Gastric Cancer (2001) 4: 166–174

Review article

Surgery for gastric cancer: 10-year experience worldwide

YOSUKE ADACHI[1], SEIGO KITANO[1], and KEIZO SUGIMACHI[2]

[1] First Department of Surgery, Oita Medical University, 1-1 Idaigaoka, Hasama-machi, Oita 879-5593, Japan
[2] Second Department of Surgery, Kyushu University, Fukuoka, Japan

Abstract
To demonstrate recent experience of gastric cancer surgery worldwide and to evaluate modern strategies for the treatment of gastric cancer, we investigated the English-language literature of the past 10 years, based on papers published in well-known medical journals. In many countries, the increased detection of early gastric cancer, advanced operative procedures, and careful postoperative management have improved the surgical results of gastric cancer over the years. Although randomized controlled trials in Europe showed no survival benefit of D2 resection over D1 resection, the results must be interpreted with caution and cannot be extrapolated to Japanese patients, because the morbidity and mortality after D2 gastrectomy in Japan are much less than those after D1 gastrectomy in Europe. Recently, less invasive treatments, including endoscopic mucosal resection and laparoscopic gastrectomy, have become feasible for patients with early gastric cancer, but their risks and benefits compared with traditional gastrectomy are unclear.

Key words Cancer · Gastric cancer · Lymph node metastasis · Lymph node dissection · Quality of life · Surgery

Introduction

Recently, the characteristics of gastric cancer have become more clearly understood, and the treatment strategies for gastric cancer have been changing. There are decreasing numbers of deaths from gastric cancer, the increasing detection of early gastric cancer or proximal gastric cancer, and the introduction of several new therapeutic tools. Although randomized controlled trials in Europe showed no survival benefit of D2 resection over D1 resection, radical gastrectomy and extended lymph node dissection has been traditional in Japan, and critical studies from several Western countries suggest that there are improved surgical results after extended lymph node dissection. Therefore, it is important to evaluate the current information on the clinical and pathological characteristics of, and the surgical results for gastric cancer worldwide.

To demonstrate recent experience of gastric cancer surgery throughout the world and to evaluate modern strategies for the treatment of gastric cancer, we investigated the English-language literature of the past 10 years, reviewed more than 100 studies concerning controversial issues in gastric cancer treatment, and assessed the current status of gastric cancer surgery worldwide. This review was generally based on promising papers published in well known medical journals, and focused on the following items: (1) surgical results worldwide, (2) lymph node metastasis, (3) lymph node dissection, (4) splenectomy, (5) prognostic factors, and (6) new therapeutic trends.

Surgical results worldwide

The review of English-language publications from 1970 to 1990 showed that the operative mortality rate following surgery for gastric cancer had declined to a mean of 8% and a median of 5% [1]. In the British hospital, operative mortality decreased from 15% to 7%, and the 5-year survival rate increased from 5% to 11% [2]. In another British hospital, the proportion of patients with early gastric cancer rose from 1% to 15%, that of stage I disease rose from 4% to 26%, and that of potentially curative resection rose from 31% to 53% [3]. After curative resection, the 5-year survival rate was 60%, and the operative mortality and morbidity rates were 6% and 17%, respectively.

In Sweden, the 5-year surival rate after gastrectomy for cancer increased from 19% to 25%, mainly owing to

Offprint requests to: Y. Adachi
Received: February 28, 2001 / Accepted: August 3, 2001

improved surgical and postoperative management [4]. Although the proportion of radical total gastrectomy increased from 36% to 50%, the postoperative mortality decreased from 11% to 4%, and the 5-year survival rate increased from 25% to 36%. It was demonstrated that the time period during which the diagnosis was made independently influenced the survival rate [5].

In a French study, the use of endoscopy increased from 3% to 77%, and the proportion of curative resections increased from 38% to 50% [6]. The operative mortality rate decreased from 26% to 14%, and the 5-year survival rate increased from 13% to 26%. In a recent Turkish study, the morbidity, mortality, and 5-year survival rates after D2 gastrectomy were 28%, 4%, and 39%, respectively [7]. Thus, the detection of gastric cancer at an earlier stage and curative gastrectomy followed by careful postoperative management resulted in improved surgical outcome in several countries other than Japan.

However, studies from the United States show unchanged mortality and survival rates. A study by the American College of Surgeons indicated that the location of the lesion was the upper-third or entire stomach in 41% of the patients, and the stage of disease was III or IV in 67% of the patients [8]. The operative mortality rate was 7%, and the 5-year survival rates after all gastrectomies and margin-free gastrectomies were 19% and 35%, respectively. Some American surgeons, in a review, concluded that gastric cancer remained a disease with a dismal prognosis and that radical gastrectomy with lymph node dissection was not generally acceptable because of increased morbidity and mortality [9].

Recent clinical trials in Europe have demonstrated that morbidity, mortality, and 5-year survival rate after gastrectomy for cancer were 25%–46%, 4%–13%, and 33%–35%, respectively [10–13]. The high morbidity and mortality rates after radical gastrectomy were thought to be caused by the higher age of the Western patients, the frequent presence of preexisting cardiopulmonary diseases, the variations in experiences in gastric cancer surgery, and the different ways of managing the postoperative complications [10,11].

The better surgical results in Japan mostly reflect a higher rate of detection of asymptomatic or early-stage gastric cancer [14–16]; and survival rates, comparing the same stage, are higher in Japan than in other countries. It is considered that this survival difference results from differences in the location of tumors and in pathological staging systems, the stage migration phenomenon, and differences in the level of lymph node dissection [17,18]. A review of the Japanese experience of radical gastrectomy shows that the survival differences between Japan and the United States or Europe are due mainly to a greater frequency of early gastric cancer; meticulous histopathologic evaluation of the surgical specimens, which results in more accurate pathologic staging; and the presumed benefit of extended lymph node dissection in Japan [19].

