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

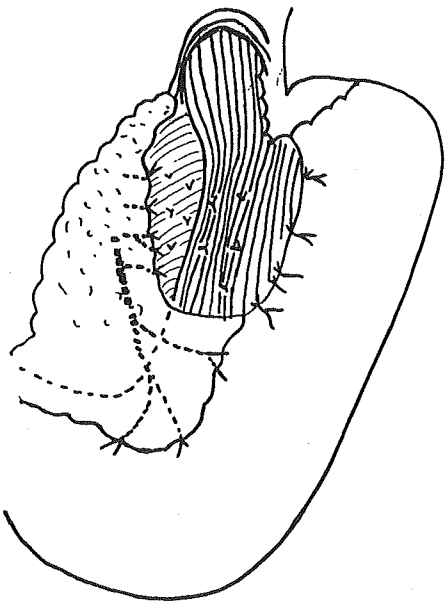

Figure 25.13. Clearance of right cardia nodes in distal gastric resection.

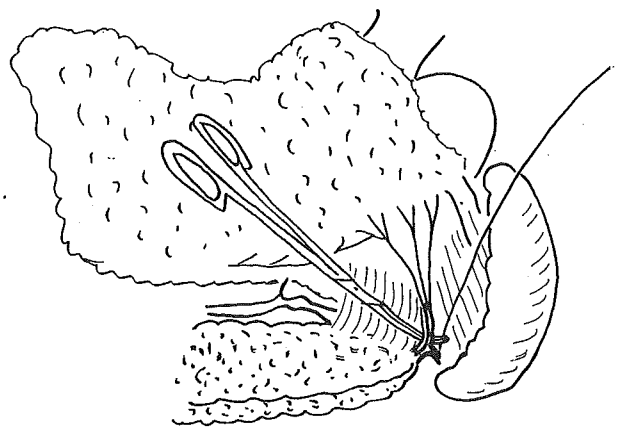

Figure 25.14. Identification of left gastro-epiploic vessels, usually last branch of splenic vessels.

6. Maki T, Shiratori T, Hatafuki T, Suganuma K. Pylorus-preserving gastrectomy as an improved operation for gastric ulcer. Surgery 1967;61:838–45.
7. Johnson H, Masood S, Belluco C et al. Prognostic factors in node-negative breast cancer. Arch Surg 1992;127: 1386–91.
8. Yeh IT, Fowble B, Viglione MJ et al. Pathologic assessment and pathologic factors in operable breast cancer. In: Breast cancer treatment.
9. Sasako M. What is reasonable treatment for gastric adenocarcinoma? J Gastroenterol 2000;35(suppl XII): 116–20.
10. Katai H, Maruyama K, Sasako M et al. Mode of recurrence after gastric cancer surgery. Dig Surg 1994; 11:99–103.
11. Gunderson LL, Sosin H. Adenocarcinoma of the stomach: Areas of failure in a re-operation series (second or symptomatic look) clinicopathological correlation and implications for adjuvant therapy. Int J Radiat Oncol Biol Phys 1982;8:1–11.
12. Hermans J, Bonenkamp JJ, Boon MC et al. Adjuvant therapy after curative resection for gastric cancer: meta-analysis of randomized trials. J Clin Oncol 1993;11:1441–7.
13. Macdonald JS, Smalley SR, Benedetti J et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med 2001;345:725–30.
14. Hundahl SA, Macdonald JS, Benedetti J, Fitzsimmons T, for the Southwest Oncology Group and the Gastric Intergroup. Surgical treatment variation in a prospective, randomized trial of chemoradotherapy in gastric cancer: The effect of undertreatment. Ann Surg Oncol 2002;9:278–86.
15. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma, first English edn. Tokyo: Kanehara, 1995.
16. Cuschieri A, Fayers P, Fielding J et al for the Surgical Cooperative Group. Postoperative morbidity and mortality after D1 and D2 resections for gastric cancer: preliminary results of the MRC randomized controlled surgical trial. Lancet 1996;347:995–9.
17. Bonenkamp JJ, Hermans J, Sasako M, van De Velde CJH, for the Dutch Gastric Cancer Group. Extended lymph-node dissection for gastric cancer. N Engl J Med 1999;340:908–14.
18. Appleby LH. The celiac axis in the expansion of the operation for gastric carcinoma. Cancer 1953;6:704–7.
19. Maruyama K, Sasako M, Kinoshita T et al. World J Surg 1995;19:532–6.
20. Nomura S, Sasako M, Katai H et al. Decreasing complication rates with stapled esophagojejunostomy following a learning curve. Gastric Cancer 2000;3:97–101.
21. Sasako M, Katai H, Sano T, Maruyama K. Management of complications after gastrectomy with extended lymphadenectomy. Surg Oncol 2000;9:31–4.

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Short communication

Increasing body mass index in Japanese patients with gastric cancer

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Abstract
We studied the body mass index (BMI) of 986 patients who underwent potentially curative gastrectomy for gastric cancer at the National Cancer Center Hospital, Tokyo, in 1971, 1981, 1991, and 2001. The median BMI increased from 20.8 kg/m² in 1971 to 22.6 kg/m² in 2001 ($P < 0.01$). The increase was significant in both early and advanced gastric cancers, and in males, but not in females. The proportion of overweight patients (BMI ≥ 25.0 kg/m²) increased from 9.2% in 1971 to 24.0% in 2001. Obese patients (BMI ≥ 30.0 kg/m²) were rare. In conclusion, surgeons at the National Cancer Center Hospital, Tokyo, are increasingly having to operate on fat patients, but obese patients are still uncommon compared to the West.

Key words Body mass index · Gastric cancer · Gastrectomy · Operative morbidity

Introduction

Operative morbidity and mortality rates for gastric cancer in Asian countries have been reported to be better than those in the West [1]. Possible explanations for this are that Western gastric cancer patients are older and fatter, and more frequently have significant comorbidities compared with their Asian counterparts. While it is true that Japanese surgeons have developed and practiced surgical techniques in thin and fit patients, there is a consensus that Japanese patients are becoming fatter and sometimes require special caution or even technical modifications to the D2 lymphadenectomy and postoperative management. In order to validate this impression, we examined the changes in body mass index (BMI) of Japanese patients over the past three decades.

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Subjects and methods

The National Cancer Center Hospital, Tokyo, is a specialized referral center, established in 1963, where more than 10000 gastric cancer patients have undergone gastrectomy. The vast majority of patients are residents of the metropolitan area. We reviewed the records of all of the patients who underwent potentially curative gastrectomy (R0) at our hospital in the years 1971, 1981, 1991, and 2001 — a total of 986 patients. We excluded patients with noncurative operations, as these patients may have had considerable weight changes preoperatively due to gastrointestinal obstruction, cachexia, ascites, or other conditions related to advanced malignancy. The height and weight data were collected from the preoperative summary charts or anesthetic records. The disease was categorized as either early or advanced according to the histological depth of tumor invasion (pT1 vs pT2/3/4).

The BMI was calculated as the weight in kilograms divided by the square of the height in meters (kg/m²), and was categorized according to the WHO cutoff points [2], i.e., underweight, less than 18.5 kg/m²; normal, from 18.5 to 24.9 kg/m²; and overweight, 25.0 kg/m² or more. The trends of BMI and patients' age were statistically examined using Dunn's test for multiple comparisons setting the values of 1971 as the reference.

