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Survival Benefit of Extended D2 Lymphadenectomy in Gastric Cancer With Involvement of Second Level Lymph Nodes: A Longitudinal Multicenter Study

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Background: The survival benefit of extended lymphadenectomy in the surgical treatment of gastric cancer is still being debated. The aim of this longitudinal multicenter study was to evaluate long-term survival in a group of patients with involvement of second level lymph nodes, which would not have been removed in the case of a limited lymphadenectomy. Results were compared with those in patients with involvement of first level lymph nodes.

Methods: Between 1991 and 1997, 451 patients with primary gastric cancer underwent curative resection with extended lymphadenectomy at three surgical departments in Italy according to the rules of the Japanese Research Society for Gastric Cancer.

Results: In 451 cases treated by extended lymphadenectomy, morbidity and mortality rates were 17.1% and 2%, respectively. In 126 patients (27.9%) (group A), metastases were found in lymph node stations 7 to 12; 109 patients (24.2%) had metastases confined to the first level (group B). Lymph node stations 7 and 8 showed the highest incidence of metastases in the second level (17.1% and 12.4%, respectively). A significant difference in 5-year survival was observed between group A and group B (32% vs. 54%; $P = .0005$). This difference disappeared when cases were stratified according to the number of positive lymph nodes. By multivariate analysis, only the number of positive lymph nodes (relative risk, 1.8; $P < .0001$) and the depth of invasion (relative risk, 2.1; $P < .0001$), but not the level of involved nodes, showed to be independent predictors of poor prognosis.

Conclusions: Japanese-type extended lymphadenectomy yields low morbidity and mortality rates if performed in specialized centers. This procedure could provide a good probability of long-term survival, even for patients with involvement of regional lymph nodes.

Key Words: Gastric cancer—Surgery—Lymphadenectomy—Lymph node metastasis—Prognostic factors—Follow-up.

Despite the general reduction in the incidence of gastric carcinoma, this type of cancer is still one of the leading causes of death by neoplasia in the world. As chemotherapy and radiotherapy are of limited use in treating this neoplasm, surgery still represents the most effective therapy, even though overall survival after radical treatment remains low.[1] The involvement of lymph node stations is of particular importance in the development of the disease since the lymph nodes are not only the most frequent site of spreading, but their involvement represents one of the most important prognostic factors.[2] However, the usefulness of removing regional lymph node stations is still controversial. Japanese surgeons routinely remove first and second level lymph nodes (D2 lymphadenectomy) and, in some cases, also third and fourth level stations. They report very low postoperative mortality and morbidity rates and high long-term sur-

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vival, even in advanced cases.[3,4] Extended D2 lymphadenectomy is performed in only a few Western centers. The incidence of complications observed in centers specializing in this surgical procedure has proven to be low; generally, it is only slightly higher than that reported by Japanese authors.[5–7] On the contrary, very high morbidity and mortality rates were observed in two randomized European studies reported in the literature; those studies did not show a long-term survival benefit for D2 lymphadenectomy compared with limited dissection (D1).[8,9] Such results have left the problem concerning the usefulness of extended lymphadenectomy in the treatment of gastric cancer unresolved.

In the present study, we report the results of extended D2 lymphadenectomy, performed in accordance with the criteria described by the Japanese authors, in three specialized Italian centers where this technique has been used for years. With the goal of assessing the potential benefit of the treatment, we analyzed the outcome of its use in a group of patients who presented involvement of second level lymph nodes (stations 7-12), which would not have been removed with a D1 lymphadenectomy; the results were compared with those observed in the group of patients with lymph node involvement confined to the first level (stations 1-6).

METHODS

In the present longitudinal study, we collected data on patients with confirmed gastric adenocarcinoma who had been operated on between 1991 and 1997 at three Italian surgical centers that routinely perform gastrectomy with extended D2 lymphadenectomy in accordance with the Japanese Research Society for Gastric Cancer guidelines.[10] The centers involved in the study were the Institute of Surgical Science, University of Siena (80 cases); the First Division of General Surgery, University of Verona (166 cases); and the First Department of Surgery, "Morgagni" Hospital in Forlì (205 cases). The total number of patients was 451. Data regarding each of the patients were collected in a single wide database containing clinical, surgical, pathological, and follow-up information.