Lymph node metastasis

Although lymph-node staging of gastric cancer has been based principally on the anatomical distribution of lymph node metastasis [20], quantitative evaluation of lymph node metastasis has been advocated since 1990. Okusa et al. [21] showed that the number of lymph node metastases and the proportion of dissected lymph nodes showing metastases were closely related to the 5-year survival rate (none, 81%; 1–3 nodes, 63%; 4–6 nodes, 47%; ≥7 nodes, 29%; 1%–25%, 66%; 25%–50%, 30%; ≥50%, 23%). Makino et al. [22] indicated that the number of metastatic nodes was associated with 5-year survival rate (none, 89%; 1–3 nodes, 77%; 4–6 nodes, 58%; ≥7 nodes, 36%). In a multivariate analysis, the number of positive nodes was an independent prognostic factor (≤3 vs ≥4 nodes [23–26], ≤4 vs ≥5 nodes [27], ≤6 vs ≥7 nodes [28,29]).

In 1997, the American Joint Committee on Cancer (AJCC)/International Union against Cancer (UICC) adopted the number of involved nodes as lymph node staging for the TNM classification of gastric cancer (N1, 1–6 nodes; N2, 7–14 nodes; N3, ≥15 nodes), and recent studies confirmed the prognostic significance of the number of involved nodes [30,31]. When the number-based staging system was compared with the level-based staging system, the former was superior to the latter in a multivariate prognostic study [32–35].

Here, we must emphasize that this number-based staging of lymph nodes is suitable only when a meticulous examination of harvested lymph nodes is accomplished. Fifteen or more lymph nodes are needed for an accurate number-based staging of lymph node metastasis. Furthermore, operative curability or radicality with reference to lymph node dissection cannot be judged by the number-based staging system. The extent of lymph node metastasis must be determined by the anatomical distribution of involved lymph nodes, and the completeness of lymph node dissection should be evaluated by the anatomical level of the removed lymph nodes.

Several authors found that the number of positive perigastric lymph nodes was useful for predicting the survival of patients with gastric cancer [36,37]. Because the number of perigastric lymph nodes can be used in the same way for patients who underwent limited dissection (D1) and those who underwent extended dissection (D2, D3), this parameter will contribute to the comparison of surgical results among various hospitals or countries throughout the world.

Micrometastasis is a recent topic in the study of gastric cancer. Even when a routine histologic examination shows no lymph node metastasis, studies by immunohistochemistry or molecular biology often detect micrometastases in the regional lymph nodes [38–44]. The proportion of patients with immunohistochemically node-positive gastric cancer was 19% in mucosal cancer [40], 34% in submucosal cancer [41], and 43% in histologically node-negative gastric cancer [42]. When 24 patients who died of recurrence after operation for histologically node-negative early gastric cancer were examined, 8 (24%) had presented with cytokeratin-positive cells in the regional lymph nodes [43]. Although some studies suggest the prognostic importance of micrometastasis in the lymph nodes of gastric cancer [42,43], at present, the biologic behavior and clinical implications of micrometastases are unclear [44,45].

Lymph node dissection

In Japan, radical gastrectomy with extended lymph node dissection (D2, D3) has been a standard operation for gastric cancer, and systematic lymph node dissection [46] or more aggressive lymph node dissection [47] has been recommended. Morbidity after radical gastrectomy is acceptable, and the operative mortality rate is less than 3%, even when the operations are performed by a junior trainee in a non-specialized hospital [48]. However, the proportion of operations for radical gastrectomy is less than 10% in the United States, and only a small group of Western surgeons are eager to use extended lymph node dissection. Whether radical gastrectomy with extended lymph node dissection is useful for patients with gastric cancer must be evaluated with respect to the survival rate and morbidity or mortality rate after the operation.

In a German multicenter study, when radical lymphadenectomy (≥26 dissected nodes; $n = 1096$) was compared with standard lymphadenectomy (≤25 dissected nodes; $n = 558$), morbidity and mortality rates were not different (31% vs 29%; 5% vs 5%), but the 5-year survival rates for stages II and IIIa were different (55% vs 27%; 38% vs 25%) [49]. The frequent occurrence of nodal microinvolvement in pN0 cases and a low operative mortality (<1%) also supported the routine use of D2 lymph node dissection [50,51].

In Italy, when extensive lymph node dissection (D2, D3; $n = 157$) was compared with limited lymph node dissection (D1; $n = 163$), morbidity and mortality rates were not different (22% vs 28%; 4% vs 7%), but the 5-year survival rate after curative gastrectomy was different (65% vs 50%) [52]. Multivariate analysis revealed that the extent of lymph node dissection (D1 vs D2 vs D4) independently affected the survival [25].

Findings in studies from the United States are controversial. Extended resection (D2, D2.5; $n = 46$) and limited resection (D1, D1.5; $n = 55$) showed different 5-year survival rates (35% vs 27%) and median survival periods (50 months vs 26 months) [53], whereas D2 ($n = 683$), D1 ($n = 1500$), and D0 ($n = 666$) dissections had similar 5-year survival rates (26% vs 30% vs 36%) and median survival periods (20 months vs 25 months vs 30 months) [54].

In Japan, Otsuji et al. [55] showed that the time period during which gastrectomy was performed was an independent prognostic indicator, and they suggested that recent advances in surgical approaches had resulted in improved survival. In patients with node-positive gastric cancer, however, the 10-year survival rate after curative gastrectomy was not significantly different between D2 and D3 dissections (n1, 66% vs 58%; n2, 28% vs 31%) [56]. These studies are retrospective and cannot avoid a selection bias in the evaluation of surgical outcome. Even if the controls are matched to the cases and survival rates are compared in patients in the same stages, there is a stage migration phenomenon, or Will Rogers effect as a source of misleading statistics for survival [57–60].