Results and discussion

The patient demographics and BMIs are shown in Table 1. The male/female ratio was almost constant, while the median patient age in 2001was significantly higher than that in the other three periods in both males and females. The proportion of early gastric cancer in potentially curative cases steadily increased, from 41.8% in 1971 to 61.8% in 2001.

Table 1. Patient demographics and body mass indices

Year of surgery	1971	1981	1991	2001
Number of patients	153	184	232	417
Age in years; median (range)	58 (19–80)	57.5 (27–83)	59 (31–87)	62 (26–87)
Sex ratio (M/F)	1.5	2.0	2.1	1.8
Early cancer (%)	41.8	53.8	56.6	61.8
BMI; median (range)	20.8 (14.6–31.2)	20.9 (12.0–34.2)	21.8 (14.8–35.3)	22.6 (15.0–31.8)
Male	20.5	21.0	22.8	23.0
Female	21.1	20.6	20.7	21.9

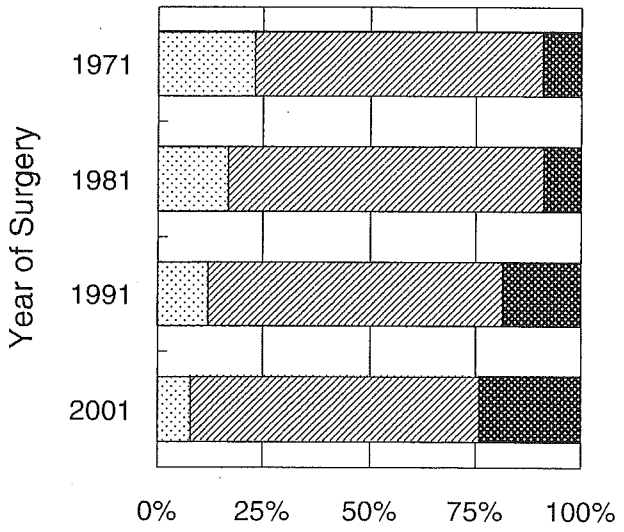

Fig. 1. Trend of body mass index (BMI) distribution. *Dotted bars*, BMI < 18.5; *gray hatched bars*, normal; *dark gray bars*, BMI > 25

The median BMI increased from 20.8 kg/m² in 1971 to 22.6 kg/m² in 2001 ($P < 0.01$). The increase was statistically significant in males but not in females. The median BMI in patients with early cancer (22.1 kg/m²) was significantly higher than that in patients with advanced cancers (21.5 kg/m²; Mann-Whitney *U*-test; $P = 0.013$), possibly reflecting disease-related weight loss in the advanced group. In both early and advanced cancers, the patients' median BMI increased significantly from the first two periods to the last two periods.

In 1971, only 9.2% of patients were overweight, while 22.9% were underweight. In 2001, in contrast, 24.3% of patients were overweight, while only 7.9% were underweight (Fig. 1). Obese patients (BMI ≥ 30.0 kg/m²) were rare at all times (0.7% in 1971 and 1.4% in 2001). These results confirm that surgeons in our institution are operating, with increasing frequency, on older and fatter patients with gastric cancer, especially in the past 20 years.

The trend seems to reflect the changes in age and BMI of the Japanese population. The median age of the total Japanese population has increased rapidly, from 29.1 years in 1970 to 41.4 years in 2000 [3]. The National Nutrition Survey showed that, in the 20-year period from 1976 to 1995, the BMIs of Japanese men in all age groups, and that of elderly women, increased, while that in younger women, especially in metropolitan areas, decreased [4]. In addition, the expansion of indications for gastrectomy in old and obese patients in recent years may have facilitated the trend in this study, i.e., we are now frequently operating on old or overweight patients, for whom gastrectomy might not have been performed 30 years ago.

BMI does not necessarily measure the body fat volume. Interestingly, the relationship between BMI and body fat varies considerably among ethnic groups, and Asian people tend to have more fat for a given BMI than Caucasians [5]; some researchers have proposed 23.0 kg/m² instead of 25.0 kg/m² as a BMI cutoff point of overweight for Asians [6]. If we apply this criterion, 43.9% of our patients in 2001 were overweight compared with 24.2% in 1971.

Nevertheless, the majority of our patients are still normal or underweight according to the WHO criteria and, as compared to Western series, we have only limited occasions to operate on obese patients (BMI ≥ 30.0 kg/m²). Barry et al. [7], in the United Kingdom, reported that nearly half of their patients who had undergone potentially curative gastrectomy were overweight, and 7% had a BMI of more than 30 kg/m². Gretschel et al. [8], in Germany, reported that 58.8% of their 199 patients with total gastrectomy had a BMI of more than 25 kg/m² and 18.1% had a BMI of more than 30 kg/m². It is interesting that these two European groups maintain that BMI does not affect operative morbidity or survival after D2 gastrectomy, whereas Japanese surgeons report high BMI as an important risk factor for morbidity and recurrence [9,10]. This may suggest that D2 gastrectomy in obese patients requires some different surgical techniques that are not quite familiar to Japanese surgeons.

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References

1. Davis P, Sano T. The difference in gastric cancer between Japan, USA and Europe: what are the facts? What are the suggestions? Crit Rev Oncol Hematol 2001;40:77–94.
2. World Health Organization. Obesity: preventing and managing the global epidemic. WHO Obesity Technical Report Series 894. Geneva, Switzerland: World Health Organization; 2000.
3. National Institute of Population and Social Security Research. Population statistics of Japan 2003. http://www.ipss.go.jp/index-e.html
4. Yoshiike N, Seino F, Tajima S, Arai Y, Kawano M, Furuhata T, et al. Twenty-year changes in the prevalence of overweight in Japanese adults: the National Nutrition Survey 1976–95. Obesity Rev 2002;3:183–90.
5. Prentice AM, Jebb SA. Beyond body mass index. Obesity Rev 2001;2:141–7.
6. James PT, Leach R, Kalamara E, Shayeghi M. The worldwide obesity epidemic. Obesity Res 2001;9:228S–33S.
7. Barry JD, Blackshaw GRJC, Edwards P, Lewis WG, Murphy P, Hodzovic I, et al. Western body mass indices need not compromise outcomes after modified D2 gastrectomy for carcinoma. Gastric Cancer 2003;6:80–5.
8. Gretschel S, Christoph F, Bembenek A, Esteves-Schwarz L, Schneider U, Schlag PM. Body mass index does not affect systematic D2 lymph node dissection and postoperative morbidity in gastric cancer patients. Ann Surg Oncol 2003;10:363–8.
9. Dhar DK, Kubota H, Tachibana M, Kotoh T, Tabara H, Masunaga R, et al. Body mass index determines the success of lymph node dissection and predicts the outcome of gastric carcinoma patients. Oncology 2000;59:18–23.
10. Inagawa S, Adachi S, Oda T, Kawamoto T, Koike N, Fukao K. Effect of fat volume on postoperative complications and survival rate after D2 dissection for gastric cancer. Gastric Cancer 2000; 3:141–4.