All patients considered in this study underwent curative resection (R0) with D2 lymphadenectomy; no distant metastases in other organs or peritoneal spreading was found either preoperatively or upon laparotomy. Immediately after laparotomy, 1 mL of India ink solution was injected directly into a regional lymph node close to the tumor, in accordance with the technique described by Maruyama et al.[4] Generally, when the neoplasm was located in the lower and middle third of the stomach, a subtotal gastrectomy was performed, providing that a distance of at least 5 cm between the tumor and the proximal section line was maintained; in the other cases, a total gastrectomy was performed. An intraoperative frozen section of the surgical resection line was always examined histologically. For reconstruction, the Roux-en-Y and Billroth II techniques were preferred. Resection of the pancreas and splenectomy were performed only when necessary, in cases of direct extension of the neoplasm to these organs or when there was macroscopic involvement of lymph node stations located in the splenic hilum (station 10) or along the splenic artery (station 11).

D2 lymphadenectomy consisted of the removal of lymph node stations 7 (left gastric artery), 8 (common hepatic artery), 9 (celiac artery), 11 (splenic artery), and, optionally, 10 (splenic hilum). The removal of station 12 (hepatoduodenal ligament) has often been associated with D2 lymphadenectomy. Each lymph node station was removed and classified either during the operation or from the resected specimen immediately afterwards, in accordance with the procedures established by the Japanese Research Society for Gastric Cancer,[10] by three surgeons who visited the National Cancer Center Hospital in Tokyo (F.R., G.D.M., P.M.). As this method indicates, single lymph nodes were retrieved in the fresh specimen and then submitted to histopathological examination.

Our study group (group A) included patients who underwent extended lymphadenectomy with a minimum of 15 lymph nodes removed during the operation and with lymph node metastases identified in stations 7 to 12 in the pathological report. A total of 126 patients (27.9% of the extended lymphadenectomies performed) met these criteria. The mean age was 65 years (range, 30–87 years); 82 patients were male and 44 were female (ratio, 1:86). The operation most frequently performed was a total gastrectomy (56.3%). In 8 patients (6.3%) a pancreaticosplenectomy was performed, whereas in 10 cases (7.9%) a splenectomy alone was performed.

As a control group, patients with involvement of first level lymph nodes (stations 1-6) were taken into consideration (group B). This group consisted of 109 patients (24.2%), 68 males and 41 females (mean age, 65 years; range, 30–88 years).

For histological classification, Lauren's criteria were applied.[11] Pathological staging and the definition of radicality (R0, R1, R2) were in accordance with the Union Internationale Contre le Cancer criteria.[12] Complications and postoperative mortalities were considered when they were recorded during hospitalization or within 30 days

after surgery. None of the patients included in this study was subjected to postoperative chemo- or radiotherapy.

The same follow-up schedule was used by all three centers, consisting of a clinical examination, chest x-ray, abdominal ultrasound, tumor marker assay (CEA, CA 19-9, CA 72-4), endoscopic evaluation, and, when necessary, abdominal computed tomography scan. The end date of follow-up was April 30, 2001. The mean ± SD overall follow-up period (including deceased patients) was 34 ± 29 months (range, 2–109 months) in group A and 47 ± 30 months (range, 2–108) in group B (analysis of variance [ANOVA], $P < .0001$). The mean follow-up period for surviving patients was 68 ± 23 months (range, 32–109) in group A and 72 ± 20 months (range, 30–108) in group B (ANOVA, $P = .266$). No patient was lost at follow-up.

For statistical analysis, SPSS™ statistical software (version 8.0) (SPSS, Inc, Chicago, IL) was used. The Pearson's χ^2 test was used to compare parametric data, and ANOVA was used to compare nonparametric variables. Univariate survival analysis was performed with the Kaplan-Meier method, and results were compared by means of the log-rank test. Only cancer-related mortalities were considered for survival analysis; mortalities from other causes were considered as censored observations at the time of death. Multivariate analysis was carried out using the Cox proportional hazards model for prognostic evaluation of the following variables: gender, age, location (upper, middle, lower), Lauren's histotype (intestinal, diffuse-mixed), depth of invasion (T1, T2, T3, T4), level of lymph node involvement (N1, N2), number of positive lymph nodes (<6, 7–15, >15), tumor size (<4, 4–7.9 >8 cm), and type of operation (subtotal or total gastrectomy).

RESULTS

The postoperative morbidity and mortality rates for the 451 patients treated with extended lymphadenectomy were 17.1% and 2%, respectively. Postoperative complications observed in our patients are reported in Table 1. In the group of patients with involvement of second level lymph nodes (group A), morbidity and mortality were 21.4% and 3.2%, whereas in patients with involvement of first level lymph nodes (group B), these rates were 18.3% and 1.8%, respectively ($P = .607$ and .814, respectively).

