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

Dimitrios H. Roukos, MD, Mathias Lorenz, MD, *and* **Albrecht Encke, MD,** *Ioannina, Greece, and Frankfurt, Germany*

Background. *The use of extended (D2) lymph node dissection in gastric cancer achieves better locoregional tumor control than limited (D1) lymphadenectomy, but its influence on survival is controversial. The value of D2 resection is unproven in randomized trials. However, a survival benefit in favor of D2 resection has been shown in reports from some specialized centers. This study was undertaken to assess whether D2 resection improves survival. We evaluated the efficacy of D2 resection on the basis of a new concept that eliminates the stage migration phenomenon.*

Methods. *D2 resection achieved with a standardized technique in this prospective study included dissection of the perigastric lymph nodes (stations 1 through 6, D1 resection), as well as those at the celiac axis (stations 7 through 11) and at hepatoduodenal ligament (station 12, N2 level). We evaluated survival data of patients with involved nodes at stations 7 through 12 (N2 disease) because these nodes are left behind in a D1 resection.*

Results. *D2 resection resulted in a resection of cure in 31 patients with N2 disease, a 25% (31 of 125) increase of the curative resection compared with a supposed D1 resection. The 5-year survival rate for N2 patients was 17%, which demonstrates the therapeutic benefit of the D2 resection. In patients with pN0 and pN1 disease, the 5-year survival rates were 71% and 53%, respectively. Overall hospital mortality and morbidity were 1.3% (2 of 146) and 33.4% (40 of 146), respectively.*

Conclusions. *D2 resection can be performed safely and is of therapeutic value in patients with advanced lymph node metastases. Furthermore, the survival data suggest indirectly a possible beneficial effect for patients with node-negative disease (N0) or early node metastases (N1). (Surgery 1998;123:573-8.)*

From the Department of Surgery, University Hospital of Frankfurt, Frankfurt, Germany

THE PROGNOSIS OF RESECTABLE gastric cancer in the West remains poor, with no significant improvement reported in recent decades.[1] In Japan, extended lymph node dissection has been performed as a standard procedure during the last three decades, and the 5-year survival rate is twofold to threefold higher than in the West. In a report from the National Cancer Center Hospital in Tokyo (NCCH) the 5-year survival rate increased from 44.5% in the 1960s to 70% in the 1980s for all resected cases.[2] These superior Japanese results cannot be explained only by the detection of a high percentage of early (T1 stage) gastric cancer. Japanese surgeons are so convinced that extended lymphadenectomy in patients with positive nodes reduces the incidence of local recurrence[3] and improves survival[4] that a randomized trial comparing D1 and D2 resection would be regarded in Japan as ethically unacceptable.

However, results from the application of the Japanese-type extended resection in the West are controversial,[5-8] and four randomized trials could not solve the problem. Postoperative morbidity and mortality were significantly higher after D2 than after D1 resection in these trials, but no survival benefit from D2 resection was found.[9-13]

The worldwide debate with regard to the therapeutic value of extended lymphadenectomy prompted us to perform this prospective study. Scientific well-documented evidence of the benefi-

Accepted for publication Oct. 23, 1997.

Reprint requests: Dimitrios Roukos, MD, Lecturer in Surgery, Roma 19, GR-452 21 Ioannina, Greece.

0039-6060/98/$5.00 + 0 **11/56/88094**

cial effect of D2 resection on survival is difficult to establish, even in randomized trials. The stage migration[14] phenomenon, which increases the accuracy of staging as a result of more extensive lymphadenectomy, improves the stage-specific survival without improvement of overall survival and confounds survival comparisons between the two surgical techniques.[15] Our concern is that the more distant nodes (N2 and N3 levels) are left behind in a D1 resection, resulting in the dismal survival rate of patients with residual involved nodes after operation.[16] Consequently, the evaluation of survival data of patients with N2 nodes after a D2 curative resection could prove whether D2 resection improves survival. The therapeutic benefit will be as great as the proportion of possible N2 long-term survivors.

PATIENTS AND METHODS

To ensure standard surgical treatment and pathologic assessment, the guidelines of the Japanese Research Society for the Study of Gastric Cancer (JRSGC) were used.[17] According to these guidelines, lymph nodes are grouped into 16 stations, which are subsequently divided into four levels (N1 through N4) according to tumor location, and operations are classified according to the level of lymph node dissection (D1 to D4). D1 procedure includes dissection of perigastric nodes directly attached to the stomach (stations 1 to 6, N1 level), whereas in D2 procedures the lymph nodes along the left gastric artery (station 7), common hepatic artery (station 8), celiac artery (station 9), splenic artery (station 11), and at the splenic hilus (station 10) (N2 level) are also dissected.