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Mitsuru Sasako

Clinical trials of surgical treatment of malignant diseases

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Abstract The Dutch Gastric Cancer Study Group Trial was the first clinical phase III trial to be carried out in the field of cancer surgery. In spite of the excellent quality of the trial, it was heavily criticized for the poor quality of the treatment itself. Actually, the hospital mortality after the new surgical treatment (D2 lymph node dissection for gastric cancer) was unacceptably high. In surgical trials, special attention should be paid to quality issues specific to surgery. The first and the most important issue is the quality of treatment given. Reproducibility, homogeneity, and verifiability are the greatest problems in surgical trials. There are also some patient factors. If the patient is old, or fragile, or obese, the results of the surgical treatment can easily be affected by these factors. The surgeon can also be a prognostic factor, especially in complicated procedures or those requiring experience and training. Experience, including postoperative care, and dexterity affect the results. If surgeons do not know how to manage complications, mortality becomes very high. Because blinding is impossible in surgical trials, the treatment may easily be affected by personal preference or prejudice. To minimize the influence of these hampering factors, the procedures should be defined in as detailed a way as possible. If pretrial training or a feasibility study (phase II) is needed, it should be carried out properly for the patients' sake. An excellent design and excellent statistical analysis cannot lead to meaningful results if the quality of treatment is poor. Nonsense in, nonsense out.

Key words Clinical trials of surgical treatment · Quality assurance of treatment · Gastric cancer · Lymph node dissection

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Quality control in the Dutch Gastric Cancer trial

The Dutch Gastric Cancer Study Group Trial was the first well-designed, large-sized, randomized clinical trial (RCT) comparing the surgical procedures in cancer treatment (Fig. 1). In this trial, randomization was carried out before surgery, because the quality controller of the surgery, who usually came from outside the hospital, should be in the operation theater at every D2 dissection. So the group randomized patients before operation, based on the clinical staging, but they expected that some of these patients, about 30% of them, might have peritoneal seeding, and the operation would turn out to be non-curative in such patients. The estimated survival rates of the D1 and D2 surgery arms were 20% and 32%, respectively, but with these non-curative cases, the rates were 14% and 21% for D1 and D2, respectively in all randomised patients. The projected sample size was 531 in each arm.[1]

Not following the principles of phase III clinical trials, even the first patient in this RCT was randomized. When this trial started, only one Dutch surgeon knew what a D2 dissection was and had some experience of carrying out D2 gastrectomy. Although none of the other surgeons involved had ever had experience of D2 gastrectomy, they did not plan any feasibility study before starting a phase III study. Instead, they invited the author (M.S.) to carry out D2 dissections and to teach them how to do it. Therefore, they could randomize the first patient in whom he carried out a D2 dissection for the Dutch surgeons. Inviting a surgeon who knows well the new treatment seemed to be a good option and was much better than letting surgeons do a new treatment after just looking at a videotape of the procedure. However, the tutor could not stay there to participate in all D2 surgery during the entire period of the trial. Therefore, in just 4 months he had to teach them how to carry out the procedure. Surgery of this type is not easy to learn without doing it oneself. It was obvious that he could not teach all the participating surgeons of about 80 hospitals. This length of time was not sufficient to teach even the 12 quality controllers of the D2 surgery.[2] A feasibility study or intensive

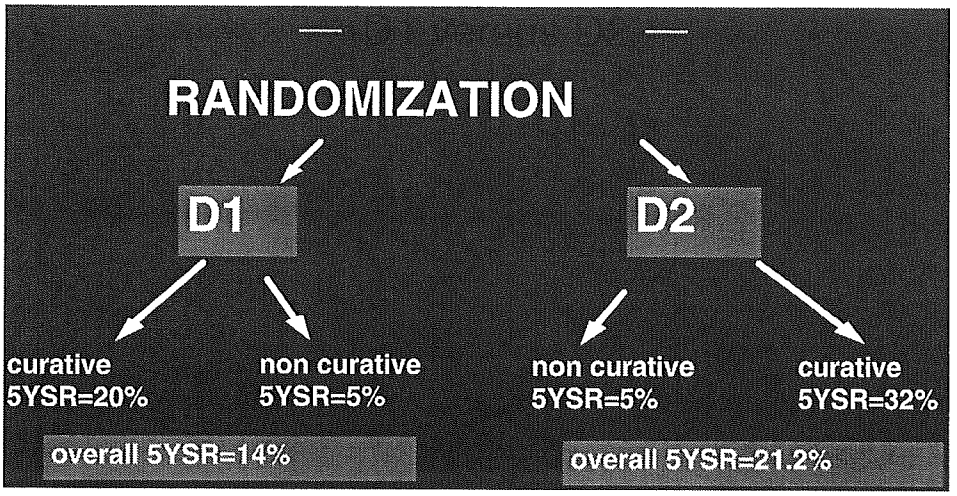


Fig. 1. Dutch trial on lymphadenectomy for gastric cancer.[1] Alpha = 0.05, power = 0.90, 531 patients in each arm requested; *5YSR*, 5-year survival rate

Table 1. Morbidity and mortality after D2 dissection for gastric cancer

Trial	Type	Number of patients	Number of patients per hospital/year	Mortality	Morbidity
Hong Kong[4]	RCT	30	7.5	3%	57%
MRC[5]	RCT	200	1.5	13%	46%
Dutch[1]	RCT	331	1.0	10%	43%
Italian[6]	P-II	191	8.0	3%	21%
Sue-Ling et al.[7]	Retro	142	14.2	5%	17%
Pacelli et al.[8]	Retro	157	15.7	4%	22%

pretrial training should have been carried out. From the scientific and ethical points of view, this kind of setting for a phase III trial of a new surgical technique is not allowed anymore.

The author's major task in this surgical trial was to teach the surgeons how to do a D2 gastrectomy. He himself did 27 operations and instructed the Dutch surgeons as the first assistant in operations for six patients. He also gave many lectures, using videotapes of this operation; the organizers distributed a videotape of the D2 operation on a Dutch patient, which was filmed during this period of the trial, and also distributed a booklet with detailed color photographs showing the anatomy and the technique. This is all that we did for teaching. However, this was not good enough for many of the quality controllers to master the technique sufficiently. Actually, in spite of all the efforts, the morbidity and mortality of this trial was shockingly high for the organizers. Postoperative hospital deaths reached nearly 10% in the D2 arm, much higher than in the D1 arm. This was something unexpected by them before they started this trial. Retrospectively, they should have stopped this trial much earlier and gone back to the feasibility study for the sake of the patients.

Causes of mortality and hospital volume

Theoretically, factors which may influence the morbidity and mortality after this type of surgery are patient factors, tumor factors, operative procedures, and hospital and surgeon factors. Obviously, older patients and obese patients may have more morbidities. But, unexpectedly, sex actually influenced the mortality in this trial very much. And, of course, so did tumor location and histology, the procedures, lymph node dissection, the type of gastrectomy (total or distal), and combined organ resection. Postoperative hospital mortality after D2 in women was as low as that for D1 dissection, but that in male patients reached 14%, or three times higher than that for D1.[3]

Table 1 shows the postoperative hospital mortalities after D2 dissection in various reports.[1,4–8] In the Dutch trial and the MRC (Medical Research Council) trial (British trial), each hospital had very small numbers of cases annually (hospital volume). These two trials had smaller hospital volumes and much higher hospital mortality than in other reports. With such a limited case load, learning how to manage these complications was almost impossible. Actually, the mortality after major surgical complications in the Dutch trial was significantly higher than that experienced at the National Cancer Center Hospital Tokyo (NCCH). The mortality after anastomotic leak and after intraabdominal abscess or pancreatic juice leakage was 41% and 20%, respectively, in the Dutch trial. But, in the same period, the 1980s, the corresponding figures at the NCCH showed much lower 14% after anastomotic leak, and only 3% after intraabdominal abscess.[3] This suggests that experience is needed to manage these major adverse effects to avoid treatment-related deaths. Even in patients with medical treatment, we should know how to manage febrile neu-

tropenia. If not, the patient may die. Greater effort and more experience are needed in the treatment of complications after surgical treatment.