Recently, randomized controlled trials comparing D2 dissection with D1 dissection have been performed in Europe [10–13]. The short-term results in 996 Dutch patients showed that D2 patients had higher operative mortality and morbidity than D1 patients (10% vs 4%; 43% vs 25%) [10]; the short-term results in 400 British patients showed that D2 resections had higher operative mortality and morbidity than D1 resections (13% vs 7%; 46% vs 28%) [11]. Long-term results indicated that the 5-year survival rates in the Dutch trial were similar in the D1 and D2 groups (34% vs 33%) [12], and the 5-year survival rates in the British trial were not different between D1 and D2 resections (35% vs 33%) [13]. These trials concluded that D2 dissection should not be used as standard treatment for Western patients with gastric cancer.

Other randomized controlled trials have evaluated several operative procedures for gastric cancer (Table 1). Robertson et al. [61] examined D1 subtotal ($n = 25$) and D3 total ($n = 30$) gastrectomies and showed that the D3 group had a longer operating time, a greater volume of blood transfusion, a longer hospital stay, a higher morbidity, and a shorter survival time. Bozzetti et al. [62,63] investigated subtotal ($n = 320$) and total ($n = 304$) gastrectomies and showed similar morbidity rates (9% vs 13%) and 5-year survival rates (65% vs 62%).

These surgical trials have several problems. In the Dutch multicenter trial, 331 curative D2 gastrectomies were performed by 85 surgeons over a period of 4 years. This means that every surgeon did only one curative D2

Table 1. Randomized controlled trials of surgery for gastric cancer

Authors Year	Arms	Number of patients	Mortality (%)	Morbidity (%)	Five-year survival rate (%)
Bonenkamp [10,12]	D1	380	4	25	34
1995, 1999	D2	331	10	43	33
Cuschieri [11,13]	D1	200	7	28	35
1996, 1999	D2	200	13	46	33
Robertson [61]	D1 subtotal	25	0	0	1511[a]
1994	D3 total	30	3	47	922[a]
Bozzetti [62,63]	Subtotal	320	1	9	65
1997, 1999	Total	304	2	13	62

[a] Median survival period (days)

gastrectomy per year on average [64]. It is well known that the learning curve for gastric cancer surgery does not reach a plateau until 30 or more operations are achieved independently [65]. When the strategy for gastric cancer surgery is converted from D1 to D2 gastrectomy, it takes more than 10 years to get the operative mortality rate down to less than 5% [3,64]. Furthermore, the number and location of dissected lymph nodes were not given in the above reports of randomized controlled trials [10–13]. The quality control of surgical procedures in the Dutch randomized trial of D1 and D2 gastrectomies was somewhat questionable [66], and a high rate of protocol deviations may also have reduced the ability to detect differences between the two treatments [67]. Thus, it has been proved that randomized controlled trials comparing different surgical techniques are difficult in the clinical setting.

Therefore, the results of these surgical trials must be interpreted with caution and cannot be extrapolated to Japanese patients. Although a randomized controlled trial comparing D1 and D2 gastrectomies is considered to be ethically unacceptable in Japan, we must clarify the survival benefits of extended lymph node dissection (D2, D3) in a prospective study based on Japanese patients and surgeons. Because the morbidity and mortality after radical gastrectomy in Japan (D2, D3) [68,69] are much less than those after less aggressive gastrectomy in the Western surgical trials (D1, D2), it seems appropriate that D2 gastrectomy should not be abandoned as standard treatment for gastric cancer in Japan.

Splenectomy

Brady et al. [70] studied 392 patients who underwent curative resection of gastric cancer, and showed that splenectomy had no influence on survival, but that postoperative complications occurred more frequently in patients with splenectomy than in those without splenectomy (45% vs 21%). Kwon et al. [71] reviewed 492 patients who underwent curative total gastrectomy, but could not find any beneficial effects of splenectomy. Griffith et al. [72] demonstrated that morbidity and mortality rates after gastrectomy with splenectomy were higher than those after gastrectomy without splenectomy (41% vs 14%; 12% vs 3%), and they found that splenectomy was a predictor of poor survival in a multivariate analysis (hazard ratio, 1.5). Wanebo et al. [73] found a reduced 5-year survival rate for the splenectomy group in stage II (25% vs 38%) and stage III (14% vs 18%).

Recent Japanese studies have indicated that combined resection of the spleen increased the frequency of abdominal abscess, but did not improve the survival [69,74–76] (Table 2). Okajima and Isozaki [77] reviewed the Japanese experience, and recommended that the spleen should be preserved in patients with stage I, II, and III gastric cancer with curative operation. Thus, the results suggest that splenectomy increases operative morbidity but does not increase survival rate. However, all these studies were based on retrospective analyses, and the operative procedures were associated with the stage of tumors: the more advanced the tumor was, the more often the spleen was removed. This selection bias may have exaggerated the operative disadvantage of the splenectomy and obscured the survival benefit of the splenectomy.

In the *Japanese classification of gastric carcinoma*, defined by the Japanese Gastric Cancer Association [78], lymph nodes at the splenic hilum (no. 10) are included in the group 2 nodes when the tumor is located in the upper stomach, and splenectomy is necessary for a standard D2 gastrectomy. Furthermore, a small but definite group of patients with involved lymph nodes at the splenic hilum survive owing to the splenectomy. Therefore, effect of splenectomy in the treatment of gastric cancer must be confirmed by a randomized controlled trial comparing gastrectomy with splenectomy and that without splenectomy.