According to the pathological report, the mean ± SD number of lymph nodes removed was 35 ± 15 (range, 16–83) in group A and 34 ± 14 (range, 15–74) in group B (ANOVA, $P = .521$). The mean ± SD number of metastatic lymph nodes was 13 ± 9 (range, 1–42) in group A and 4 ± 4 (range, 1–24) in group B (ANOVA, $P < .0001$). Table 2 shows both the absolute incidence of lymph node metastases in stations 7 to 12, with respect to the 451 total cases, and the incidence relative to the 126 cases in group A. The stations mostly affected by cancer were 7 (left gastric artery) and 8 (common hepatic artery) (relative incidence 61.1% and 44.4%, respectively); in 4% of the cases, station 12 (hepatoduodenal ligament) was involved.

The 5-year (± SE) survival rates in the two groups of patients are shown in Fig. 1. A statistically significant difference between the two groups was observed (32 ± 4% vs. 54 ± 4%; log-rank test, $P = .0005$). At the follow-up end date, 37 patients in group A were still living and were disease-free, whereas the other 89 patients had died: 3 from causes other than the neoplasia, 4 from postoperative complications, and 82 because of disease recurrence. In group B, 50 patients were still living, whereas 2 had died from postoperative complications, 53 from tumor recurrence, and 4 because of other causes. A comparison of 5-year survival rates between the two groups was performed by stratifying on the basis of the parameters of gender, age group, location, histological type, diameter, depth of invasion, the number of positive lymph nodes, and the type of gastrectomy (Table 3). A lower 5-year survival of group A versus group B was observed in males, advanced age, upper or lower location, intestinal histotype, large tumor size, and in cases with serosal involvement. Interestingly, no difference in 5-year survival between group A and group B

TABLE 1. *Postoperative complications after D2 lymphadenectomy in 451 patients*

Surgical	No. of Cases	% of 451 cases
Anastomotic or duodenal stump leakage	20 (2)	4.4
Pancreatitis	11 (1)	2.4
Abdominal abscess	7	1.6
Wound infection	4	.9
Hemorrhage	3	.7
Intestinal obstruction	3	.7
Stenosis of anastomosis	2	.4
Intestinal perforation	2	.4
Biliary duct injury	1	.2
Total	53 (3)	11.8
Nonsurgical		
Pleuropulmonary	13 (2)	2.9
Cardiac insufficiency	3 (2)	.7
Ictus cerebri	3 (1)	.7
Acute respiratory distress syndrome	2 (1)	.4
Urinary tract infection	2	.4
Pulmonary embolism	1	.2
Total	24 (6)	5.3

Numbers in parentheses represent deaths.

TABLE 2. *Absolute and relative incidence of lymph node metastases in stations 7–12*

Station No.	Positive cases	Ratio positive cases/total cases (n = 451)	Ratio positive cases/N2 positive cases (n = 126)
7 (left gastric artery)	77	17.1	61.1
8 (hepatic artery)	56	12.4	44.4
9 (celiac axis)	47	10.4	37.3
10 (splenic hilum)	13	2.9	10.3
11 (splenic artery)	17	3.8	13.5
12 (hepatoduodenal ligament)	5	1.1	4

was observed by stratifying for the number of positive lymph nodes or in neoplasms not involving the serosa.

The results of the multivariate analysis performed in all lymph node-positive cases indicated both the number of positive lymph nodes (relative risk, 1.8; $P < .0001$) and the depth of invasion (relative risk, 2.1; $P < .0001$) as the only independent and significant prognostic variables. On the contrary, the level of lymph node involvement (N1 or N2) did not prove to be a significant predictor of poor prognosis in our cases.

DISCUSSION

Despite the numerous studies published regarding the value of extended lymphadenectomy in gastric carcinoma, its role is still much debated. The standardization of this procedure, the excellent results reported, and its routine use for several years do not permit a randomization limited versus extended lymphadenectomy in Japan, for obvious ethical reasons. To assess the incidence of complications and the survival benefit associated with this procedure, two European randomized studies were conducted following the criteria and technical procedures established by the Japanese. Both the Dutch trial[8] and the Medical Research Council trial[9] did not demonstrate any survival benefit for D2 dissection compared with D1. Furthermore, both trials revealed mortality and morbidity rates following D2 lymphadenectomy that were much higher than in the D1 arm and than those reported by the Japanese authors. These results could be explained by both the high number of participating centers, not all of which specialized in this type of surgery, and by the inappropriate design of the trials, which included routine pancreaticosplenectomy in the D2 procedure. The correct execution of an extended lymphadenectomy requires specialized experience in gastro-