High treatment-related death (TRD) rate offsets treatment effect

Figure 2 shows the survival curves of the Dutch trial.[9] The curve of the D2 arm started at 10% below the D1 arm but caught up with the D1 curve at about 4 years after surgery. However, the difference between the two arms did not become statistically significant at any time. As expected from this, the hazard ratio between the two treatments changed with time; at the beginning, three to four times higher risk for D2 was observed, but the hazard ratio of D2/D1 became less than 1 after 3 years, even with the upper limit of the 95% confidence interval below 1. So, after 3 years, patients who underwent D2 had a significantly lower risk of death than those who underwent D1. These hazard ratio curves by time were completely different for men and women. The curve for women showed a more or less constant hazard ratio, suggesting the applicability of statistical methods based on the hypothesis of a constant hazard ratio. The most common method used to evaluate two survival curves is the log rank test, which is based on the assumption that the hazard ratio is roughly constant. This means that the above statistical methods cannot be properly applied to survival analyses in male patients.

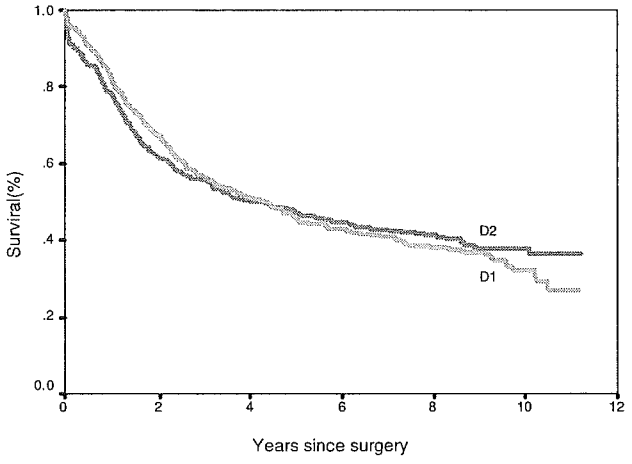
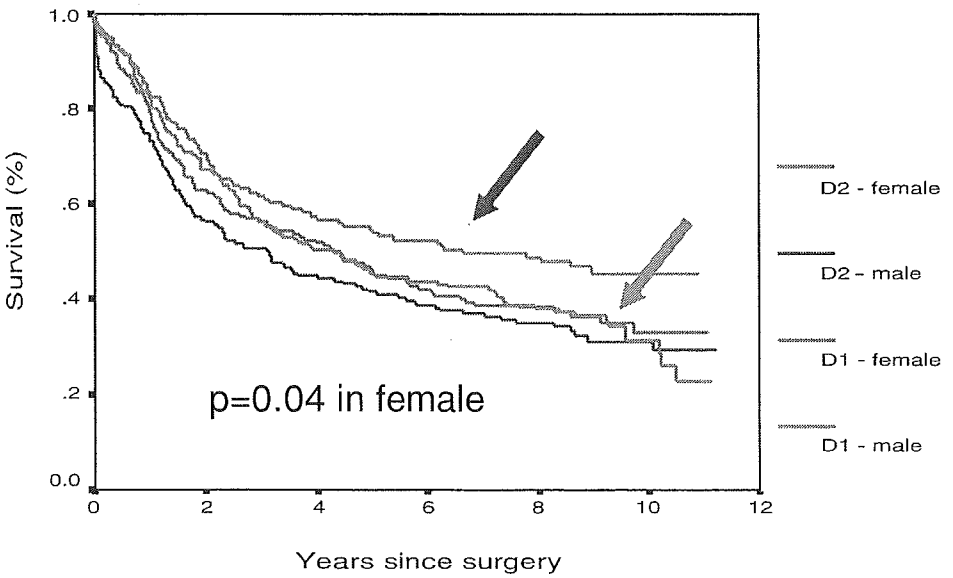


Fig. 2. Survival curves in the Dutch trial[9]

Figure 3 shows the survival curves by treatment by sex in the Dutch trial.[3] The survival curve for the female patients in the D2 arm shows clearly better survival than that for the female patients in the D1 arm. Although the *P* value of the difference by log rank test was 0.04, this cannot be regarded as statistically significant because of the multiplicity of the analysis.

In summary, the conclusion which should be drawn at the moment is that all the RCTs of lymphadenectomy for curable gastric cancer failed to prove the effect of D2 dissection.[10] As discussed already, however, the quality of D2 dissection in these trials was questionable, especially that in the MRC trial. With quite small hospital volumes, each of these trials had treatment-related death (TRD) rates after D2 as high as 10%. The quality of postoperative care to avoid TRD was very poor, and the high TRD rate offset the long-term effect of treatment. This was also confirmed in the French and German studies of squamous cell cancer, reported at Americal Society of Clinical Oncology (ASCO) meetings in 2002[11] and 2003, respectively.[12] Proper D2 dissection is a technically demanding procedure, requiring experience in postoperative care, and should be carried out at specialized centers, at least in low-volume areas.

Fig. 3. Survival curves by treatment (D1 or D2) by sex in the Dutch trial.[3]



Surgical trials with low TRD rate

The results of a Japanese trial, Japan Clinical Oncology Group (JCOG) 9501, a study comparing standard D2 gastrectomy with D2 plus paraaortic lymph node dissection (D3), made a clear contrast to these trials.[13] Unlike the Dutch trial, it was possible to randomize the patients during surgery after confirming the absence of the peritoneal seeding and negative cytology of the peritoneal washing fluid, because every participating surgeon knew the technique and therefore a quality controller from outside the hospital was not needed. This randomization during surgery was done at the central data center by telephone. The primary endpoint was survival and morbidity/mortality, and the projected sample size was 412 at the beginning. But the sample size was amended in June 2000, to increase the statistical power, and we can now evaluate an 8% difference between the two treatment arms. Five hundred twenty-three patients were enrolled, and the results of the survival analysis in 2006 are awaited. The postoperative morbidity and mortality of this trial is shown in Table 2. The D2 arm showed 20% morbidity, including all complications and although slightly more complications were observed in the D3 arm, there was no difference in mortality, at 0.8%, in the two arms. No differences were observed in major surgical complications such as anastomotic leak or pancreatic juice fistula, but an increased of diarrhea juice and ileus was observed after D3.

Table 2. Morbidity and mortality: JCOG 9501 (523 patients)

	D2	D3	All
Morbidity (any*)	20.9%	28.1%	24.5%
Anastomotic leak	2.3%	1.9%	2.1%
Pancreatic fistula	5.3%	6.2%	4.0%
Abdominal abscess	5.3%	5.8%	5.5%
Pneumonia**	4.6%	1.5%	3.2%
Miscellaneous***	9.1%	20.0%	14.5%
Reoperation	1.9%	2.7%	2.3%
Mortality (in hospital)	0.8%	0.8%	0.8%

* $P = 0.067$; ** $P = 0.0724$; *** $P = 0.0005$ (ileus, lymphorrhea, diarrhea)

Figure 4 shows the survival curve for all the patients in JCOG 9501. The investigators do not know yet how are the survival curves for the two treatment arms, but the survival curve for all the patients is quite good, considering the T stage of the patients. So far, from this result, it can be said that morbidity and mortality after extended surgery did not increase much, if the surgery was done by experienced surgeons in countries of high incidence. The incidence of the major complications was the same in both arms, with a slight increase of minor complications in the D3 arm. D3 increased the operation time by 60 min and the blood loss by 230 ml. Unlike the two trials in Europe (Dutch trial[1] and MRC trial[5]), postoperative mortality will not affect the results in the long term.

