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Lymphadenectomy for Gastric Cancer in Clinical Trials: Update

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Abstract. The controversy over the value of extended lymph node dissection for treatment of gastric cancer is fiercely debated. Whereas Japanese surgeons claim that the superior survival rates in their series are due to extensive resection (D2 resection), many Western authorities believe that their results only reflect differences in the prevalence of prognostic factors, inconsistencies between Japanese and Western staging systems, and the phenomenon of "stage migration," which occurs with extensive resection. Two small randomized prospective trials from Hong Kong and Cape Town showed a tendency toward high morbidity with extensive lymph node dissection but no survival benefit. In contrast, the recently completed prospective German Gastric Carcinoma Study demonstrated a clear survival advantage with D2 resection for tumor stages II and IIIa with no increase in perioperative morbidity or mortality. The long-term results of the still ongoing randomized MRC and Dutch trials are therefore eagerly awaited.

In the Western world the overall prognosis of patients with gastric cancer is poor, with a 20% overall 5-year survival rate. For resected patients the 5-year survival rate increases only marginally to about 30% [1–3]. This dismal prognosis and, more important, the absence of any substantial prognostic improvement over the last decades has puzzled researchers. In contrast to the grim outlook for patients with gastric carcinoma in the Western hemisphere, excellent results have been reported with overall 5-year survival rates of up to 50% in Japanese series [4, 5]. They claim that, apart from early detection, gastric resection with extended lymphadenectomy markedly contributes to these results has generated worldwide controversy over the value of an extended resection for gastric cancer treatment.

In general, complete tumor removal with adequate margins of clearance in the area of the primary tumor *and* its lymphatic drainage is the aim of such a radical resection. This technique extends the UICC definition of a so-called R0 resection to the area of lymphatic drainage [6]. Because of the superior Japanese results, an extended resection is now recommended as standard treatment by the Japanese Research Society for the Study of Gastric Cancer (JRSGC) [7]. In most Western countries, however, lymph nodes are still regarded as indicators rather than governors of disease. According to this philosophy, extended resection and lymph node dissection merely improve the accuracy of tumor staging. This view is supported by the lack of prospective randomized trials showing a beneficial effect of extended resection and reports of increased morbidity and mortality with this approach.

Several prospective trials analyzing the role of extended lymphadenectomy for gastric cancer treatment have recently been completed, and more are still ongoing. An understanding of the lymphatic drainage of the stomach, the extent of standard and radical lymph node dissection, the role of lymph node metastases as a prognostic factor, and the different staging systems used are a prerequisite for an analysis of these trials.

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Classification of Lymph Node Dissection

Lymph node studies in Japan during the 1950s and 1960s revealed pathways of lymphatic drainage related to the location of the primary tumor within the stomach. These anatomic and pathologic studies allowed identification of different locations of lymph nodes in different so-called lymph node stations. Initially it was thought that lymphatic spread was sequential, but it is now well established that in some cases metastases to more distant lymph nodes can occur without evidence of involvement of perigastric nodes (i.e., skipping of lymph node stations). This situation is rare, however, and was observed in only 1.3% of patients undergoing systematic lymph node dissection in a detailed analysis from Erlangen, Germany [8].

According to the rules of the JRSGC, the gastric lymph node stations are numbered from 1 to 16 (Fig. 1) and subsequently grouped into four lymph node levels, designated N1 to N4 or compartments 1 to 4 [7]. The grouping of stations into levels depends on the location of the primary tumor (Table 1). By convention, N1 and N2 are considered regional lymph node levels, whereas involvement of N3 and N4 level lymph nodes are regarded distant metastases.