Table 2. Influence of splenectomy on surgical results for gastric cancer

Authors Year	Splenectomy	Number of patients	Morbidity (%)	Mortality (%)	Five-year survival rate (%)
Brady [70]	No	229	21	4	50
1991	Yes	163	45	5	38
Maehara [74]	No	104	NA	NA	37[b]
1991	Yes	149	NA	NA	52[b]
Griffith [72]	No	119	14	3	71
1995	Yes	76	41	12	45
Otsuji [75]	No	91	7[a]	NA	47
1996	Yes	154	16[a]	NA	46
Adachi [69]	No	50	40	0	47[b]
1997	Yes	56	64	0	26[b]
Kwon [71]	No	232	13	0	NA
1997	Yes	260	22	3	NA
Wanebo [73]	No	2565	NA	9	31
1997	Yes	912	NA	10	21
Yoshino [76]	No	192	NA	NA	47
1997	Yes	272	NA	NA	27

NA, Not available
[a] Anastomotic leakage
[b] Ten-year survival rate (%)

Prognostic factors

Siewert and colleagues (Roder et al. [79] and Siewert et al. [80]) reviewed the 10-year results of 1654 patients enrolled in the German Gastric Cancer Study and showed that relevant prognostic factors after curative gastrectomy were lymph node status, depth of invasion, postoperative complications, distant metastases, and tumor diameter. Maruyama [81] examined 4734 patients treated at the National Cancer Center in Japan and indicated that the most important prognostic factors for gastric cancer patients were depth of invasion (relative risk, 4.69), lymph node metastasis (4.04), gross type (1.76), location (1.50), and histologic type (1.16). Kim et al. [82] analyzed 10783 patients who underwent operation at the Seoul National University Hospital, and demonstrated that independent prognostic factors in gastric cancer were curability (relative risk, 3.67), depth of invasion (2.18), and lymph node metastasis (2.06). Thus, the studies are unanimous in terms of the prognostic importance of the depth of invasion and status of lymph node metastasis [23,83,84].

Recently, the detection of proximal gastric cancer has been increasing. Some authors show that proximal gastric cancer is more frequently associated with advanced stage and poor prognosis than distal gastric cancer [85,86], whereas others show that survival rate after resection is not different between patients with proximal gastric cancer and those with distal gastric cancer [87]. When tumors are compared among the proximal, middle, and distal one-third of the stomach, the 5-year survival rate for proximal tumors is inferior to that for middle or distal tumors, because of esophageal invasion [88]. Siewert et al. [89] investigated the surgical results of 1002 patients with adenocarcinoma of the esophagogastric junction, and showed that the 10-year survival rate was lowest in those with subcardial gastric cancer invading the esophagus. Thus, although two major factors that predict survival after gastrectomy for cancer are the depth of invasion and the status of lymph node metastasis, the proximal location of the tumor is another important prognostic indicator for gastric cancer.

New therapeutic trends

Endoscopic mucosal resection (EMR) is a useful technique for the treatment of early gastric cancer. At the National Cancer Center Hospital in Japan, the technique has been employed in patients with mucosal gastric cancer measuring less than 3 cm, grossly elevated or depressed type without ulceration, and histologically well or moderately differentiated type [90]. When the resected specimen showed submucosal invasion, vessel involvement, or incomplete resection, additional surgical intervention was recommended. Of 479 tumors in 445 patients, 405 were histologically limited to the mucosa and 74 had invaded the submucosa; and 33 patients with mucosal cancer and 44 with submucosal cancer subsequently underwent operation. Twenty-one of 25 patients who experienced perforation associated with EMR were successfully treated with endoscopic clipping, and there were no deaths due to gastric cancer during a median follow-up period of 38 months.

Laparoscopic surgery is another approach for the treatment of early gastric cancer [91–96]. Ohgami et al.

[91] first developed laparoscopic wedge resection of the stomach, using a lesion-lifting method. This technique is useful not only for mucosal gastric cancer but also for stromal tumors, which rarely metastasize to the lymph nodes [92]. Kitano et al. [93] and Nagai et al. [94] independently developed laparoscopy-assisted distal gastrectomy for the cure of early gastric cancer. The procedure consists of: (1) ligation of gastric vessels and mobilization of the stomach under pneumoperitoneum, and (2) resection of the distal two-thirds of the stomach, with a hand-sewn gastroduodenal anastomosis through a 5-cm-long minilaparotomy incision. When compared with conventional open gastrectomy, laparoscopy-assisted gastrectomy has several clinical advantages [97], including less pain, less inflammatory response, rapid return of gut function, shorter hospital stay, less impaired nutrition, and better quality of life [98–100]. Uyama et al. [101,102] demonstrated that total gastrectomy with distal pancreatosplenectomy and D2 lymphadenectomy was technically feasible for patients with advanced gastric cancer.

Thus, EMR and laparoscopic gastrectomy is safe and useful when the procedure is employed for small early gastric cancers and performed by skilled endoscopists or surgeons [103,104]. However, the long-term results of these less invasive treatments are not known, and the employment of a laparoscopic technique in advanced gastric cancer should be limited to controlled clinical trials in specialized centers.

For patients with unresectable gastric cancer, palliative operations have been employed to control clinical symptoms. Devine exclusion with gastrojejunostomy is safe and effective in relieving gastric outlet obstruction, and provides a longer survival period [105,106]. Kaminishi et al. [107] developed stomach-partitioning gastrojejunostomy for patients with unresectable gastric cancer, and showed that the procedure achieved an improved quality of life and a longer survival time compared with conventional gastrojejunostomy. Thus, palliative operation can enhance the quality of life in patients with advanced gastric cancer.

Conclusion

In many countries, the increased detection of early gastric cancer, advanced operative procedures, and careful postoperative management have improved the surgical results of gastric cancer over the years. Although randomized controlled trials in Europe showed no survival benefit of D2 resection over D1 resection, the results must be interpreted with caution and cannot be extrapolated to Japanese patients, because the morbidity and mortality after D2 gastrectomy in Japan are much less than those after D1 gastrectomy in Europe. Recently, less invasive treatments, including endoscopic mucosal resection and laparoscopic gastrectomy, have become feasible for early gastric cancer, but their risks and benefits compared with traditional gastrectomy are unclear.