The only clinical phase II trial of D2 dissection was carried out by the Italian Gastric Cancer Study Group in Turin.[6] This was carried out to confirm the feasibility of D2 carried out by Italian surgeons after the reports of the Dutch[1] and MRC[5] trials. The Italian group achieved 3% mortality. In the Dutch trial, the number of participating hospitals was 80 and the number of D2 dissections per year per hospital was just 1, while in the Italian trial, the number of hospitals was 9 and the number of D2 dissections per year was 7. The hospital volume differred enormously between these two trials. Another important difference that may have affected the morbidity and mortality was the indication for pancreas tail resection. In the Dutch trial, a total gastrectomy was always combined with pancreaticosplenectomy, but in the Italian trial, the pancreas was preserved in principle.

After achieving this 3% mortality, the Italian group started a phase III trial, comparing D1 versus D2 dissection. However, they have actually had much difficulty in enrolling patients. As there was no difference between the mortality rates of D1 and D2, some surgeons had refrained from enrolling patients with a preference for D2. The feeling was, why should they go back to D1 when there

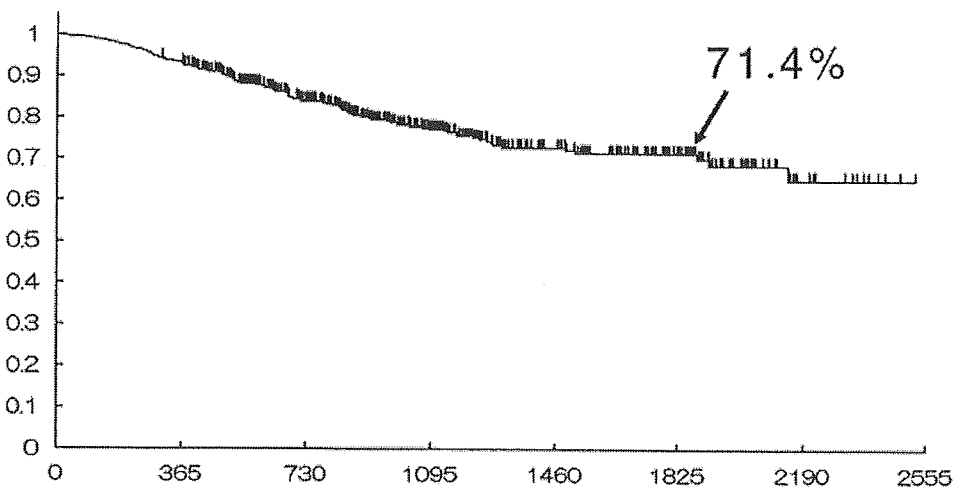


Fig. 4. Survival curve in all patients in the Japan Clinical Oncology Group (JCOG) 9501 trial. Actual proportion of 5 year survivors = 71.4%

is a low mortality for D2 in their hands. If they do enroll patients, it is questionable whether D1 performed by such surgeons can be real D1. If the mortality rates after pancreatico-duodenectomy or three-field dissection for esophageal cancer (major surgery) at specialist institutes in Japan, and in Western countries are compared, they are less than 5%.

Why did the Dutch and the MRC trials have higher mortality than pancreatico-duodenectomy or three-field dissection? Radical pancreatico-duodenectomy is usually more aggressive than D2 gastrectomy. The only difference was that the patients with esophageal or pancreatic cancer were treated at specialist centers, while those with gastric cancer were treated at general hospitals. In both the MRC and the Dutch trials, many hospitals had very low hospital volumes. On the other hand, in the Japanese JCOG trial, both procedures (i.e., D2 and D3 gastrectomy) have commonly been carried out, and all participants had high hospital volumes. Besides, in this trial, together with strict patient selection and quality assurance, according to the number of dissected nodes, each participant showed their operative procedure on videotapes in regular group meetings.

Factors hampering surgical trials

There are several factors which make clinical trials in surgery difficult.[14,15] First of all, skill and experience affect the results. In this aspect, all surgeons cannot be the same. So inter-surgeon variation is unavoidable; some are dexterous and some are "all thumbs" by nature, and techniques suitable only for dexterous surgeons exist. Experience is also a very important factor – knowledge, familiarity, and knacks included. There is a learning curve for most surgical techniques. Surgery is usually followed by sequelae, and, therefore, quality-of-life evaluation is essential in surgical trials when comparing surgical techniques. However, there is no well-established measurement to assess these sequelae. Unlike medical treatment, masking of the allocated arm is impossible, and auditing the treatment given is very difficult in surgical trials.

In the past, we surgeons have experienced the introduction of laparoscopic cholecystectomy, and in this procedure, we heard for the first time, the term, "learning curve". Many articles state that at least 30 cases are needed to reach the plateau of the curve, while some argue that 250 cases are needed. We also observed expansions of indications of this procedure. At the beginning, this technique was not indicated for gallstone disease with acute cholecystitis, or for patients with previous operations in the upper abdomen, or during pregnancy. But actually, many surgeons are now doing laparoscopic cholecystectomy, even in patients with these conditions. Finally, in regard to laparoscopic cholecystectomy, RCTs were carried out, but they were only small trials and the results were reported only after an NIH consensus meeting, and, actually, these RCTs did not have any impact on clinical practice.[16]

Quality of surgical trials

The quality of surgical trials can be summarized in two categories. One category is quality issues that are common to all clinical trials. Indicators of the quality of a trial are, for example, the randomizing of patients (either by the envelope method or by a central computer system), the blinding of the arms, the proportion of excluded cases or protocol violations, sample size projection, the quality and independence of the data center and respect for multiplicity in the analysis, the prospective setting of the interim analysis, and the existence of an independent monitoring committee. If all these factors are fulfilled, the quality of the trial itself should be regarded as excellent. The South West Oncology Group (SWOG), the East Clinical Oncology Group (ECOG), the European Organization for Reseach and Treatment of Cancer (EORTC) and the JCOG are good examples of organizations which support various subgroups of different specialties and can carry out high-quality clinical trials.

The second category is specific to surgical trials. First, and most important, is the quality of treatment given. Reproducibility, homogeneity and verifiability are the greatest problems in surgical trials. There are also some patient factors. If the patient is old, or fragile, or obese, the results of the surgical treatment can easily be affected by these patient factors. Some surgery in obese patients is much more difficult than in slim patients. The surgeon can also be a prognostic factor, especially in complicated procedures or those requiring experience and training.

