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高度進行胃がんの治療に関する研究

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総括研究報告書

高度進行胃がんの治療に関する研究

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研究要旨

予後不良の進行胃がんであるスキルス胃がん及び大型3型胃がんに対して、術前にTS-1+シスプラチンによる化学療法を2コース実施後に、根治手術を行う治療法の開発に取り組んだ。昨年まで登録を行った第Ⅱ相試験の結果を集計・解析した。本治療法はGrade3以上の有害事象が15%以下と安全に行えること、治療完遂率が62%と期待通りの治療効果を認めること、ことに組織学的腫瘍効果で優れた成績を示すこと（Grade1b以上が48%）が判明した。第Ⅲ相試験のプロトコールを作成し、JCOG臨床試験審査委員会で第1回目の審査を受け、審査意見に基づいた最終バージョンを作成する段階である。

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A. 研究目的

全体では70%近い治療率を達成した胃がんにおいて、依然10%程度の5年生存率にとどまっているスキルス胃がんあるいはそれに準ずる大きな3型胃がんの予後改善が本研究の目的である。スキルス胃がんは20代の若年者にも多く発生し、数多くの悲劇を生んできた。就労期の患者が多数を占める同疾患の予後改善の必要性は高く、その社会的な意義もきわめて大きい。

B. 研究方法

治療法：術前にTS-1+シスプラチン療法（TS-1は3週間投与、1週休薬、シスプラチンday8に投与）を2コース実施後に、D2郭清以上の郭清を伴う根治手術を行う。

治療法の評価方法：第Ⅱ相試験において治療の安全性と高い完遂率が期待できることが判明したことから、従来治療である手術単独療法を対照群とした第Ⅲ相試験を行う。第Ⅲ相試験はJCOG胃がん外科グループの臨床試験として行う。本試験のプロトコールはJCOGのプロトコール審査委員会で承認された後、各参加施設の倫理審査委員会の審査・承認を受けている。また、データ管理はJCOGデータセンターに委託し、委託費を支払う。

（倫理面への配慮）

先行した第Ⅱ相試験に続いて開始された第Ⅲ相試験ともJCOG臨床試験審査委員会において科学性・倫理性の厳しい審査を受けて承認されている。その後参加各施設の倫理審査委員会が試験の実施を承認するダブルチェックシステムをとっており、プロトコールは、ヘルシンキ宣言のみならず、被験者の個人情報保護等に関する条項も満たすべく作成されている。被験者は文書と口頭による十分な説明を受けたのち、自由意志に基づいて、文書にて同意する仕組みを取っている。

C. 研究結果

現在登録中の第Ⅲ相試験に先行した第Ⅱ相試験症例の治療成績の概略は以下の

通りであった。登録50例中、治療関連死は1例で、治療中の胃の原発巣からの出血死であった。Grade4の血液学的有害事象は低ナトリウム血症の1例のみで、Grade3は白血球減少6%、好中球減少14%、貧血10%と低率であった。非血液学的有害事象ではGrade4は無く、Grade3は食欲不振14%、悪心6%、その他は各1例ずつであった。有害事象のための治療中止は3例であった。50例中化学療法中の治療関連し（出血）1例と手術拒否の1例を除いた48例が手術を受け、治癒切除は35例で行われた。組織学的所見を含めての根治手術達成（総合的治癒切除）は31例であった。術後の合併症は膵液瘻8%、腹腔内膿瘍6%、肺炎4%等、きわめて低頻度であった。プライマリーエンドポイントである治療的遂割合は62%で、前述の安全性と短期的な治療効果を確認することができた。組織学的効果判定ではCRを2例含めて、画像上のPRに匹敵すると思われる組織学的効果Grade1b以上の症例が24例で、奏効率48%と解釈することができた。

第Ⅲ相試験のプロトコールはJCOGプロトコール審査委員会に平成17年2月に提出され、慎重な審査と修正作業の後に、平成17年9月16日付で承認された。その後各参加予定施設内の倫理審査委員会により審査が行われ、第1例目は平成17年11月に登録された。その後現在まで30施設でプロトコールが承認され、平成18年3月31日現在4例が登録されている。

