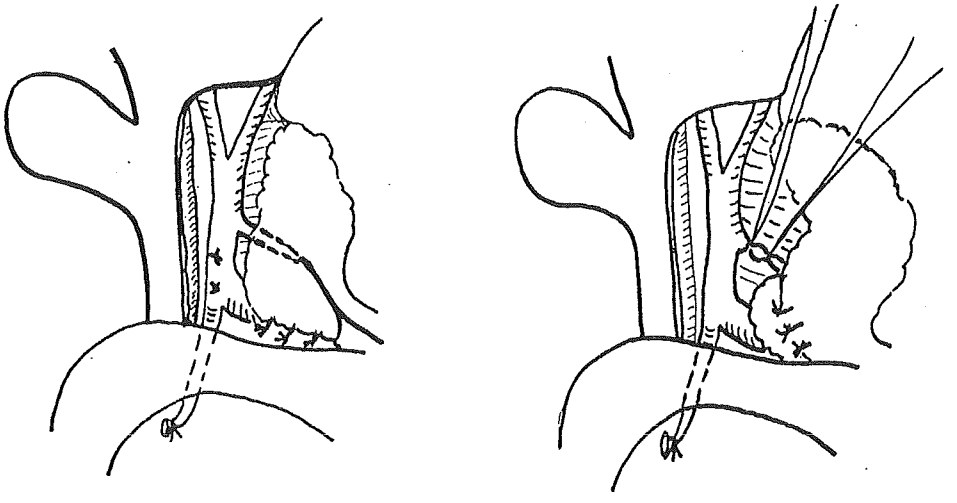

**Figure 25.6.** Identification and ligation of right gastric artery.

tered, most commonly behind the common hepatic artery (Figure 25.8). As a second frequent variation, this vein crosses over the common hepatic or splenic artery, flowing into the splenic vein. This vein is carefully found and then ligated and divided near its origin. The adipose tissue and thick nerve structures on the crus surrounding the oesophageal hiatus are divided from the crus, thus skeletonising the right side of coeliac artery and the origin of the left gastric artery. When the left hepatic artery is a branch of the left gastric artery, it should be preserved up to the origin of the hepatic artery in poor risk patients, to avoid necrosis of the lateral segment. Otherwise it should be ligated and divided at its origin.

The splenic artery nodes are dissected from the splenic artery around the origin of the posterior gastric artery (Figure 25.9). Near the origin of the posterior gastric artery, the great pancreatic artery branches off and comes into the pancreatic parenchyma. The splenic artery is now ligated and divided distal to the origin of the great pancreatic artery. In most cases, one of the large branches of the splenic vein appears on the anterior surface of the pancreatic tail. Then the pancreatic tail is mobilised completely from the retroperitoneum along Toldt's retropancreatic fascia. Traditionally the mobilisation started lateral to the spleen and the spleen is mobilised medially, pulling the spleen up with the operator's left hand. In this technique, the dissection on the left adrenal gland is carried out blindly, sometimes injuring the gland. To avoid this and the loss of the plane of dissection, it is better to mobilise the pancreatic body along Toldt's fascia at the upper border of the organ and continue towards the spleen. The lateral retroperitoneum is incised last (Fig 25.10). When the pancreas left of the coeliac artery is completely mobilised, the lymph nodes on the posterior surface of the pancreatic tail are dissected carefully, preserving the branches of splenic vein to the pancreas (Figure 25.11). All the branches from splenic vein to the stomach are carefully ligated and divided. After the pancreatic tail vein is preserved, the trunk of the splenic vein is ligated and divided. The vein commonly divides before the tip of the pancreatic tail and the branches are ligated separately. Now the pancreatic tail is naked and separated completely from the stomach and the spleen (Figure 25.12). The last step of the procedure is to dissect the left side of the oesophageal hiatus