Histopathologic staging according to the tumor-node-metastasis (TNM) classification of the UICC[18] was also used to compare our results with those of other Western studies. However, the terms D1 and D2 are taken from the rules of the JRSGC. The definition of the pN2 stage of disease of UICC, which characterizes involved nodes in a distance more than 3 cm from tumor but without their exact location, is inappropriate and confounds the comparison between D1 and D2 groups. We used a combination of both staging systems in this study. We defined pN2a disease as involvement of nodes from stations 1 through 6 at a distance of more than 3 cm from the tumor, whereas involvement of stations 7 through 11 was defined as pN2b disease (N2 level). Metastasis to station 12 is classified as N3 level according to the JRSGC and as pM1-Lym in the TNM system.

In this prospective study, extended lymphadenectomy was performed with a systematic and standardized technique that included dissection of nodal stations 7 through 11 (UICC, pN2b; JRSGC, N2 1evel), as well as those from the hepatoduodenal ligament (station 12, part of N3 level). We defined this dissection as D2 resection, although it included the dissection of nodes at station 12.

The extent of gastric resection was determined by tumor type (Lauren classification) and location of the lesion. Total gastrectomy was the standard procedure, whereas subtotal gastrectomy was reserved for intestinal-type early (pT1) gastric cancer, with location at the distal third of the stomach. Distal pancreatectomy was performed only in patients with macroscopic suspicion of pancreas involvement by the primary tumor. There was no specific strategy for the resection or preservation of the spleen.

Patient population. The data of 210 consecutive patients with histologically proven adenocarcinoma of the stomach, who underwent gastrectomy between 1986 and 1992 at the Department of Surgery, University of Frankfurt, were documented prospectively. Sixty-four patients who underwent a Western-type, conventional, limited D1 resection were excluded from the study. The cause for a D1 application was either clear evidence of surgical incurability (n = 39) or old age (median age, 80 years) with serious comorbid cardiorespiratory disease (n = 19). Also excluded were six patients for the following reasons: tumor bleeding with emergency operation (n = l), refusing blood transfusion for religious reasons (n = l), and serious adhesions after other operations or chronic pancreatic disease (n = 4).

A total of 146 patients who underwent a complete, systematic, and standardized extended lymphadenectomy, which included the dissection of nodal stations 7 through 12, remained eligible and all formed the study population. Quality control of the D2 technique was confirmed by pathologic evidence of lymph nodes at stations 7 through 12 in all specimens. Details of the surgical procedure, histopathologic tumor features, and follow-up data were documented prospectively. A resection was defined as potentially curative when, at the time of operation, there was no distant metastasis (liver, peritoneal) and all tumors were completely resected macroscopically and microscopically (UICC R0). The effect of D2 lymphadenectomy on short-term morbidity was calculated for the whole patient population. Because the curative value of apparently complete resection of regional nodes was to be examined, the long-term survival was calculated separately for the UICC R0 resected group. To eliminate stage migration, patients with metastasis