In surgical trials, quality control should include postoperative care as well. If surgeons do not know how to manage complications, mortality becomes very high, especially in intra-abdominal or intra-thoracic surgery. Therefore, experience and hospital volume are very important factors in surgical trials. Because blinding is impossible in surgical trials, the treatment may easily be affected by personal preference or prejudice. When surgical trials are planned, details of each procedure in each arm should be defined carefully after discussion among the participants to avoid unacceptable heterogeneity. For example, the Gastric Surgery Division of the JCOG now is carrying out an RCT of total gastrectomy with or without splenectomy, and there are several possible techniques in each procedure to be decided among the participants. They had to decide whether or not mobilization of the spleen was allowed for dissection of lymph nodes along the distal pancreas, whether or not a frozen section for splenic hilum node was acceptable, and where the splenic artery and vein should be divided, and also the indications for splenectomy in the spleen-preserving arm. This is because the spleen occasionally has to be taken out if it is injured, to control bleeding, even if the patient is allocated to the spleen-preserving arm. When these details are decided, leading surgeons should demonstrate to all participants, the procedures in detail on a videotape and each step of the procedures should be decided as precisely as possible. Even after starting the trial, it is recommended that the participating surgeons should

visit reciprocally to see others' operations. At each regular meeting among the participants, some of them, perhaps three or four, demonstrate their operation on videotape and discuss the technical details, repeatedly. Each participating center should demonstrate the technique at least once in the course of a trial, and any technical issue should be reevaluated, if needed, even after starting the trial, which may lead to protocol revision. Another difficult issue in surgical trials is how to audit the treatment given. Videotape recording for every patient is the best way. But, as this is not realistic, an onsite visit by referees is also another good way of auditing, but this is also very difficult to perform. Checking a close-up photograph of the operation field after dissection is one of the possible options. Actually, the Colorectal Surgery Division of the JCOG is adopting this method for an ongoing trial of rectal surgery. Close and intensive assessment of resected material, including lymph nodes, is a feasible technique if collaboration of pathologists is available, and was adopted in the Dutch trial on rectal surgery. All these methods to evaluate the quality of surgery become effective when proper feedback of the results to the operators is given regularly.

How to set up clinical trials in surgery

When surgical trials are set up, the following points should be considered. First, when to start phase III trial should be decided. For some surgical techniques that are complicated and surgically demanding, a feasibility study is absolutely needed, because there is usually a learning curve. Assessment of the experience of each participant is also important. Even if the procedures in each arm of a study are familiar to the surgeons, each participant's experience of each technique has to be assessed. A phase III trial should be started after sufficient experience of the procedures. In this regard, a phase III trial comparing two commonly performed operations is much easier than a comparison of old and new techniques. Open colon surgery versus laparoscopic colon surgery for colon cancer is a good example of a difficult trial, because the learning curve is a serious issue for laparoscopic colectomy. Selection of participants is also very important. The more institutes are involved, the faster is the accrual. On the other hand, the more institutes are involved, the more difficult is the quality control of surgery. Careful selection of participating hospitals which have acceptable quality of surgery is essential. The two procedures compared in a trial should be defined in every detail and in each technical point. Some method to verify the treatment given should be included, and the maximum effort should be made to avoid personal preferences affecting the results. Quality-of-life evaluation (i.e., a quality-of-life score or symptom score) should be included in most surgical trials.

References

1. Bonenkamp JJ, Songun I, Hermans J, et al. (1995) Randomized comparison of morbidity after D1 and D2 dissection for gastric cancer in 996 Dutch patients. Lancet 345:745–748
2. Sasako M, Maruyama K, Kinoshita T, et al. (1991) Quality control of surgical technique in a multicenter, prospective, randomized, controlled study on the surgical treatment of gastric cancer. Jpn J Clin Oncol 22:41–48
3. Sasako M (2004) Role of surgery in multidisciplinary treatment for solid cancers. Int J Clin Oncol 9:346–351
4. Robertson CS, Chung SCS, Woods SDS, et al. (1994) A prospective randomized trial comparing R1 subtotal gastrectomy with R3 total gastrectomy for antral cancer. Ann Surg 220:175–182
5. Cuschieri A, Fayers P, Fielding J, et al. (1996) Postoperative morbidity and mortality after D1 and D2 resections for gastric cancer: preliminary results of the MRC randomised controlled surgical trial. Lancet 347:995–999
6. Degiuli M, Sasako M, Ponti A, et al. (1998) Morbidity and mortality after D2 gastrectomy for gastric cancer: results of the Italian Gastric Cancer Study Group prospective multicenter surgical study. J Clin Oncol 16:1490–1493
7. Sue-Ling HM, Johnston D, Martin IG, et al. (1993) Gastric cancer: a curable disease in Britain. BMJ 307:591–596
8. Pacelli F, Doglietto GB, Bellantone R, et al. (1993) Extensive versus limited lymph node dissection for gastric cancer: a comparative study of 320 patients. Br J Surg 80:1153–1156
9. Hartgrink HH, van de Velde CJH, Putter H, et al. (2004) Extended lymph node dissection for gastric cancer: who may benefit? Final results of the randomized Dutch Gastric Cancer Study Group Trial. J Clin Oncol 22:2069–2077
10. McCulloch P, Niita ME, Kazi H, et al. (2005) Gastrectomy with extended lymphadenectomy for primary treatment of gastric cancer. Br J Surg 92:5–13
11. Bedenne L, Michel P, Bouche O, et al. (2002) Randomized phase III trial in locally advanced esophageal cancer: radiochemotherapy followed by surgery versus radiochemotherapy alone (FFCD 9102). Proc ASCO 2002:519
12. Stahl M, Wilke H, Walz MK, et al. (2003) Randomized phase III trial in locally advanced squamous cell carcinoma (SCC) of the esophagus: chemoradiation with and without surgery. Proc ASCO 2003:1001
13. Sano T, Sasako M, Yamamoto S, et al. (2004) Gastric cancer surgery: morbidity and mortality results from a prospective randomized controlled trial comparing D2 and extended para-aortic lymphadenectomy – Japan Clinical Oncology Group Study 9501. J Clin Oncol 22:2767–2773
14. Van Der Linden W (1980) Pitfalls in randomized surgical trials. Surgery 87:258–262
15. McCulloch P, Taylor I, Sasako M, et al. (2002) Randomized trials in surgery: problems and possible solutions. BMJ 324:1448–1451
16. Hatlie MJ (1993) Climbing the learning curve: new technologies, emerging obligations. JAMA 270:1364–1365

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Original article

Risk factors for pancreas-related abscess after total gastrectomy

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Abstract

Background. **European clinical trials of gastrectomy have shown that pancreas-related complications are the major cause of mortality. The aim of this study was to determine the risk factors for pancreas-related abscess after gastrectomy and to evaluate the effects of the abscess on postoperative mortality.**

Methods. **Between 1992 and 1999, 663 consecutive patients with gastric carcinoma underwent total gastrectomy. Data from these patients were analyzed, to identify the predictors of pancreas-related abscess caused by pancreatic juice leakage, by a multiple logistic regression model.**

Results. **On multivariate analysis, increasing age ($P = 0.018$) and body mass index ($P = 0.006$) were independent preoperative risk factors. Dissection along the distal splenic artery was an intraoperative risk factor. The hazard ratios were increased 9.13-fold ($P = 0.000$) with a pancreas-preserving operation and 16.72-fold ($P = 0.000$) by distal pancreatectomy. Patients with the abscess had a higher postoperative mortality rate ($P = 0.008$), and a higher re-operation rate ($P < 0.001$) than patients without the abscess.**

Conclusion. **Pancreas-related abscess is more likely to occur in older, obese patients undergoing node dissection along the distal splenic artery. Abscess formation is associated with a higher mortality and re-operation rate. Spleen preservation should be evaluated in Japan.**

Key words Gastric cancer · Morbidity

Introduction

The most frequent major complication after gastrectomy with extended dissection is pancreatic juice leakage [1], because recently, the incidence of anastomotic leakage has decreased remarkably [2]. Pancreatic juice leakage is often followed by contamination, resulting in a peripancreatic abscess. Secondary hemorrhage from major arteries damaged by contamination can be fatal. European clinical trials of gastrectomy have shown that pancreas-related complications are a major cause of mortality [3,4].