A standard gastrectomy with removal of the fatty tissue adherent to the stomach (greater and lesser omenta) includes all lymph nodes of the first level (N1). This operation reflects the so-called

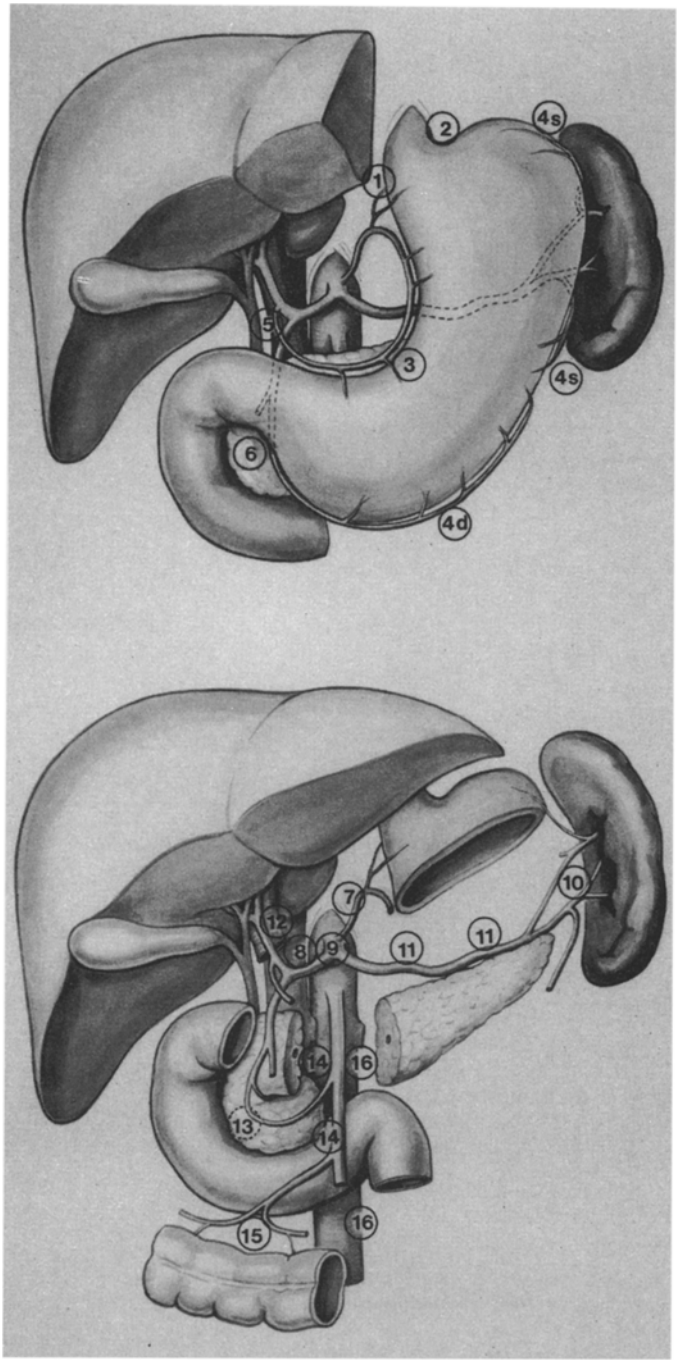

Fig. 1. Lymph node locations according to the JRSGC. 1: right cardial; 2: left cardial; 3: along the lesser curvature; 4: along the greater curvature: (s) left gastroepiploic artery, (d) right gastroepiploic artery; 5: suprapyloric; 6: infrapyloric; 7: along the left gastric artery; 8: along the common hepatic artery; 9: around the celiac axis; 10: at the hilus of the spleen; 11: along the splenic artery; 12: in the hepatoduodenal ligament; 13: retropancreatic; 14: at the root of the mesentery; 15: in the transverse mesocolon; 16: para-aortic.

D1 resection. A more extensive surgical procedure is required (i.e., the so-called D2 resection [7]) to remove all lymph nodes of the second level (N2) along the main arteries of the celiac trunk, in the splenic hilus, and at the pancreatic tail.

Table 1. Grouping of lymph node locations according to the JRSGC.