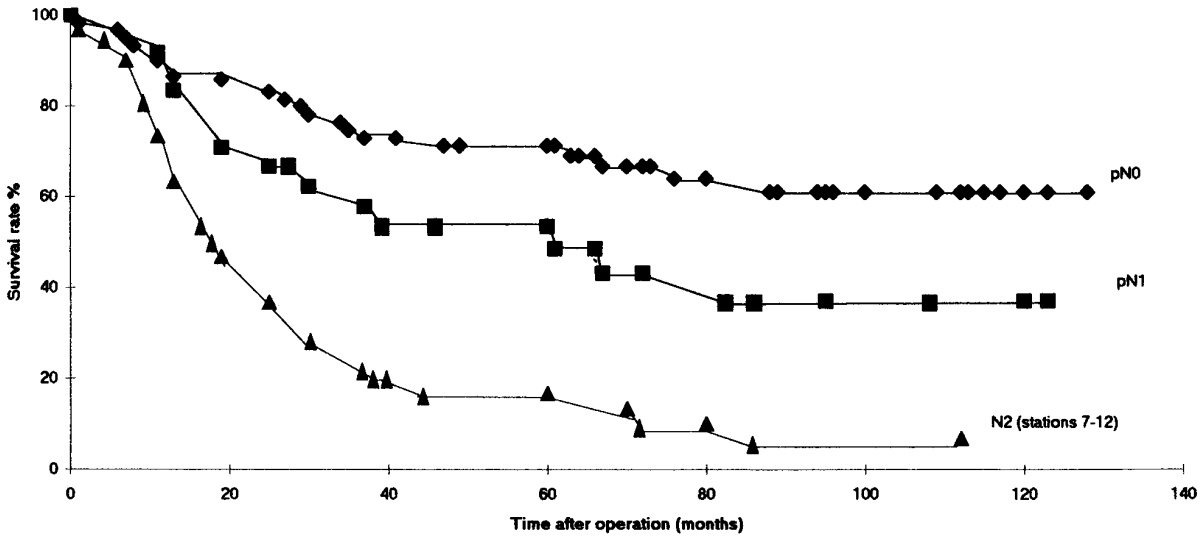

Fig. 1. Survival for patients who underwent a potentially curative D2 resection in relation to lymph node stage of disease. pN0 vs pN1, $p < 0.01$; pN1 vs N2, $p < 0.001$.

to station 12 but with complete tumor resection at the end of operation were also included in the curatively resected group to allow for comparison with patients from Japan. Special interest was given to the evaluation of the incidence of metastases to lymph node stations 7 through 12 and of the survival data of these patients in relation to tumor site and depth of invasion. The effect of D2 lymphadenectomy on survival also was evaluated separately for the noncurative resected subgroup of patients ($n = 21$).

Statistical analysis. Survival curves were calculated according to the Kaplan-Meier method.[19] Because there is a strong correlation between N stage of disease and effectiveness of extent of lymphadenectomy, the log-rank test[20] was used to assess statistical differences of survival data between patients with pN0, pN1, and N2 disease. Any death after operation, including operative death and death from causes other than cancer, was included in the survival analysis. Postoperative hospital mortality included deaths within 30 days after operation, as well as deaths after 30 days in patients who never left the hospital. Data of intensive follow-up were documented prospectively. The most recent follow-up of all survivors was in February 1997. A separate survival analysis was made for patients with metastasis to nodal stations 7 through 12.

RESULTS

The characteristics of 125 patients who underwent a potentially curative D2 gastrectomy are shown in Table I. Total gastrectomy was the standard procedure (89%), whereas distal pancreatectomy was rarely performed (5.6%). The overall hospital mortality rate was only 1.37% (2 of 146). One of the patients died of duodenal stump leakage and sepsis and the other of cardiac complications. The overall morbidity was 33.5% (49 of 146). Thirty patients (20%) had one or more of the following surgical complications: anastomotic leakage (6%), intraabdominal infection (2.7%), pancreatic leakage/fistula (2.7%), lymph fistula (2.7%), hemorrhage (2%), ileus (0.7%), and relaparotomy (8.2%). Nineteen patients had a nonsurgical complication (pulmonary, respiratory, urinary tract, thromboembolic).

Table I. Characteristics of 125 patients who underwent a D2 resection with curative intent

Median age (range) (yr)	65 (29-86)
Gender (male/female)	77/48
Site of tumor*	
Cardia, upper third	35 (28%)
Middle third	29 (23%)
Distal third	53 (42%)
More than two thirds	8 (7%)
Type of resection	
Total gastrectomy	111 (89%)
Distal gastrectomy	11 (9%)
Total esophagogastrectomy	3 (2%)
Other surgery*	
Splenectomy	69 (55%)
Distal pancreatectomy	7 (5.6%)
Lauren intestinal-type	48 (38%)

*Data missing for some patients.

Complete dissection in each lymph node station was achieved in most patients in this study. The high proportion of total gastrectomy allowed the dissection of cardial right (station 1) and cardial

Table II. Lymph node (LN) stage according to the depth of tumor invasion

				*D2 resection**			
				D1 resection			
pT Stage	*No. of patients*	*pN0*	*pN+ Total*	*pN1*	*pN2a*	*pN2b*	*N3 station 12*
pT1	25 (20%)	23 (92%)	2 (8%)	1	0	1 (4%)	0
pT2	33 (26%)	19 (58%)	14 (42%)	5	4	2 (6%)	3 (9%)
pT3	67 (54%)	18 (27%)	49 (73%)	18	6	16 (24%)	9 (13%)
Total	125	60	65 (52%)	24	10	19 (15%)	12 (10%)

N category according to both UICC and JRSGC.

pN0, Lymph nodes without metastases; *pN1*, lymph nodes with metastases < 3 cm from the primary tumor; *pN2a*, lymph nodes with metastases > 3 cm from tumor that are attached to the stomach (i.e., nodal stations 1 through 6 according to JRSGC); *pN2b*, lymph node involvement at the vessels surrounding the celiac axis (i.e., according to JRSGC stations 7 through 11); lymph node involvement at station 12 (hepatoduodenal ligament, part of N3 level) according to UICC is considered as pM1 (Lym); *pN+*, node-positive.