The prediction and early detection of pancreas-related complications may be helpful. The aim of this study was to determine risk factors for pancreas-related abscess after gastrectomy, caused by pancreatic juice leakage, and to evaluate the effects of the abscess on postoperative mortality.

Patients and methods

Six hundred and sixty-three consecutive patients with gastric carcinoma underwent total gastrectomy, between 1992 and 1999, at the National Cancer Center Hospital, Tokyo. Data for these patients were analyzed to identify the predictors of pancreas-related abscess caused by pancreatic juice leakage, using a multivariate logistic regression model.

The diagnosis of a pancreas-related abscess was made when purulent fluid containing turbid necrotic debris drained from the peripancreatic area for more than 7 days. The abscess cavity was assessed by computed tomography (CT) scan and contrast study through drains. We recorded an abscess regardless of its cavity size. When we found anastomotic leakage radiologically on initial diagnosis of the abscess, we excluded these patients from the pancreas-related abscess group.

The preoperative and perioperative data were collected from the patients' records and stored on our gastric surgical database.

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Operative techniques

Total gastrectomy with Roux-en-Y esophagojejunostomy was performed in 623 patients (94.0%), as the standard operation. Forty patients (6.0%) underwent jejunal interposition. Pouch formations were added in 7 patients (1.1%). The extent of nodal dissection along the distal splenic artery and splenic hilum varied, including no dissection of these nodes. Distal pancreatectomy or the Maruyama pancreas-preserving method [5] was usually performed for advanced tumor (T2, T3, and T4). The splenic arteries were sacrificed distally to the dorsal pancreatic arteries, in all patients, when we performed pancreas-preserving total gastrectomy. At least one drainage tube was applied in the left subphrenic space in all patients. In most cases, the amylase level of the drainage fluid was determined on the first postoperative day. All patients received antibiotic prophylaxis for the same period.

Statistical methods

Univariate analyses were performed in order to predict those preoperative and perioperative variables that were associated with a pancreas-related abscess. Fischer's exact test and the Mann-Whitney test were used as appropriate.

To develop a model for predicting postoperative pancreas-related abscess in terms of pre- and perioperative variables, three preoperative and six perioperative variables were entered in multiple logistic regression analysis. All the statistical procedures were performed with the SPSS 11.5 statistical package (SPSS Japan, Tokyo, Japan). The limit for statistical significance was $P < 0.05$.

Results

The overall incidence of pancreas-related abscess was 11.5%. The median amylase level of the drainage fluid on the first postoperative day was 1942 I/l (range, 22–387 000) U/l overall, and it was 1682 (22–303 800) U/l in patients without abscess and 6590 (96–387 000) U/l in patients with abscess.

The male-to-female ratio was 2.5:1, and the mean age was 59.9 ± 11.6 years. The proportion of patients with early gastric cancer (T1) was 21.1%. Operation with curative intent was performed in 82.5% of the patients. Nodal dissection along the distal splenic artery was performed in 68.0% of the patients and D2 dissection or more was carried out in 67.6 % of the patients. The median operation time was 263 min (90–580 min). Median blood loss was 567 ml (250–4457 ml).

Univariate analysis identified several preoperative patient-related factors as having a high association with pancreas-related abscess. The preoperative demographic data are shown in Table 1, for patients with and without the abscess. Increasing age ($P = 0.004$) and increasing body mass index ($P = 0.008$) had a strong association with postoperative pancreas-related abscess.

Perioperative data are also presented in Table 1. Univariate analysis showed that depth of tumor invasion ($P = 0.007$), operation time ($P = 0.024$), extent of dissection ($P = 0.000$), and dissection along the distal splenic artery ($P = 0.000$) were all associated with a greater incidence of abscess formation. The method of dissection along the distal splenic artery was categorized into one of five variations.

Multivariate analysis identified three independent factors as predictors of postoperative pancreas-related abscess formation (Table 2). Increasing age and increasing body mass index increased the risk of the abscess by 1.4- and 1.1-fold, respectively.

Dissection of nodes along the distal splenic artery and in the splenic hilum was an intraoperative risk factor. If the relative risk for the abscess was set at 1 for patients with neither splenectomy nor pancreatectomy, the hazard ratios were 9.1 for pancreas-preserving operation and 16.7 for distal pancreatectomy.

The postoperative outcomes of the patients with and without pancreas-related abscess were compared (Table 3). The patients with the abscess had a higher postoperative mortality rate. Patients with pancreas-related abscess had 7.6-fold increased mortality compared to patients without the abscess. The re-operation rate for patients with pancreas-related abscess was 32-fold greater than that for patients without the abscess.

Discussion

Increasing body mass index increases the risks of pancreas-related abscess. The literature also reports fat volume as being a risk factor in increasing postoperative complications [6,7]. Nodal dissection along the distal pancreas and in the splenic hilum in obese patients is a difficult task, even in the hands of experienced surgeons specializing in the treatment of gastric carcinoma.

Patients in the West usually have a higher body mass index than those in Japan [8]. The observed high morbidity rates in Western randomized trials for D2 dissection may be related to the greater obesity of these patients.

Increasing age also increases the risk of abscess formation. Patients in the West receiving gastrectomies are usually older than those in Japan, as well as having a

Table 1. Univariate analysis of variables associated with pancreas-related abscess

	No abscess (n = 587)	Abscess (n = 76)	P value; patients with vs without abscess
Preoperative variables			
Sex			
Male	413 (87.1%)	61 (12.9%)	0.080
Female	174 (92.1%)	15 (7.9%)	
Age (years)	59.5 (22–91)[a]	62.8 (44–84)[a]	0.004
Body mass index (kg/m^2)	21.7 (12.2–37.7)[a]	22.6 (15.0–31.5)[a]	0.008
Perioperative variables			
Depth of tumor invasion			
Early (T1)	133 (95.0%)	7 (5.0%)	0.007
Advanced (T2, T3, T4)	454 (86.8%)	69 (13.2%)	
Curability of operation			
Curative (R0)	480 (87.8%)	67 (12.2%)	0.200
Noncurative (R ≧ 1)	107 (92.2%)	9 (7.8%)	
Operation time (min)	260 (90–580)[a]	286 (140–540)[a]	0.024
Blood loss (ml)	565 (25–3776)[a]	587.5 (70–4457)[a]	0.123
Extent of dissection			
D0, D1	207 (96.3%)	8 (3.7%)	0.000
D2, D3	380 (84.8%)	68 (15.2%)	
Dissection methods for nodes along the distal splenic artery			
1. Splenectomy: No; Distal pancreatectomy: No; Dissection along distal splenic artery: No	155 (98.1%)	3 (1.9%)	0.000
2. Splenectomy: Yes; Distal pancreatectomy: No; Dissection along distal splenic artery: No	49 (90.7%)	5 (9.3%)	
3. Splenectomy: No; Distal pancreatectomy: No; Dissection along distal splenic artery: Yes	10 (83.3%)	2 (16.7%)	
4. Splenectomy: Yes; Distal pancreatectomy: No; Dissection along distal splenic artery: Yes	309 (86.3%)	49 (13.7%)	
5. Splenectomy: Yes; Distal pancreatectomy: Yes; Dissection along distal splenic artery: Yes	64 (79.0%)	17 (21.0%)	