References

1. Macintyre IMC, Akoh JA. Improving survival in gastric cancer: review of operative mortality in English language publications from 1970 (review). Br J Surg 1991;78:773–8.
2. Akoh JA, Sedgwick DM, Macintyre IMC. Improving results in the treatment of gastric cancer: an 11-year audit. Br J Surg 1991;78:349–51.
3. Sue-Ling HM, Johnston D, Martin IG, Dixon MF, Lansdown MRJ, McMahon MJ, et al. Gastric cancer: a curable disease in Britain. BMJ 1993;307:591–6.
4. Hansson LE, Sparén P, Nyrén O. Survival in stomach cancer is improving: results of a nationwide population-based Swedish study. Ann Surg 1999;230:162–9.
5. Borch K, Jönsson B, Tarpila E, Franzén T, Berglund J, Kullman E, et al. Changing pattern of histologic type, location, stage and outcome of surgical treatment of gastric carcinoma. Br J Surg 2000;87:618–29.
6. Msika S, Tazi MA, Benhamiche AM, Couillault C, Harb M, Faivre J. Population-based study of diagnosis, treatment and prognosis of gastric cancer. Br J Surg 1997;84:1474–8.
7. Yildirim E, Celen O, Berberoglu U. The Turkish experience with curative gastrectomies for gastric carcinoma: is D2 dissection worthwhile? J Am Coll Surg 2001;192:25–37.
8. Wanebo HJ, Kennedy BJ, Chmiel J, Steele G Jr, Wincester D, Osteen R. Cancer of the stomach: a patient care study by the American College of Surgeons. Ann Surg 1993;218:583–92.
9. Thompson GB, van Heerden JA, Sarr MG. Adenocarcinoma of the stomach: are we making progress? Lancet 1993;342:713–8.
10. Bonenkamp JJ, Songun I, Hermans J, Sasako M, Welvaart K, Plukker JTM, et al. Randomised comparison of morbidity after D1 and D2 dissection for gastric cancer in 996 Dutch patients. Lancet 1995;345:745–8.
11. 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 randomised controlled surgical trial. Lancet 1996;347:995–9.
12. Bonenkamp JJ, Hermans J, Sasako M, van de Velde CJH, Dutch Gastric Cancer Group. Extended lymph-node dissection for gastric cancer. New Engl J Med 1999;340:908–14.
13. Cuschieri A, Weeden S, Fielding J, Bancewicz J, Craven J, Joypaul V, et al. Patient survival after D1 and D2 resections for gastric cancer: long-term results of the MRC randomized surgical trial. Br J Cancer 1999;79:1522–30.
14. Matsukuma A, Furusawa M, Tomoda H, Seo Y. A clinicopathological study of asymptomatic gastric cancer. Br J Cancer 1996; 74:1647–50.
15. Martin IG, Young S, Sue-Ling H, Johnston D. Delays in the diagnosis of esophagogastric cancer: a consecutive case series. BMJ 1997;314:467–71.
16. Schlemper RJ, Itabashi M, Kato Y, Lewin KJ, Riddell RH, Shimoda T, et al. Differences in diagnostic criteria for gastric carcinoma between Japanese and Western pathologists. Lancet 1997;349:1725–9.
17. Hundahl SA, Stemmermann GN, Oishi A. Racial factors cannot explain superior Japanese outcomes in stomach cancer. Arch Surg 1996;131:170–5.
18. Noguchi Y, Yoshikawa T, Tsuburaya A, Motohashi H, Karpeh MS, Brennan MF. Is gastric carcinoma different between Japa-