*D2 resection included lymph nodes dissected with a D1 resection and dissection of lymph nodes at stations 7 through 12.

left (station 2) nodal stations, as well as along the short gastric vessels (station 4sa) in nearly all patients. The other stations 3 to 12 (except 10, which requires splenectomy) were also completely dissected in all patients.

The extent of lymphatic spread and its relationship to the depth of invasion of the primary tumor are shown in Table II. Metastases to at least one lymph node was found in 65 of 125 patients (52%). There was a steady increase in the proportion of node-positive cases with increasing depth of invasion, from 8% when the tumor invaded the mucosa and submucosa to 73% when the tumor invaded the serosa. The frequency of involvement of the more distant nodes (stations 7 through 12) also rose steadily with depth of invasion.

Long-term survival. The follow-up rate for all eligible patients was 97.2% (142 of 146). For survivors, the mean observation time was 90 months, with a range from 28 to 128 months.

The cumulative overall 5- and 10-year survival rates for patients with a resection of cure (n = 123) were 52.3% and 40%. Among 19 patients who underwent a noncurative resection, there were only two long-term survivors, both with a pT2/3N0M0 stage and involvement of distal resections line (5-year survival rate, 10.5%).

For patients with curative resection, survival was strongly correlated with the N stage of disease (Fig. 1). The cumulative 5- to 10-year survival rates were 71% (61%) in pN0 patients, 53% (37%) in pN1 patients, and 16.7% (6.7%) in N2 (stations 7 through 12) patients.

Incidence of node metastases and long-term survival of patients with metastases at nodal stations 7 through 12. A resection with curative intent could be achieved in 31 patients with involved nodes at stations 7 through 12. Because these nodes are left behind in a D1 resection, the D2 resection increased the curative resection rate by 25% (31 of 125). Nineteen patients had metastases at stations 7 through 11 and 12 patients at station 12. Six of these 12 patients had metastases in both stations 7 through 11 and station 12. Lymphatic spread was strongly related to the depth of invasion (Table II) and the site of the primary tumor. The incidence of metastasis to the hepatoduodenal nodes was 13.3% (12 of 90) for tumors (all 12 patients had a pT2/T3 tumor) located at the distal two thirds of the stomach and 0% to nodes at the splenic hilus. On the other hand, the incidence for proximal tumors was 14.3% (5 of 35) at station 10 (all 5 patients had a pT3-tumor stage) and 0% at station 12.

An overall mean of 8.4 (range, 2 to 29) involved lymph nodes from a mean of 36.3 (range, 21 to 58) resected and examined nodes per specimen was found. Follow-up was complete in 30 of 31 N2 patients. The median overall survival time was 20 months (mean, 29.7 months; range, 1 to 112 months), 38 months (mean, 49.5 months) for nine patients with involved/examined lymph node ratio smaller than 0.15, and 16 months (mean, 22.9 months) for 21 patients with ratio greater than 0.15. Five patients were alive and disease free 5 years after operation. Two patients died of causes other than cancer, one died as a result of operative complications, and the other 22 patients died of tumor recurrence. Among 12 patients with metastases at the hepatoduodenal ligament (station 12), four patients survived more than 5 years.

DISCUSSION

Data supporting the therapeutic value of D2 resection in gastric cancer are lacking. The Japanese claims in favor of extended lymphadenectomy were based on historical comparisons,[21] which are of little scientific value.[15] Sasako et al.,[4] however, from the NCCH in Tokyo reported a survival benefit of extended lymphadenectomy for patients with advanced lymph node metastases