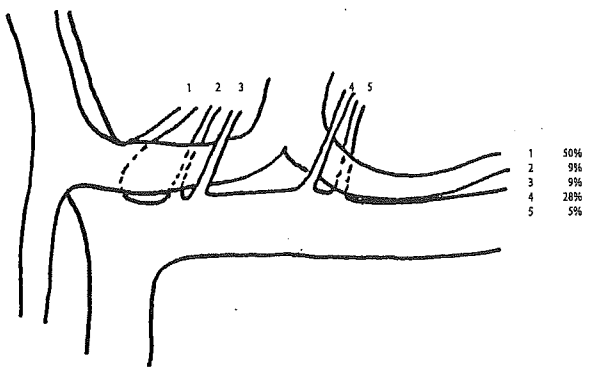


**Figure 25.8.** Variations in anatomy of left gastric vein.

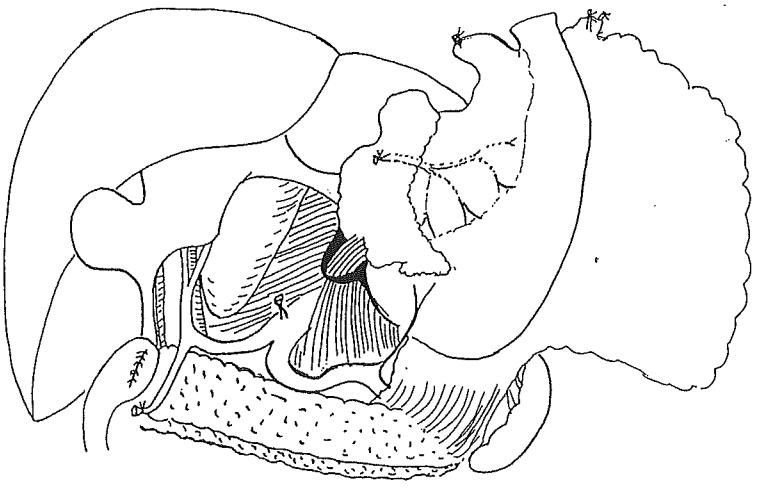

**Figure 25.9.** Origin of posterior gastric artery, defining point of division of splenic artery.

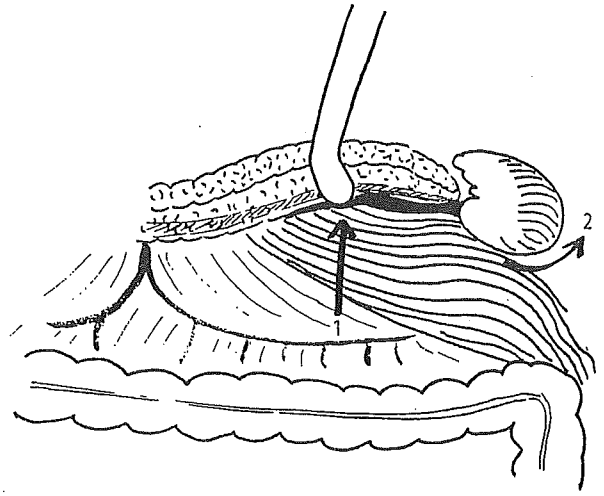


**Figure 25.10.** Mobilisation of the pancreatic tail along Todt's fascia.

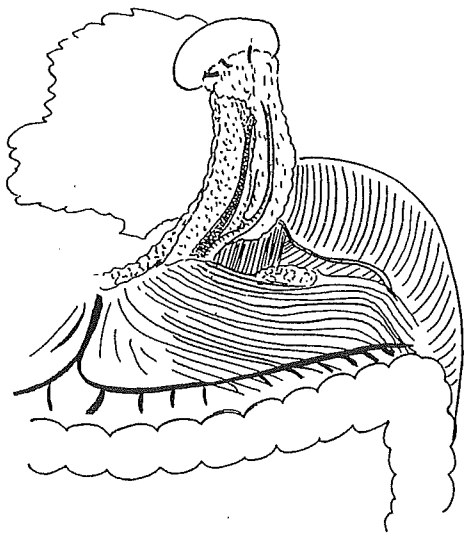

**Figure 25.11.** Dissection of pancreas to region of celiac axis preserving venous drainage to pancreas.

by ligating the oesophagocardiac branch of the inferior phrenic vessels. Both vagal nerves are divided 2–3 cm proximal to the cardia and the abdominal oesophagus is transected. An alternative technique is to divide the oesophagus as the primary step and the splenic artery nodes are dissected by pulling the entire specimen downward.