Splenectomy (yes), pancreatectomy (no), dissection along distal splenic artery (yes) indicates pancreas-preserving total gastrectomy method
[a]Median values, with ranges in parentheses

Table 2. Multivariate predictors of pancreas-related abscess

Variables	P value	Odds ratio	95% Confidence interval of odds ratio
Preoperative variables			
Age (continuous)	0.018	1.414	1.060–1.886
Body mass index (continuous)	0.006	1.126	1.035–1.225
Perioperative variables			
Dissection methods for nodes along the distal splenic artery			
1. Splenectomy: No; Distal pancreatectomy: No; Dissection along distal splenic artery: No		1	
2. Splenectomy: Yes; Distal pancreatectomy: No; Dissection along distal splenic artery: No	0.012	6.601	1.505–28.953
3. Splenectomy: No; Distal pancreatectomy: No; Dissection along distal splenic artery: Yes	0.011	11.973	1.760–81.468
4. Splenectomy: Yes; Distal pancreatectomy: No; Dissection along distal splenic artery: Yes	0.000	9.130	2.791–29.864
5. Splenectomy: Yes; Distal pancreatectomy: Yes; Dissection along distal splenic artery: Yes	0.000	16.724	4.675–59.823

Table 3. Relationship of postoperative events to pancreas-related abscess

Variables	No abscess ($n = 587$)	Abscess ($n = 76$)	P value
Re-operation	4 (0.7%)	17 (22.4%)	< 0.001
Operation-related death	4 (0.7%)	4 (5.3%)	0.008

higher body mass index [9,10]. The observed high morbidity rates in Western trials were related to the age distribution [11], similar to our findings here.

Our study shows that the dissection of nodes alongside the distal splenic artery and nodes in the splenic hilum is an intraoperative risk factor. Distal pancreatectomy with splenectomy had the highest odds ratio. However, even when we performed pancreas-preserving total gastrectomy to avoid pancreas-related complications, there was still a considerably higher odds ratio of abscess formation. Pancreas-preserving splenectomy is part of the standard operation in specialized centers in Japan. Splenectomy without dissection along the distal splenic artery also had a high risk of abscess formation.

Japanese retrospective studies have shown that 20%–30% of patients with advanced cancer in the proximal stomach have nodal metastasis in the splenic hilum, and that gastrectomy with resection of these nodes can yield a 5-year survival of 20%–25% [12]. Consequently, in Japan, dissection of nodes in these areas is performed routinely.

Although mortality rates from gastrectomy complicated by pancreas-related abscess are lower in Japan than those reported in Western series [3,4], pancreas-related abscess formation remains a strong factor in the mortality and morbidity rates in both Japanese and Western centers.

Evaluation of the role of splenectomy for proximal gastric cancer is important. Spleen preservation, avoiding thorough nodal dissection in the splenic hilum as well as in the distal splenic artery, as described by groups in the United Kingdom [13,14], should be evaluated in Japan. The Japan Clinical Oncology Group have recently started a randomized controlled trial to evaluate the effect of splenectomy on postoperative morbidity and longterm cancer-free survival [15].

Conclusions

Pancreas-related abscess after gastrectomy is more likely to occur in older, obese patients undergoing node dissection along the distal splenic artery. Because the abscesses are associated with high mortality and re-operation rates, the role and oncologic value of splenectomy has to be considered more carefully. This now forms the basis of a nationwide trial.

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References

1. Sasako M, Katai H, Sano T, Maruyama K. Management of complications after gastrectomy with extended lymphadenectomy. Surg Oncol 2000;9:31–4.
2. Nomura S, Sasako M, Katai H, Sano T, Maruyama K. Decreasing complication rates with stapled esophagojejunostomy following a learning curve. Gastric Cancer 2000;3:97–101.
3. Bonenkamp JJ, Songun I, Hermans J, Sasako M, Welvaart K, Plukker JT, et al. Randomized comparison of morbidity after D1 and D2 dissection for gastric cancer in 996 Dutch patients. Lancet 1995;345:745–8.
4. Cuschieri A, Fayers P, Fielding J, Craven J, Bancewicz J, Joypaul V, et al. Postoperative morbidity and mortality after D1 and D2 resections for gastric cancer: preliminary results of the MRC randomized controlled surgical trial. The Surgical Cooperative Group. Lancet 1996;347:995–9.
5. Maruyama K, Sasako M, Kinoshita T, Sano T, Katai H, Okajima K. Pancreas-preserving total gastrectomy for proximal gastric cancer. World J Surg 1995;19:532–6.
6. Inagawa S, Adachi S, Oda T, Kawamoto T, Koike N, Fukao K. Effect of fat volume on postoperative complications and survival rate after D2 dissection for gastric cancer. Gastric Cancer 2000;3:141–4.
7. Dhar DK, Kubota H, Tachibana M, Kotoh T, Tabara H, Masunaga R, et al. Body mass index determines the success of lymph node dissection and predicts the outcome of gastric carcinoma patients. Oncology 2000;59:18–23.
8. Davis PA, Sano T. The difference in gastric cancer between Japan, USA and Europe: what are the facts? What are the suggestions? Crit Rev Oncol Hematol 2001;40:77–94.
9. Bonenkamp JJ, van deVelde CJ, Kampschoer GH, Hermans J, Hermanek P, Bemelmans M, et al. Comparison of factors influencing the prognosis of Japanese, German, and Dutch gastric cancer patients. World J Surg 1993;17:410–4.
10. Bollschweiler E, Boettcher K, Hoelscher AH, Sasako M, Kinoshita T, Maruyama K, et al. Is the prognosis for Japanese and German patients with gastric cancer really different? Cancer 1993;71:2918–25.
11. Sasako M. Risk factors for surgical treatment in the Dutch Gastric Cancer Trial. Br J Surg 1997;84:1567–71.
12. Sasako M, McCulloch P, Kinoshita T, Maruyama K. New method to evaluate the therapeutic value of lymph node dissection for gastric cancer. Br J Surg 1995;82:346–51.
13. Griffith JP, Sue-Ling HM, Martin I, Dixon MF, McMahon MJ, Axon AT, et al. Preservation of the spleen improves survival after radical surgery for gastric cancer. Gut 1995;36:684–90.

14. Barry JD, Blackshaw GR, Edwards P, Lewis WG, Murphy P, Hodzovic I, et al. Western body mass indices need not compromise outcomes after modified D2 gastrectomy for carcinoma. Gastric Cancer 2003;6:80–5.
15. Sano T, Yamamoto S, Sasako M for the Gastric Cancer Surgical Study Group of Japan Clinical Oncology Group. Randomized controlled trial to evaluate splenectomy in total gastrectomy for proximal gastric carcinoma: Japan Clinical Oncology Study JCOG 0110-MF. Jpn J Clin Oncol 2002;32:363–4.

Original article

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

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

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

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

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

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Introduction

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

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

Patients and methods

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

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

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

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

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

Results

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

Table 1 Complications

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

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

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

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

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

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

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

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

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

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

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

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

Discussion

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