(N2, N3), eliminating the stage migration phenomenon; however, the impact of D2 resection on morbidity and long-term survival in the West is controversial. Recently published reports from specialized centers showed a stage-specific survival benefit of D2 resection.[7,8] However, these studies did not eliminate stage migration phenomenon and failed to show a survival advantage for patients with advanced node metastases.[7,8] Furthermore, other recent series from the United States did not find any survival benefit after a D2 resection.[5,6] Interestingly, it was reported that the improvement of stage (II/IIIA)-specific survival was most likely caused by the Will Rogers phenomenon.[22,23] The value of D2 resection could be determined with certainty from randomized trials. Unfortunately, all four randomized Western trials failed to show any survival benefit for D2 resection, while finding an association between D2 resection and increased morbidity and mortality.[9-13]

This study is the first prospective trial in the West that, in an attempt to prove whether D2 dissection improves patient outcome, introduces a new concept for the evaluation of the effectiveness of D2 resection. On the basis of the fact that involved nodes at stations 7 through 12 are left behind in a D1 dissection, eliminating the chance for cure in these patients, we evaluated whether a resection with curative intent was possible and whether there were long-term survivors among these patients. A potentially curative resection was achieved in 31 patients with involved nodal stations 7 through 12, and the 5-year survival rate among these patients was 17%. Even higher (41.6%) was the 5-year survival rate for the subgroup of patients with metastases to hepatoduodenal nodes. These results demonstrate the therapeutic benefit of the D2 resection because there probably would not have been any long-term survivors if a D1 resection had been performed. However, the benefit from the standard use of prophylactic lymphadenectomy in patients with curative resection was low (4%, 5 of 125). The most important prognostic factor in our study once metastases to the nodal stations 7 through 12 had occurred was the lymph node ratio.

Patients with pN0 or pN1 disease had high survival rates, suggesting indirectly a positive effect of the D2 resection on survival; however, these data are inconclusive. Recently, Siewert et al.[24] expressed the view that D2 resection improves survival in patients with pN0 disease in routine histologic examination because they found frequent occurrence of microinvolvement in patients with pN0 disease. However, these data require further investigation.[25]

The major question is why all randomized trials failed to show any survival advantage for D2 resection. The two early trials[9,10] were too small to draw conclusions. The two large multicenter trials, the Dutch trial[11,13] and the MRC trial from Great Britain[12] showed a significant increase of postoperative complications and hospital mortality after a D2 rather than after a D1 resection, but there was no survival benefit for D2 resection. The inappropriate design of these trials in which a distal pancreaticosplenectomy was performed as a standard procedure for D2 resection, the low expected overall survival benefit of the prophylactic D2 resection, and the surgeon's experience with the technique of D2 dissection are all possible explanations for the adverse effect on morbidity and mortality. There is no doubt that a learning curve exists for D2 resection. Comparison of the results after a D2 resection of the present study with those of our previous report[26] shows that hospital mortality declined from 6% to 1.3%, the curative resection rate increased from 2.4% to 25%, and the 5-year survival rate for patients with N2 disease increased from 0% to 17%. D2 resection was performed in our prospective study more systematically; the use of a standardized technique and the increased experience of the surgeon contributed to the improved results.

Our data and those from the literature suggest that D2 resection has a beneficial effect on patients with node-positive disease. The optimal extent of lymphadenectomy, therefore, should include the dissection of tumor-containing nodes. However, the diagnostic accuracy of involved nodes remains unreliable. Lymphatic spread is strongly related to tumor site and is distinctly different in distal than in proximal tumors. By using information with regard to the site of the primary tumor, the depth of tumor invasion, and the expected long-term survival, the surgeon can avoid useless and high-risk resection of the spleen, pancreas, and lymph nodes. For example, in our study dissection of hepatoduodenal nodes in patients with distal advanced tumors resulted in a considerable survival benefit, whereas splenectomy for these patients was not of therapeutic value. On the other hand, for proximal advanced tumors, resection of the spleen increased the curative resection rate, whereas dissection of hepatoduodenal nodes had no prognostic significance. These data are similar to those of large Japanese series.[4] The encouraging long-term results for patients with involved hepatoduodenal nodes provide evidence in favor of the

routine use of dissection at nodal station 12 for patients with advanced distal tumors and raise questions about the validity of the UICC classification of these patients as having pM1-Lym disease.

Results from this study prove that extended lymph node dissection can be performed with safety and is of therapeutic value for patients with gastric cancer who have advanced lymph node metastases (N2 disease). Furthermore, it provides indirect evidence that D2 dissection has a possible beneficial effect on patients with node-negative disease (N0) or early node metastases (N1 disease). Information with regard to tumor site and depth of invasion is of paramount importance in planning the extent of lymphadenectomy.