	No., by tumor site			
Group[a]	CMA	A,AM	M,MA,MC	C,CM
1 (N1)	1	3	1	1
	2	4	3	2
	3	5	4	3
	4	6	5	4
	5	6	6	
2 (N2)	7	7	2[b]	5[b]
	8	8	7	6[b]
	9	9	8	7
	10	1	9	8
	11	10[b]	9	
	11	10	11	
3 (N3)	12	2[b]	12	12
	13	10[b]	13	13
	14	11	14	14
	12	13	14	

A: lower third; M: middle third; C: upper third. Combinations extend to more than one-third of the stomach.

[a]Group 4 (N4) Comprises more distant node groups, including the transverse mesocolon, paraaortic, and perirenal nodes.

[b]Dissection is optional.

Table 2. Independent prognostic factors in gastric carcinoma on multivariate analyses in the literature.

Prognostic factor	Studies that show an independent prognostic effect (refs.)
Factors that may be influenced by the extent of resection	
Residual tumor after resection	[9, 10, 11]
Lymph node dissection	[2, 11–13]
No. of resected nodes (lymph node ratio)	[9, 10, 11, 13]
Factors that are given at the time of resection and cannot be influenced by the extent of surgery	
Nodal status	[9, 11, 12, 14, 15]
Depth of tumor invasion	[9–15]
Borrmann classification	[12, 14]
Tumor diameter	[9, 11, 12]
Tumor grading	[13]
Sex	[14]

Lymph Node Dissection as Prognostic Factor

Complete macroscopic and microscopic tumor removal and lymph node dissection are identified as independent predictors of survival in most studies assessing prognostic factors in patients with gastric cancer. The number of resected nodes and the so-called lymph node ratio (i.e., the ratio between the number of positive and removed nodes) are additional independent prognostic factors in some studies (Table 2). Thus the extent of the surgical procedure may improve survival by achieving complete tumor removal in the area of the primary tumor and its lymphatic drainage, increasing the number of removed lymph nodes and thus reducing the lymph node ratio. It suggests that the extensive resection performed in Japanese series is responsible for their superior survival rates.

In addition to procedure-related factors, several other indepen-

Table 3. Incidence of prognostic variables in patients with gastric cancer undergoing resection at three institutions.

Parameter	NCC	GGCS	UHL
No. of patients	1391	1654	129
Mean age (years)	58.8	62.5	62.1
Sex ratio (F/M)	1.0:2.0	1.0:1.7	1.0:2.5
Tumor diameter (cm)	6.5	6.4	6.1
Main location			
Proximal third	331 (24%)	496 (30%)	58 (44%)
Middle third	536 (39%)	643 (39%)	34 (26%)
Distal third	523 (37%)	435 (26%)	35 (26%)
Lymph node involvement			
pN(−)	420 (30%)	536 (32%)	54 (42%)
pN(+)	971 (70%)	1118 (68%)	74 (58%)
Depth of invasion[a]			
pT2	534 (38%)	605 (44%)[b]	74 (57%)
pT3	688 (50%)	639 (46%)[b]	50 (39%)
pT4	169 (12%)	131 (10%)[b]	5 (4%)
Histologic tumor type (Lauren)			
Intestinal	594 (43%)	858 (52%)	70 (54%)
Other	794 (57%)	796 (48%)	59 (46%)

NCC: National Cancer Center, Tokyo, Japan; GGSC: German Gastric Carcinoma Study, Germany; UHL: University Hospital Leiden.
[a]pT tumors are excluded.
[b]Based only on pT2, pT3, and pT4 cases (n = 1375)

Table 4. Grouping of patients of the NCC into the stages of the old and the new TNM systems and the JRSGC system.