D. 考察

以上より、本治療法（TS-1+CDDP+根治手術）は第Ⅱ相試験での評価において、第Ⅲ相試験の試験アームにふさわしいと考えられた。この第Ⅲ相試験の対象は前記第Ⅱ相臨床試験と同じ大型3型・4型胃がんで、手術単独群を対照治療とする。第Ⅱ相試験では、主たる目的がfeasibilityの確認であったことから、適格性を臨床・画像検査のみで決めたが、本第Ⅲ相試験では診断的腹腔鏡検査を実施した上で、腹膜播種が無く、洗浄細胞診陰性の症例のみを対象として実施している。診断的腹腔鏡検査の使用は徐々に我が国で拡大しつつあるが、本臨床試験が我が国における診断的腹腔鏡検査の標準的定着を促す可能性は十分に考えられる。

登録症例数が未だ少数であるが、ようやく参加施設が揃った時期であり、今後はあらゆる方法で参加施設を鼓舞しながら、積極的な試験への参加を呼びかけていく。年間60例を見込んでおり、月間5例であることから、当面は施設毎に対象症例数、その内の試験登録数と非登録例

における非登録理由の把握を実施していく。

また、JCOG胃がん外科グループでは、同じレジメンを用いて高度リンパ節転移を有する局所進行胃がん症例に対する術前化学療法の第Ⅱ相試験も実施中であり、安全性情報等は共有していく。

E. 結論

TS-1+CDDP療法は安全性と治療効果に優れ、遠隔転移のない予後不良進行胃がん症例に対する新しい治療法となりうるポテンシャルを持ち、第Ⅲ相試験を施行中である。

F. 健康危険情報

現在まで登録された症例では該当なし。

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H. 知的財産権の出願・登録状況
該当なし。

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書籍名	出版社名	出版地	出版年	ページ
<u>Sasako, M.</u> , et al.	Surgical resection of the stomach with lymph node dissection	Fielding, J. W. L., Hallissey, M. R.	Upper Gastrointestinal Surgery	Springer-Verlag	London	2005	335-347

雑誌

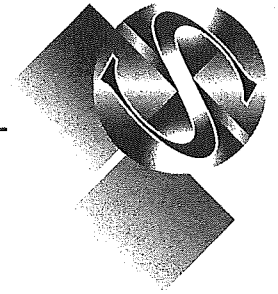
発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
<u>Kubo, M.</u> , <u>Sasako, M.</u> , et al.	Increasing body mass index in Japanese patients with gastric cancer	Gastric Cancer	8	39-41	2005
<u>Sasako, M.</u>	Clinical trials of surgical treatment of malignant diseases	Int J Clin Oncol	10	165-170	2005
<u>Katai, H.</u> , <u>Sasako, M.</u> , et al.	Risk factors for pancreas-related abscess after total gastrectomy	Gastric Cancer	8	137-141	2005
<u>Kodera, Y.</u> , <u>Sasako, M.</u> , et al.	Identification of risk factors for the development of complications following extended and superextended lymphadenectomies for gastric cancer	British Journal of Surgery	92	1103-1109	2005
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<u>阪眞、 笹子三津留</u>	特集：臨床腫瘍学の現状と展望 V. がん薬物療法の実践 4. 消化器癌 2) 胃癌 b) 進行胃癌のアジュバント療法	Progress in Medicine	25	2073-2078	2005

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
吉川貴己、 小林理、ほか	腹膜転移を有する初発 胃癌の治療戦略	癌と化学療法	32	1398-1403	2005
種村廣巳、ほか	大型3型/4型/Bulky N2 進行胃癌に対するTS- 1+CDDPを用いた術 前化学療法の経験	癌と化学療法	32	2079-2085	2005
<u>Miyashiro, I., et al.</u>	When is curative gastrectomy justified for gastric cancers with positive periton eal lavage cytology but negative macroscopic peritoneal implant?	W J Surg	29	1131-1134	2005