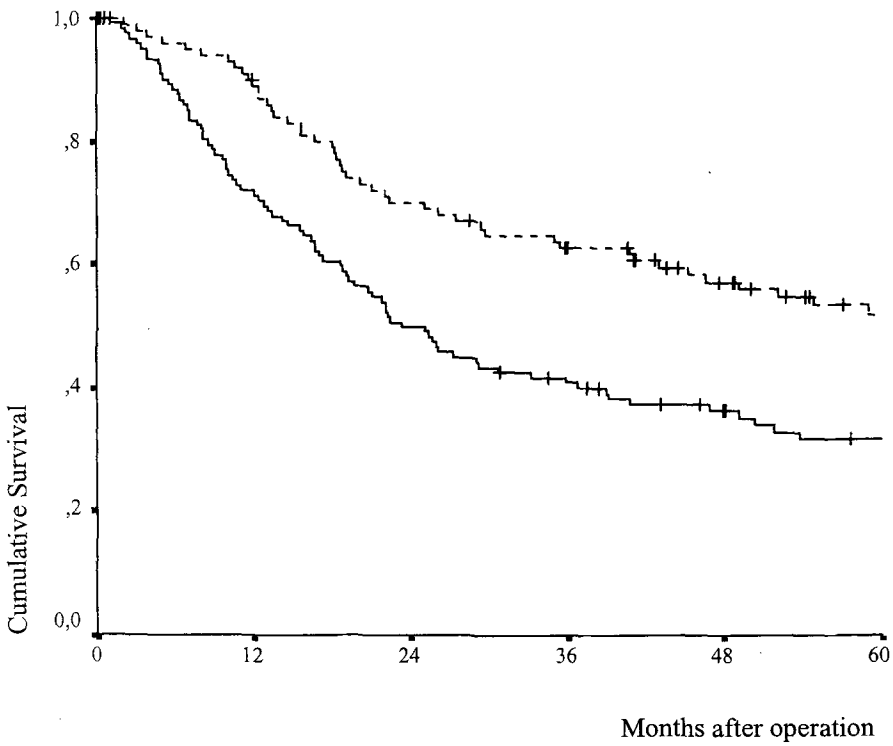

FIG. 1. Cumulative survival in group A (126 patients with metastases in second level lymph nodes) (—) and group B (109 patients with metastases in first level lymph nodes) (----). The difference between the two groups is statistically significant (log-rank, $P = .0005$). Crossmarks represent censored cases.

TABLE 3. *Cumulative 5-year survival according to different clinicopathological variables in the two groups of patients*

Variable	Group A		Group B		
	No. of Cases	5-year survival[a] (± SE)	No. of Cases	5-year survival[a] (± SE)	*P* value[b]
Gender					
Male	82	29 ± 5%	68	59 ± 6%	.0003
Female	44	37 ± 8%	41	45 ± 8%	.4120
Age group					
<50	14	36 ± 13%	12	83 ± 11%	.0575
50–69	57	34 ± 7%	49	50 ± 8%	.0599
≥70	55	29 ± 6%	48	49 ± 8%	.0155
Location					
Upper	28	18 ± 8%	27	44 ± 10%	.0084
Middle	39	44 ± 8%	33	46 ± 9%	.7358
Lower	59	31 ± 6%	49	64 ± 7%	.0007
Lauren's histotype					
Intestinal	67	28 ± 6%	65	54 ± 7%	.0007
Diffuse-mixed	59	36 ± 7%	44	54 ± 8%	.1306
Diameter (cm)					
<4	40	42 ± 8%	38	56 ± 9%	.2009
4–7.9	62	29 ± 6%	58	53 ± 7%	.0180
≥8	24	23 ± 9%	13	55 ± 15%	.0627
Depth of invasion					
T1	9	63 ± 16%	14	86 ± 9%	.3200
T2	21	67 ± 10%	30	58 ± 10%	.7019
T3	87	23 ± 5%	57	48 ± 7%	.0019
T4	9	0[c]	8	17 ± 15%	.4758
No. of positive lymph nodes					
1–6	42	53 ± 8%	90	60 ± 5%	.6679
7–15	39	26 ± 7%	16	23 ± 12%	.6831
>15	45	16 ± 5%	3	0[d]	.0245
Type of gastrectomy					
Subtotal	55	40 ± 7%	47	67 ± 7%	.0043
Total	71	26 ± 5%	62	43 ± 7%	.0214

[a] Kaplan-Meier method.
[b] Mantel-Cox test.
[c] 2-year survival: 12 ± 11%.
[d] 1-year survival: 33% ± 27%.