Stage	Old TNM	New TNM	JRSGC
I	T1N0M0	T1/T2N0M0 T1N1M0	T1/T2N0M0
II	T2/T3N0M0	T1N2M0 T2N1M0 T3N0M0	T1/T2N1M0
III	T1N1/N2M0 T2N1/N2M0 T3N1/N2M0 T1-3N3M0(cur) T4N*M0(cur)	T2N2M0 T3N1/N2M0 T4N0/N1M0	T1/T2N2M0 T3*s*1 N2M0 T3*s*2 N*M0
IV	T1-3N3M0(non cur) T4N*M0(non cur) T*N*M1	T4N2M0 T*N*M1	T4N*M0 T*N*M1

*: any; (non) cur: (not) resectable for cure.

dent predictors of survival are in existence at the time of the resection and cannot be influenced by the extent of the surgical procedure (Table 2). Differences in the prevalence of these prognostic factors may also account for the survival differences between Eastern and Western series independent of the extent of resection. A comparison of the incidence of these prognostic factors in the population treated at the National Cancer Center in Tokyo and the populations of the German and Dutch Gastric Cancer Trials, however, shows that factors associated with a poor prognosis are more common in the Japanese population than in the populations in European multicenter trials (Table 3). Differences in the distribution of tumor- or patient-dependent prognostic factors therefore do not explain the superior survival reported in Japanese series.

Comparison of Staging Systems

The use of different staging systems could invalidate international comparisons of survival reports by precluding a true stage-to-stage comparison of groups. To assess whether this point contributes to the survival differences between Japanese and Western series, 1085 patients operated between 1976 and 1981 at the National Cancer Center (NCC) in Tokyo were reviewed. All patients underwent a resection for cure with histologic examination of all lymph nodes of groups 1 and 2 according to the JRSGC. The tumors of these patients were classified according to the pathologic findings (pT and pN) and subsequently grouped by the three commonly used staging systems: the old TNM system [16], the new TNM system [6], and the rules of the JRSGC [7] (Table 4). The stages were designated I, II, III, and IV, omitting the subdivisions IA, IB, IIIA, and IIIB. The survival curves were plotted using the life table method and were compared by employing the log rank method.

A comparison of the survival curves of the various staging systems revealed only a small but significant difference between the old and the new TNM systems for stage II tumors ($p < 0.01$). There were no statistical differences between the staging systems for any of the other tumor stages (Fig. 2). A major difference between the Western staging systems (TNM) and the Japanese system (JRSGC) could thus not be substantiated. The only difference between the old and new versions of UICC's TNM system is not sufficient to explain the observed divergence in overall survival rates between Japan and the West [17].

Clinical Trials Assessing Lymph Node Dissection for Gastric Cancer

Cape Town Trial

In a prospective randomized trial at the Groote Schuur Hospital in Cape Town, South Africa, D1 gastrectomy was compared to D2 gastrectomy in patients with localized and potentially curable gastric cancer [18]. Of more than 400 evaluated patients, only 43 were included in the trial: 22 patients had a D1 gastrectomy, and 21 had a D2 resection. After a median follow-up of 3.1 years there was no significant difference in survival between these small groups of patients. D2 resection was, however, associated with a higher morbidity, larger blood transfusion requirement, and a longer hospital stay.

Hong Kong Trial

In a randomized prospective trial from the Prince of Wales Hospital in Hong Kong, 55 patients with antral cancer were randomized to undergo either a standard D1 subtotal gastrectomy or an extensive D3 total gastrectomy [19]. In this small group of patients extended surgery (D3 resection) was associated with a larger transfusion requirement and longer hospital stay compared to D1 subtotal gastrectomy. Extensive resection also resulted in a higher rate of postoperative septic complications mostly due to fistulas from the pancreatic resection. On univariate analysis overall survival was longer in those patients who had the less extensive procedure (i.e., D1 resection). Multivariate analysis, however, showed that after correction for blood transfusion there was no survival difference between the standard and extensive resections in this small group of patients with antral carcinoma.