III. 研究成果の刊行物・別刷

「がん臨床研究事業」

主任研究者 笹子 三津留



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

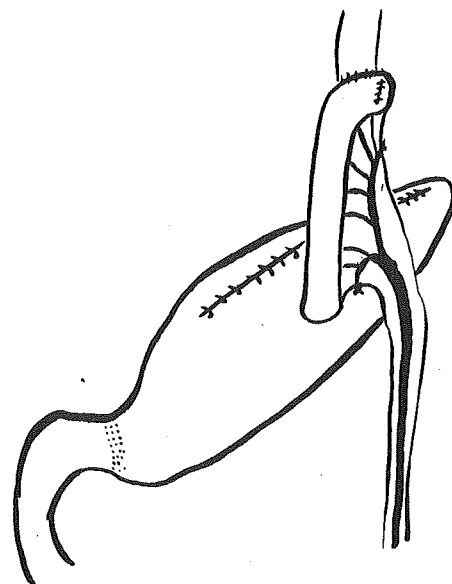


Figure 25.1. Modified Merendino's operation of proximal partial gastrectomy with jejunal interposition.

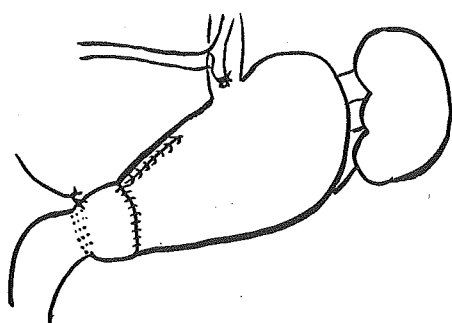


Figure 25.2. Pylorus preserving distal partial gastrectomy.

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.

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

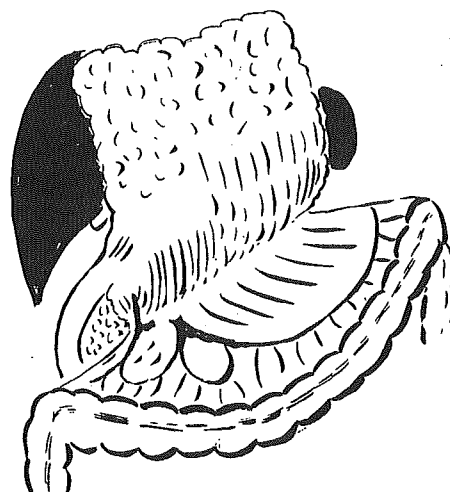


Figure 25.3. Elevation of greater omentum with anterior leaf of transverse mesocolon.

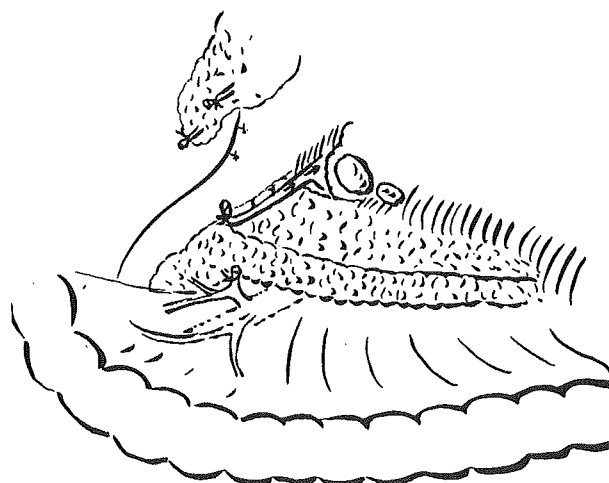


Figure 25.4. Division of right gastro-epiploic vein at Henle's trunk.

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 (Figure 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.

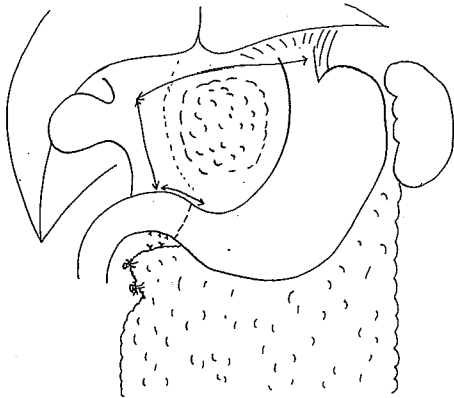


Figure 25.5. Line of division of the lesser omentum and duodenal clearance.