REFERENCES

1. Akoh JA, Maclntyre IMC. Improving survival in gastric cancer: review of 5-year survival rates in English language publications from 1970. Br J Surg 1992;79:293-9.
2. Marujama 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.
3. Katai H, Maruyama K, Sasako M, et al. Mode of recurrence after gastric cancer surgery. Digestive Surgery 1994;11:99-103.
4. Sasako M, McCulloch P, Kinoshita T, Marujama K. New method to evaluate the therapeutic value of lymph node dissection for gastric cancer. Br J Surg 1995;82:346-51.
5. Soreide JA, van-Heerden JA, Burger LJ, Donohue JH, Sarr MG, Ilstrup DM. Surgical aspects of patients with adenocarcinoma operated on for cure. Arch Surg 1996;131:481-6.
6. 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.
7. Siewert JR, Boettcher K, Roder JD, Busch R, Hermanek P, Meyer HJ, et al. Prognostic relevance of systematic lymph node dissection in gastric carcinoma. Br J Surg 1993;80:1015-8.
8. Pacellli F, Doglieto 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.
9. Dent DM, Madden MV, Price SK. Randomised comparison of R1 and R2 gastrectomy for gastric carcinoma. Br J Surg 1988;75:110-12.
10. Robertson CS, Chung SCS, Woods SDS, et al. A prospective randomised trial comparing R1 subtotal gastrectomy with R3 total gastrectomy for antral cancer. Ann Surg 1994;220:176-82.
11. Bonenkamp JJ, van de Velde CJH, Hermans J. Randomised trial of extended lymph node dissection for gastric cancer. In: Siewert JR, Roder JD, editors. 2nd International Gastric Cancer Congress Munich. vol 2. Bologna: Monduzzi Editore; 1997. p 1111-6.
12. Cuschieri A, Fayers P, Fielding J, 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.
13. Bonenkamp JJ, Songun I, Hermans J, Sasako M, et al. Randomised comparison of morbidity after D1 and D2 dissection for gastric cancer in 996 Dutch patients. Lancet 1995;345:745-8.
14. 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. N Engl J Med 1985;312:1604-8.
15. Roukos DH, Kappas AM, Encke A. Extensive lymph node dissection in gastric cancer: is it of therapeutic value [editorial]? Cancer Treat Rev 1996;22:247-252.
16. Rohde H, Gebbensleben B, Bauer. P, Stuetzer H, Zieschang J. Has there been any improvement in the staging of gastric cancer? findings from the German Gastric cancer TNM Study Group. Cancer 1989;64:2465-81.
17. Japanese Research Society for Gastric Cancer. The general rules for the gastric cancer study in surgery and pathology. Jpn J Surg 1981;11:127-39.
18. Hermanek P, Sobin LH, editors. UICC: TNM classification of malignant tumours. 4th ed. Berlin: Springer-Verlag; 1987.
19. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457-8.
20. Gehan EA. A generalized Wilcoxon for comparing arbitrary single-censored samples. Biometrica 1965;52:203-24.
21. Marujama K, Okabayashi K, Kinoshita T. Progress in gastric cancer surgery in Japan and its limits of radicality. World J Surg 1987;11:418-25.
22. Bunt AMG, Hermans J, Smit VTHBM, van de Velde CJH, Fleuren G J, Bruijn JA. Surgical / pathologic-stage migration confounds comparison of gastric cancer survival rates between Japan and Western countries. J Clin Oncol 1995;13:19-25.
23. Fass J, Hungs M, Reineke TH, Schumpelic V. The impact of D2-lymphadenectomy on staging and prognosis of gastric carcinoma. In: Siewert JR, Roder JD, editors. 2nd International Gastric Cancer Congress Munich. vol 2. Bologna: Monduzzi Editore; 1997. p 1141-6.
24. Siewert JR, Kestlmeier R, Busch R, Boettcher K, Roder JD, Mueller J, et al. Benefits of D2 lymph node dissection for patients with gastric cancer and pN0 and pN1 lymph node metastases. Br J Surg 1996;83:1144-7.
25. Roukos DH. Extended lymphadenectomy in gastric cancer: when, for whom and why. Ann R Coll Surg Engl 1998;80:16-24.
26. Roukos D, Hottenrott C, Lorenz M, Koutsogiorgas-Couchell S. A critical evaluation of effectiveness of extended lymphadenectomy in patients with carcinoma of the stomach. J Cancer Res Clin Oncol 1990;116:307-13.