There are several methods of reconstruction of the digestive tract after total gastrectomy. The commonest and simplest method is Roux-en-Y reconstruction. Another commonly used

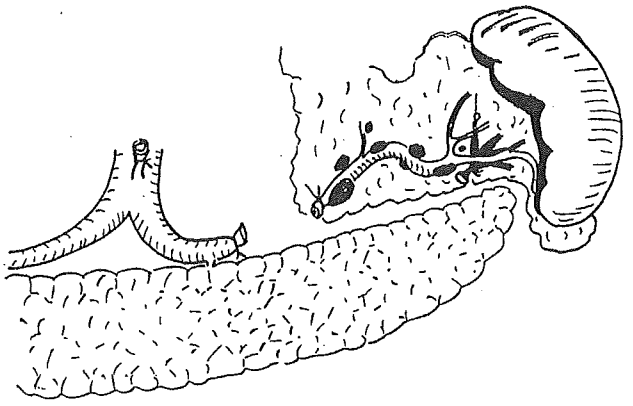

**Figure 25.12.** Separation of distal splenic artery and spleen following division of branches from splenic vein to spleen and stomach.

method is jejunal interposition. Reconstruction using a pouch in conjunction with either method has been trialled but the advantage of these techniques over simple reconstruction is not clear. The oeophagojejunal anastomosis should be end to side and can be carried out using a circular stapler, with a leakage rate of 1–2% [20]. In cases where the anastomosis lies in the mediastinum, it may be necessary to divide one or two jejunal arteries from their trunk, keeping the peripheral arcade intact, to allow the jejunum to reach the anastomotic site without tension.

## TG with PS

In a conventional D2 total gastrectomy with pancreaticosplenectomy, the pancreas is transected near the coeliac artery. The indications for a combined resection are a T4 tumour invading the pancreas, bulky nodal metastases in the suprapancreatic area or metastatic nodes invading the pancreas. In these cases, the pancreas is transected adjacent to the portal vein. When the pancreas is resected, the splenic artery is ligated and divided at its origin, preserving the common hepatic artery, and then the splenic vein is divided at the resection line of the pancreatic parenchyma or its origin from the portal vein. The remainder of the procedure is the same as pancreas preserving total gastrectomy.

## Standard Distal Gastrectomy

Most of the procedure is as described for total gastrectomy. A crucial issue in the procedure of

distal subtotal gastrectomy is splenectomy. In the MRC and the Dutch trials, some surgeons carried out splenectomy in distal gastrectomy. In D2 dissection, where the left gastric artery is ligated and divided at its origin, the blood supply to the remnant stomach is provided by the short gastric vessels, posterior gastric vessels and cardio-oesophageal branch from the inferior phrenic vessels. As the latter two are sometimes absent, the short gastric vessels are crucial to the viability of the remnant. Splenectomy should be avoided in distal gastrectomy, despite many textbooks of surgical technique showing all short gastric vessels ligated in distal subtotal gastrectomy. Mortality after D2 distal gastrectomy with splenectomy was 50% in the Dutch trial.

Another technical point is the dissection of right cardiac nodes in distal gastrectomy. These nodes are embedded in adipose tissue loosely attached to the gastric wall and easily divided from the wall without breaking the membrane enveloping the adipose tissue. All small branches to the gastric wall are divided, anterior and posterior branches separately (Figure 25.13) together with numerous small vagal fibres. The last technical point is how to dissect the greater curvature nodes along the left gastroepiploic vessels. These vessels are most commonly the last branch of the splenic vessels. At the tip of the pancreas, near the splenic hilum, they arise from the inferior border of the organ running toward the stomach in the splenogastric ligament (Fig 25.14). Unlike the right gastroepiploic artery and vein, these vessels do not have a main trunk but three or four long branches in a palm-like shape. Sometimes, the inferior polar branch of the splenic artery comes from the gastroepiploic artery. In such cases, ligation of the left gastroepiploic artery renders a small part of the spleen ischemic but rarely causes any serious problems.

## PPG

PPG was originally advocated by Maki [6] as surgical treatment for benign gastric ulcer, to avoid dumping syndrome, the most important long-term sequela of distal gastrectomy. As a result of the remarkable increase in early gastric cancer in Japan, this technique was introduced in the 1990s for early gastric cancers located near the incisura. A 3 cm antral remnant is preserved and anastomosed to the proximal gastric remnant close to the greater curvature. By preserving the hepatic branch of the anterior vagal trunk and subsequently the pyloric branch, gastric emptying function is well preserved. As a result, the suprapyloric nodes are not systematically dissected in this operation as early gastric cancers in the middle part of the stomach have a less than 1% risk of these nodes being involved. Other nodal stations in D2 distal gastrectomy can be dissected as usual. Precise evaluation of this technique in terms of both