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-

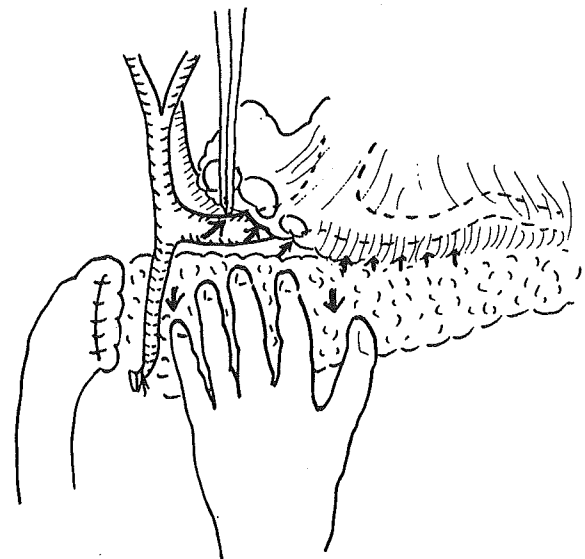


Figure 25.7. Clearance of suprapancreatic nodes along hepatic artery, celiac axis and splenic artery and peritoneum over pancreas. Note downward tension provided by assistant.

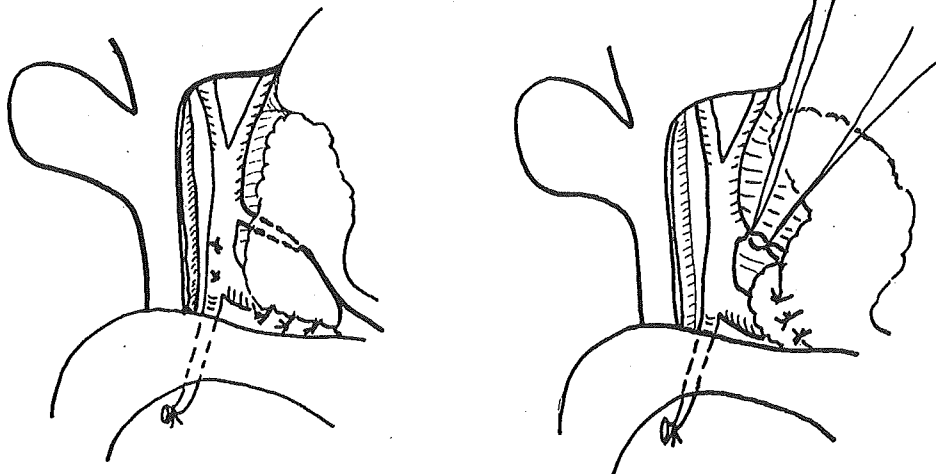


Figure 25.6. Identification and ligation of right gastric artery.



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

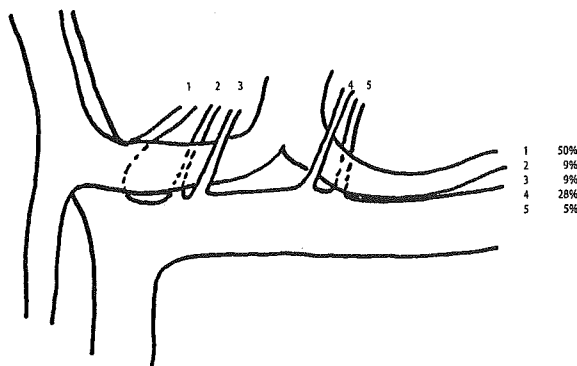


Figure 25.8. Variations in anatomy of left gastric vein.