nese and the United States?: a comparison of patient survival among three institutions. Cancer 2000;89:2237–46.
19. Noguchi M, Miyazaki I. Prognostic significance and surgical management of lymph node metastasis in gastric cancer. Br J Surg 1996;83:156–61.
20. Maruyama K, Gunvén P, Okabayashi K, Sasako M, Kinoshita T. Lymph node metastases of gastric cancer: general pattern in 1931 patients. Ann Surg 1989;210:596–602.
21. Okusa T, Nakane Y, Boku T, Takada H, Yamamura M, Hioki K, et al. Quantitative analysis of nodal involvement with respect to survival rate after curative gastrectomy for carcinoma. Surg Gynecol Obstet 1990;170:488–94.
22. Makino M, Moriwaki S, Yonekawa M, Oota M, Kimura O, Kaibara N. Prognostic significance of the number of metastatic lymph nodes in patients with gastric cancer. J Surg Oncol 1991;47:12–6.
23. Shiu MH, Perrotti M, Brennan MF. Adenocarcinoma of the stomach: a multivariate analysis of clinical, pathological and treatment factors. Hepatogastroenterology 1989;36:7–12.
24. Jaehne J, Meyer HJ, Maschek H, Geerlings H, Bruns E, Pichlmayr R. Lymphadenectomy in gastric carcinoma: a prospective and prognostic study. Arch Surg 1992;127:290–4.
25. de Manzoni G, Verlato G, Guglielmi A, Laterza E, Genna M, Cordiano C. Prognostic significance of lymph node dissection in gastric cancer. Br J Surg 1996;83:1604–7.
26. Kwon SJ, Kim GS. Prognostic significance of lymph node metastasis in advanced carcinoma of the stomach. Br J Surg 1996;83:1600–3.
27. Wu CW, Hsieh MC, Lo SS, Tsay SH, Lui WY, P'eng FK. Relation of number of positive lymph nodes to the prognosis of patients with primary gastric adenocarcinoma. Gut 1996;38:525–7.
28. Adachi Y, Kamakura T, Mori M, Baba H, Maehara Y, Sugimachi K. Prognostic significance of the number of positive lymph nodes in gastric carcinoma. Br J Surg 1994;81:414–6.
29. Roder JD, Böttcher K, Busch R, Wittekind C, Hermanek P, Siwert JR, et al. Classification of regional lymph node metastasis from gastric carcinoma. Cancer 1998;82:621–31.
30. Kodera Y, Yamamura Y, Shimizu Y, Torii A, Hirai T, Yasui K, et al. The number of metastatic lymph nodes: a promising prognostic determinant for gastric carcinoma in the latest edition of the TNM classification. J Am Coll Surg 1998;187:597–603.
31. Fujii K, Isozaki H, Okajima E, Nomura E, Niki M, Sako S, et al. Clinical evaluation of lymph node metastasis in gastric cancer defined by the fifth edition of the TNM classification in comparison with the Japanese system. Br J Surg 1999;86:685–9.
32. Ichikura T, Tomimatsu S, Uefuji K, Kimura M, Uchida T, Morita D, et al. Evaluation of the new American Joint Committee on Cancer/International Union Against Cancer classification of lymph node metastasis from gastric carcinoma in comparison with the Japanese classification. Cancer 1999;86:553–8.
33. Hayashi H, Ochiai T, Suzuki T, Shimada H, Hori S, Takeda A, et al. Superiority of a new UICC-TNM staging system for gastric carcinoma. Surgery 2000;127:129–35.
34. Kato M, Saji S, Kawaguchi Y, Kunieda K, Sugiyama Y, Takagi Y, et al. A comparison of the prognostic significance between the number of metastatic lymph nodes and nodal stage in gastric carcinoma. Hepatogastroenterology 1999;46:3281–6.
35. Karpeh MS, Leon L, Klimstra D, Brennan MF. Lymph node staging in gastric cancer: is location more important than number? Ann Surg 2000;232:362–71.
36. Adachi Y, Suematsu T, Shiraishi N, Tanimura H, Morimoto A, Kitano S. Perigastric lymph node status as a prognostic indicator in patients with gastric cancer. Br J Surg 1998;85:1281–4.
37. Yu WY, Kim HS, Choi GS, Suh IS. Perigastric lymph nodes with metastasis in gastric cancer. Hepatogastroenterology 1999;46:2658–61.
38. Kikuchi Y, Tsuchiya A, Ando Y, Yoshida T, Takenoshita S. Immunohistochemical detection of lymph node microinvolvement in node-negative gastric cancer. Gastric Cancer 1999;2:173–8.
39. Mori M, Mimori K, Inoue H, Barnard GF, Nanbara S, Ueo H, et al. Detection of cancer micrometastases in lymph nodes by reverse transcriptase-polymerase chain reaction. Cancer Res 1995;55:3417–20.
40. Cai J, Ikeguchi M, Tsujitani S, Maeta M, Kaibara N. Micrometastasis in lymph nodes of mucosal gastric cancer. Gastric Cancer 2000;3:91–6.
41. Cai J, Ikeguchi M, Maeta M, Kaibara N. Micrometastasis in lymph nodes and microinvasion of the muscularis propria in primary lesions of submucosal gastric cancer. Surgery 1999;126:32–9.
42. Harrison LE, Choe JK, Goldstein M, Meridian A, Kim S, Clarke K. Prognostic significance of immunohistochemical micrometastases in node-negative gastric cancer patients. J Surg Oncol 2000;73:153–7.
43. Maehara Y, Oshiro T, Endo K, Baba H, Oda S, Ichiyoshi Y, et al. Clinical significance of occult micrometastasis in lymph nodes from patients with early gastric cancer who died of recurrence. Surgery 1996;119:397–402.
44. Mori M, Mimori K, Ueo H, Tsuji K, Shiraishi T, Barnard GF, et al. Clinical significance of molecular detection of carcinoma cells in lymph nodes and peripheral blood by reverse transcriptase-polymerase chain reaction in patients with gastrointestinal or breast carcinomas. J Clin Oncol 1998;16:128–32.
45. Kell MR, Winter DC, O'Sullivan GC, Shanahan F, Redmond HP. Biological behaviour and clinical implications of micrometastases (review). Br J Surg 2000;87:1629–39.
46. Mishima Y, Hirayama R. The role of lymph node surgery in gastric cancer. World J Surg 1987;11:406–11.
47. Maruyama K, Okabayashi K, Kinoshita T. Progress in gastric cancer surgery in Japan and its limits of radicality. World J Surg 1987;11:418–25.
48. Moriwaki Y, Kobayashi S, Kunisaki C, Harada H, Imai S, Kasaoka C. Is D2 lymphadenectomy in gastrectomy safe with regard to the skill of the operator? Dig Surg 2001;18:111–7.
49. Siewert JR, Böttcher K, Roder JD, Busch R, Hermanek P, Meyer HJ, German Gastric Carcinoma Study Group. Prognostic relevance of systemic lymph node dissection in gastric carcinoma. Br J Surg 1993;80:1015–8.
50. Siewert JR, Kestlmeier R, Busch R, Böttcher K, Roder JD, Müller J, et al. Benefits of D2 lymph node dissection for patients with gastric cancer and pN0 and pN1 lymph node metastasis. Br J Surg 1996;83:1144–7.
51. Roukos DH, Lorenz M, Encke A. Evidence of survival benefit of extended (D2) lymphadenectomy in Western patients with gastric cancer based on a new concept: a prospective long-term follow-up study. Surgery 1998;123:573–8.
52. Pacelli F, Doglietto GB, Bellantone R, Alfieri S, Sgadari A, Crucitti F. Extensive versus limited lymph node dissection for gastric cancer: a comparative study of 320 patients. Br J Surg 1993;80:1153–6.
53. Volpe CM, Koo J, Miloro SM, Driscoll DL, Nava HR, Douglass HO Jr. The effect of extended lymphadenectomy on survival in patients with gastric adenocarcinoma. J Am Coll Surg 1995;181:56–64.
54. Wanebo HJ, Kennedy BJ, Winchester DP, Fremgen A, Stewart AK. Gastric carcinoma: does lymph node dissection alter survival? J Am Coll Surg 1996;183:616–24.
55. Otsuji E, Yamaguchi T, Sawai K, Hagiwara A, Taniguchi H, Takahashi T. Recent advances in surgical treatment have improved the survival of patients with gastric carcinoma. Cancer 1998;82:1233–7.
56. Adachi Y, Kamakura T, Mori M, Maehara Y, Sugimachi K. Role of lymph node dissection and splenectomy in node-positive gastric carcinoma. Surgery 1994;116:837–41.
57. Feinstein AR, Sosin DM, Wells CK. The Will Rogers phenomenon: stage migration and new diagnostic techniques as a source