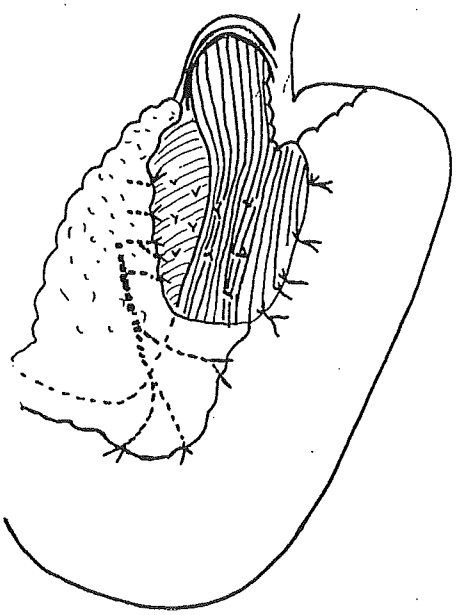

**Figure 25.13.** Clearance of right cardia nodes in distal gastric resection.

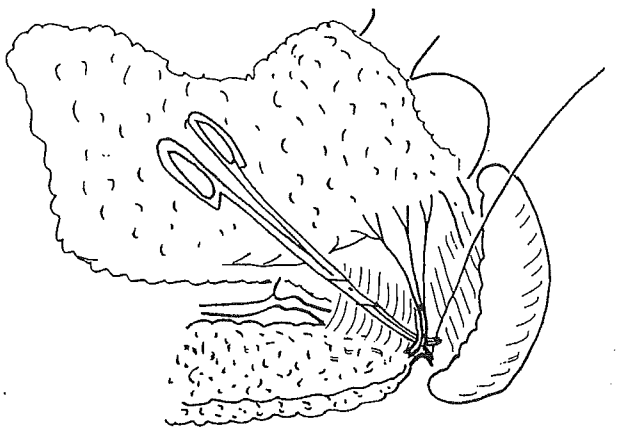

**Figure 25.14.** Identification of left gastro-epiploic vessels, usually last branch of splenic vessels.

survival and quality of life after gastrectomy should be available in the near future.

## Para-aortic Nodal Dissection

In patients with advanced gastric cancer, the incidence of metastases in the para-aortic lymph nodes is reported in as many as 30% of cases. While there are reports of long-term survivors in this group the value of routine dissection remains unproven. Therefore, a randomized controlled trial was carried out by the Japanese Clinical Oncology Group (JCOG), recruiting 523 patients with curable advanced gastric cancer. Four out of 523 patients died in hospital postoperatively; thus the overall postoperative mortality rate was 0.8%, in contrast with the MRC and Dutch trials. Long-term survival evaluation will be carried out in 2006.

# Postoperative Care after D2 Dissection

Morbidity after D2 dissection in the Dutch trial and after D2 or D4 in JCOG trial is shown in Table 25.4. The most important complications after D2 or more extended gastrectomy are those related to pancreatic resection or nodal dissection around the pancreas, including splenectomy. Therefore, prophylactic use of drainage tubes and careful drain handling is recommended. The management of pancreatic leakage is complex with outcome dependent on skilled management. This includes high volume continuous irrigation or continuous suctioning together with somatostatin analogues [21]. In low volume hospitals learning how to treat pancreatic complications after D2 dissection is difficult and, in the Dutch D2 study, many patients who developed such complications died. Anastomotic leakage used to be the most important and frequent complication after a total gastrectomy but the availability of staple guns has been instrumental in reducing this to very low levels [20]. One remarkable difference between the results of the Dutch and JCOG trials is the low mortality after major complications. All participating hospitals in the JCOG trial are high volume hospitals, whereas many of those in the Dutch trial were not. In the publication of the results, it was concluded that D2 dissection should not be carried out as the standard treatment in low volume hospitals and that gastric cancer patients should be treated in specialist centres in low incidence countries.

**Table 25.4.** Postoperative complications

| Type of complication | Incidence (%) | |
|---|---|---|
| | Dutch (D2) | JCOG (D2/4) |
| Surgical | | |
| Haemorrhage | 5 | 0.6 |
| Wound infection | 9 | 1 |
| Anastomotic leak | 9 | 2 |
| Intra-abdominal infection | 17 | 5 |
| Pancreatic leak | 3 | 4 |
| Non-surgical | | |
| Cardiac | 5 | 0.1 |
| Pulmonary | 15 | 4 |
| Urinary tract | 2 | 0.4 |
| Thromboembolic | 2 | 0.4 |

## Questions

1. What are the indications for choosing the extent of gastric resection?
2. What are the consequences of splenic resection in partial gastrectomy?
3. What are the patient factors which determine whether extended nodal dissection is feasible?

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