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

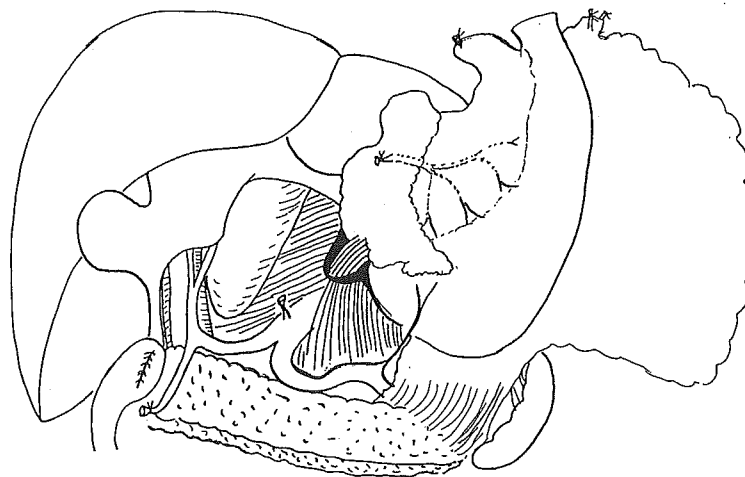


Figure 25.9. Origin of posterior gastric artery, defining point of division of splenic artery.

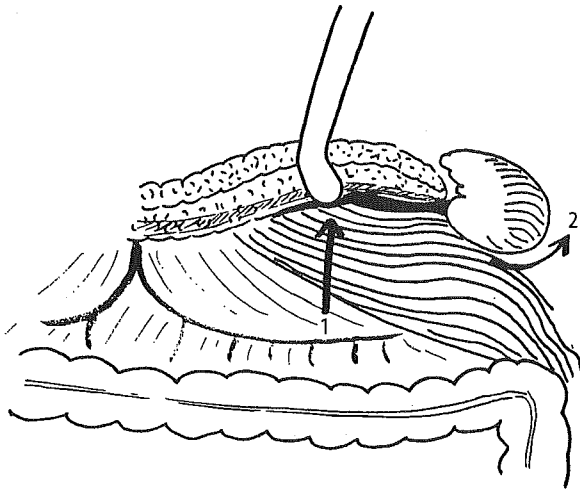


Figure 25.10. Mobilisation of the pancreatic tail along Todt's fascia.

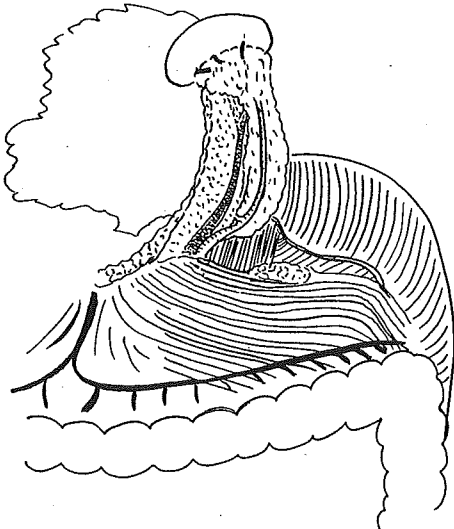


Figure 25.11. Dissection of pancreas to region of celiac axis preserving venous drainage to pancreas.

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-Y reconstruction. Another commonly used

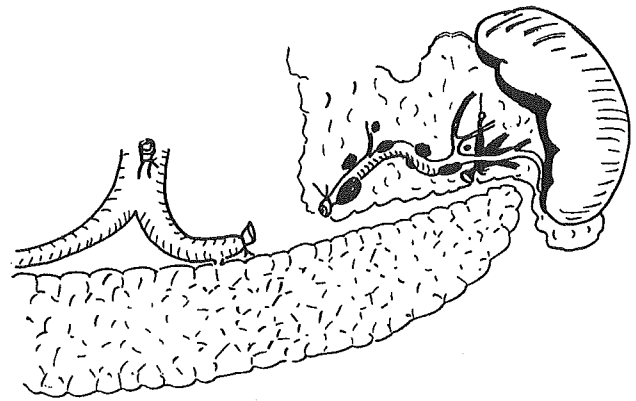


Figure 25.12. Separation of distal splenic artery and spleen following division of branches from splenic vein to spleen and stomach.

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 oesophagojejunal 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