of misleading statistics for survival in cancer. New Engl J Med 1985;312:1604–8.
58. Bodner BE. Will Rogers and gastric carcinoma (letter). Arch Surg 1998;123:1023.
59. Noda N, Sasako M, Yamaguchi N, Nakanishi Y. Ignoring small lymph nodes can be a major cause of staging error in gastric cancer. Br J Surg 1998;85:831–4.
60. Bunt AM, Hermans J, Smit VT, van de Velde CJ, Fleuren GJ, Bruijn JA. Surgical/pathologic-stage migration confounds comparisons of gastric cancer survival rates between Japanese and Western countries. J Clin Oncol 1995;13:19–25.
61. Robertson CS, Chung SCS, Woods SDS, Griffin SM, Raimes SA, Lau JTF, et al. A prospective randomized trial comparing R1 subtotal gastrectomy with R3 total gastrectomy for antral cancer. Ann Surg 1994;220:176–82.
62. Bozzetti F, Marubini E, Bonfanti G, Miceli R, Piano C, Crose N, et al. Total versus subtotal gastrectomy: surgical morbidity and mortality rates in a multicenter Italian randomized trial. Ann Surg 1997;226:613–20.
63. Bozzetti F, Marubini E, Bonfanti G, Miceli R, Piano C, Gennari L, Italian Gastrointestinal Tumor Study Group. Subtotal versus total gastrectomy for gastric cancer: 5-year survival rates in a multicenter randomized Italian trial. Ann Surg 1999;230:170–8.
64. Sue-Ling HM, Johnston D. D1 versus D2 dissection for gastric cancer (letter). Lancet 1995;345:1515–6.
65. McCulloch P. D1 versus D2 dissection for gastric cancer (letter). Lancet 1995;345:1516–7.
66. Bonenkamp JJ, Hermans J, Sasako M, van de Velde CJH. Quality control of lymph node dissection in the Dutch randomized trial of D1 and D2 lymph node dissection for gastric cancer. Gastric Cancer 1998;1:152–9.
67. Pacelli F, Sgadari A, Doglietto GB. Surgery for gastric cancer (letter). New Engl J Med 1999;341:438.
68. Noguchi Y, Imada T, Matsumoto A, Coit DG, Brennan MF. Radical surgery for gastric cancer: a review of the Japanese experience. Cancer 1989;64:2053–62.
69. Adachi Y, Mimori K, Mori M, Maehara Y, Sugimachi K. Morbidity after D2 and D3 gastrectomy for node-positive gastric carcinoma. J Am Coll Surg 1997;184:240–4.
70. Brady MS, Rogatko A, Dent L, Shiu MH. Effect of splenectomy on morbidity and survival following curative gastrectomy for carcinoma. Arch Surg 1991;126:359–64.
71. Kwon SJ, Korean Gastric Cancer Study Group. Prognostic impact of splenectomy on gastric cancer: results of the Korean Gastric Cancer Study Group. World J Surg 1997;21:837–44.
72. Griffith JP, Sue-Ling HM, Martin I, Dixon MF, McMahon MJ, Axon ATR, et al. Preservation of the spleen improves survival after radical surgery for gastric cancer. Gut 1995;36:684–90.
73. Wanebo HJ, Kennedy BJ, Winchester DP, Stewart AK, Fremgen AM. Role of splenectomy in gastric cancer surgery: adverse effect of elective splenectomy on longterm survival. J Am Coll Surg 1997;185:177–84.
74. Maehara Y, Moriguchi S, Yoshida M, Takahashi I, Korenaga D, Sugimachi K. Splenectomy does not correlate with length of survival in patients undergoing curative total gastrectomy for gastric carcinoma: univariate and multivariate analyses. Cancer 1991;67:3006–9.
75. Otsuji E, Yamaguchi T, Sawai K, Ohara M, Takahashi T. End results of simultaneous splenectomy in patients undergoing total gastrectomy for gastric carcinoma. Surgery 1996;120:40–4.
76. Yoshino K, Yamada Y, Asanuma F, Aizawa K. Splenectomy in cancer gastrectomy: recommendation of spleen-preserving for early-stages. Int Surg 1997;82:150–4.
77. Okajima K, Isozaki H. Splenectomy for treatment of gastric cancer: Japanese experience. World J Surg 1995;19:537–40.
78. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma: 2nd English ed. Gastric Cancer 1998;1:10–24.
79. Roder JD, Böttcher K, Siewert JR, Busch R, Hermanek P, Meyer HJ. Prognostic factors in gastric carcinoma: results of the German Gastric Carcinoma Study 1992. Cancer 1993;72:2089–97.
80. Siewert JR, Böttcher K, Stein HJ, Roder JD. Relevant prognostic factors in gastric cancer: 10-year results of the German Gastric Cancer Study. Ann Surg 1998;228:449–61.
81. Maruyama K. The most important prognostic factors for gastric cancer patients: a study using univariate and multivariate analyses. Scand J Gastroenterol (Suppl) 1987;22:63–8.
82. Kim JP, Lee JH, Kim SJ, Yu HJ, Yang HK. Clinicopathologic characteristics and prognostic factors in 10 783 patients with gastric cancer. Gastric Cancer 1998;1:125–33.
83. Nakamura K, Ueyama T, Yao T, Xuan ZX, Ambe K, Adachi Y, et al. Pathology and prognosis of gastric cancer: findings in 10 000 patients who underwent primary gastrectomy. Cancer 1992;70:1030–7.
84. Adachi Y, Mori M, Maehara Y, Sugimachi K. Dukes's classification: a valid prognostic indicator for gastric cancer. Gut 1994;35:1368–71.
85. Rohde H, Bauer P, Stützer H, Heitmann K, Gebbensleben B, German Gastric Cancer TNM Study Group. Proximal compared with distal adenocarcinoma of the stomach: differences and consequences. Br J Surg 1991;78:1242–8.
86. Stipa S, Giorgio AD, Ferri M. Surgical treatment of adenocarcinoma of the cardia. Surgery 1992;111:386–93.
87. Harrison LE, Karpeh MS, Brennan MF. Proximal gastric cancers resected via a transabdominal-only approach: results and comparisons to distal adenocarcinoma of the stomach. Ann Surg 1997;225:678–85.
88. Sakaguchi T, Watanabe A, Sawada H, Yamada Y, Tatsumi M, Fujimoto H, et al. Characteristics and clinical outcome of proximal-third gastric cancer. J Am Coll Surg 1998;187:352–7.
89. Siewert JR, Feith M, Werner M, Stein HJ. Adenocarcinoma of the esophagogastric junction: classification in 1002 consecutive patients. Ann Surg 2000;232:353–61.
90. Ono H, Kondo H, Gotoda T, Shirao K, Yamaguchi H, Saito D, et al. Endoscopic mucosal resection for treatment of early gastric cancer. Gut 2001;48:225–9.
91. Ohgami M, Kumai K, Otani Y, Kubota T, Kitajima M. Laparoscopic wedge resection of the stomach for early gastric cancer using a lesion-lifting method. Dig Surg 1994;11:64–7.
92. Otani Y, Ohgami M, Igarashi N, Kimata M, Kubota T, Kumai K, et al. Laparoscopic wedge resection of gastric submucosal tumors. Surg Laparosc Endosc 2000;10:19–23.
93. Kitano S, Iso Y, Moriyama M, Sugimachi K. Laparoscopy-assisted Billroth I gastrectomy. Surg Laparosc Endosc 1994;4:146–8.
94. Nagai Y, Tanimura H, Takifuji K, Kashiwagi H, Yamamoto H, Nakatani Y. Laparoscope-assisted Billroth I gastrectomy. Surg Laparosc Endosc 1995;5:281–7.
95. Watson DI, Devitt PG, Game PA. Laparoscopic Billroth II gastrectomy for early gastric cancer. Br J Surg 1995;82:661–2.
96. Ohki J, Nagai H, Hyodo M, Nagashima T. Hand-assisted laparoscopic distal gastrectomy with abdominal wall-lift method. Surg Endosc 1999;13:1148–50.
97. Goh PMY, Alponat A, Mak K, Kum CK. Early international results of laparoscopic gastrectomies. Surg Endosc 1997;11:650–2.
98. Shimizu S, Uchiyama A, Mizumoto K, Morisaki T, Nakamura K, Shimura H, et al. Laparoscopically assisted distal gastrectomy for early gastric cancer: is it superior to open surgery? Surg Endosc 2000;14:27–31.
99. Adachi Y, Shiraishi N, Shiromizu A, Bandoh T, Aramaki M, Kitano S. Laparoscopy-assisted Billroth I gastrectomy compared with conventional open gastrectomy. Arch Surg 2000;135:806–10.
100. Adachi Y, Suematsu T, Shiraishi N, Katsuta T, Morimoto A, Kitano S, et al. Quality of life after laparoscopy-assisted Billroth I gastrectomy. Ann Surg 1999;229:49–54.