esophageal surgery with an appropriate learning curve for the Japanese-style method; indeed, the complications reported in the specialized centers were overlapping with or slightly higher than those reported by the Japanese authors.[2,5–7,13,14]

The results of our study (17% morbidity and 2% mortality), which was performed in centers with proven experience in this type of surgery, confirm this point of view. Furthermore, we strongly believe that it is particularly important to limit the use of splenopancreatic resection to only selected cases, when splenic or pancreatic infiltration is present or when lymph node station 10 or 11 is macroscopically involved. Splenopancreatic resection, besides not providing a proven benefit in terms of survival, considerably increases postoperative complications.[9,15,16]

The presence of lymph node metastases in second level stations (7-12) has been reported by various authors, both Western[5] and Eastern,[17,18] who mapped each lymph node station on the resected specimen. Mapping of the resected stomach and subsequent classification of the lymph node stations according to the criteria described by the Japanese Research Society for Gastric Cancer are essential to perform this type of study. The evaluation of long-term survival in patients with second level lymph node metastases, which would not have been removed with a limited lymphadenectomy, is an indirect method to assess the potential benefits of D2 lymphadenectomy.[5,18]

In this study, the incidence of lymph node metastases in stations 7 to 12 represented approximately 28% of the extended lymphadenectomies performed. The stations surrounding the celiac trunk were the most frequently involved, as reported in Table 2. The presence of metastases to second level lymph nodes indicates disease progression, and not removing the lymph node stations would yield inadequate oncological radicality. The residual tumor variable is one of the most important prognostic factors in patients undergoing surgery for gastric

cancer, and after R1 and R2 resections, 5-year survival rates do not exceed 5%, with a median survival time of 5 to 10 months.[6,19] In our group of patients with involvement of second level lymph nodes, the 5-year survival rate was 32%, which is in accordance with the reports of other authors.[5,18] If these patients had undergone a simple D1 lymphadenectomy, even if we cannot be certain that the tumor would have recurred, it is highly probable that a tumor residual in the lymph nodes would be present after "curative" surgery. As a consequence, one effect of extended lymphadenectomy was to increase surgical radicality in 28% of our patients. On the basis of our data, and in accordance with the method suggested by other authors, we can estimate a survival benefit associated with D2 lymphadenectomy of approximately 9% (value calculated by multiplying the incidence of cases with metastases in N2 stations by survival, i.e., 28% × 32%).[5,18] Performing an extended lymphadenectomy has furthermore been suggested to yield a survival benefit even in N0 and N1 cases;[5,18,20] as such, the overall benefit of extended lymphadenectomy in patients with gastric carcinoma should be considered greater.

The 5-year survival rate of our patients with involvement of second level lymph nodes was significantly lower when compared with patients with involvement of first level nodes submitted to extended lymphadenectomy (32% vs. 54%). However, this difference disappeared when survival was compared by stratifying for the number of positive lymph nodes; furthermore, multivariate analysis confirmed the number rather than the level of involved nodes as an independent predictor of poor prognosis. These results indicate that the removal of metastatic lymph nodes is associated with a good probability of long-term survival when few lymph nodes are involved, independent of their location in the first or second level; consequently, these results are indicative of the potential curability of these cases, thus supporting the application of an extended lymphadenectomy. These data furthermore confirm the validity of the new Union Internationale Contre le Cancer—tumor, node, metastasis staging system,[12] which classifies the nodal parameter on the basis of the number of positive lymph nodes, rather than on the location of involved nodes, as also reported by other authors.[21,22]

Evaluation of prognostic variables revealed that the 5-year survival rate clearly decreases from T1 and T2 cases to neoplasms with involvement of the serosa. This emphasizes the necessity of an extended lymphadenectomy in neoplasms limited to the gastric wall, where it is more possible to perform potentially curative surgery. Infiltration of the gastric serosa reduces the impact of a radical operation on long-term survival. Some authors have achieved a significant improvement in survival in advanced cases by using intraperitoneal perfusion of antiblastic drugs in normothermia and hyperthermia as an adjuvant to surgery.[23–25] The use of these advanced methods will help improve the results of lymphadenectomy in cancer patients with microscopic peritoneal spreading.

In conclusion, the results of this study indicate that extended lymphadenectomy is a procedure associated with low rates of complications if performed in specialized centers. The incidence of metastases in second level lymph node groups, which are removed with this technique, is considerable, and even in patients presenting rather advanced neoplasias, it is possible to achieve oncological radicality with good long-term survival.

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