101. Uyama I, Sugioka A, Fujita J, Komori Y, Matsui H, Soga R, et al. Completely laparoscopic extragastric lymph node dissection for gastric malignancies located in the middle or lower third of the stomach. Gastric Cancer 1999;2:186–90.
102. Uyama I, Sugioka A, Fujita J, Komori Y, Matsui H, Hasumi A. Laparoscopic total gastrectomy with distal pancreatosplenectomy and D2 lymphadenectomy for advanced gastric cancer. Gastric Cancer 1999;2:230–4.
103. Gotoda T, Yanagisawa A, Sasako M, Ono H, Nakanishi Y, Shimoda T, et al. Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two centers. Gastric Cancer 2000;3:219–25.
104. Shiraishi N, Adachi Y, Kitano S, Bandoh T, Katsuta T, Morimoto A. Indication for and outcome of laparoscopy-assisted Billroth I gastrectomy. Br J Surg 1999;86:541–4.
105. Kwok SPY, Chung SCS, Griffin SM, Li AKC. Devine exclusion for unresectable carcinoma of the stomach. Br J Surg 1991;78: 684–5.
106. Nakata Y, Kimura K, Tomioka N, Sato M, Watanabe Y, Kawachi K. Gastric exclusion for unresectable gastric cancer. Hepatogastroenterology 1999;46:2654–7.
107. Kaminishi M, Yamaguchi H, Shimizu N, Nomura S, Yoshikawa A, Hashimoto M, et al. Stomach-partitioning gastrojejunostomy for unresectable gastric carcinoma. Arch Surg 1997;132:184–7.