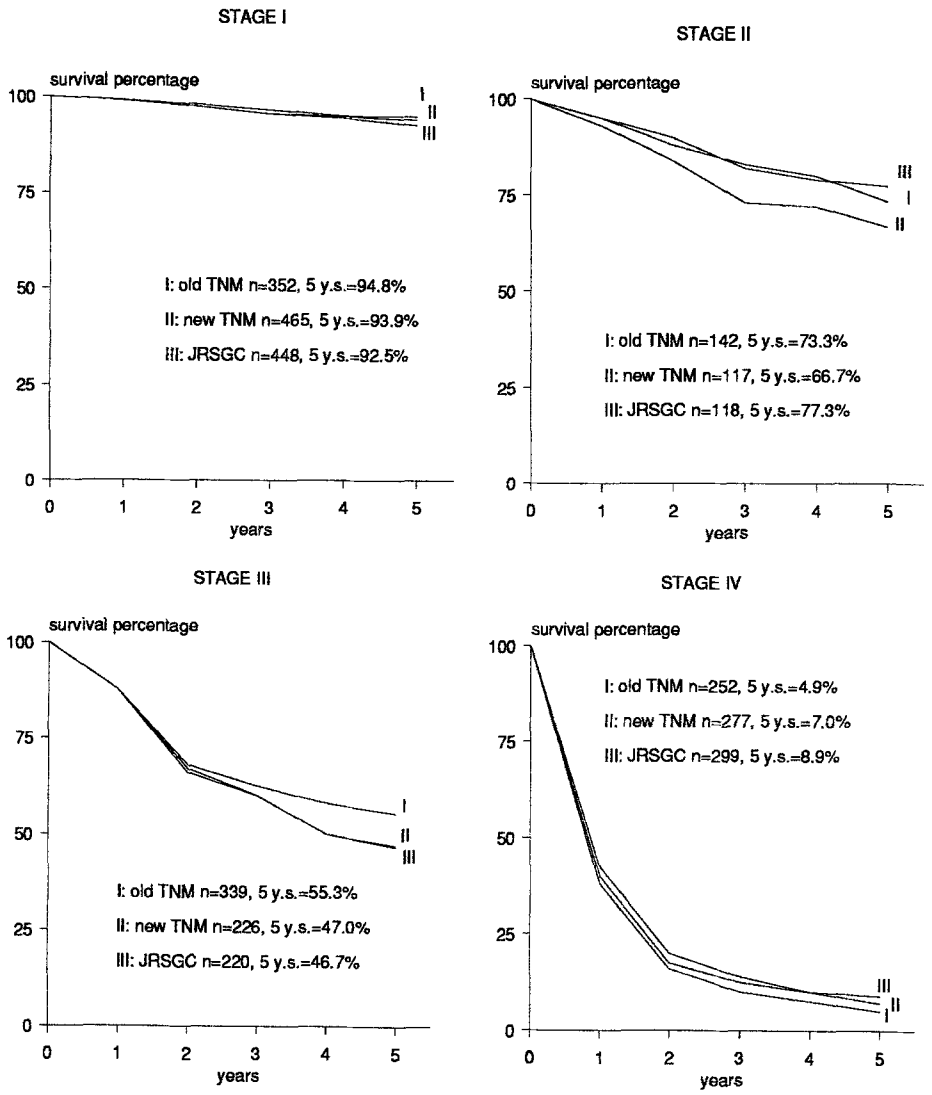

Fig. 2. Survival curves by stages of different grouping systems, using 1085 primary gastric cancer patients operated on in the NCC. The curves present observed survival excluding surgical mortality. I: old TNM; II: new TNM (4th ed.); III: Japanese rules (JRSGC). Reprinted with permission [20].

German Gastric Carcinoma Study 1992

In the German Gastric Carcinoma Study, epidemiologic data, details of the surgical procedure, histopathologic parameters, and follow-up of all patients with gastric carcinoma seen at one of 19 participating surgical university hospitals were documented prospectively [9, 20]. Over the study period (1986–1989) 1999 patients with gastric carcinoma were eligible for evaluation; 1654 patients underwent resection, accounting for a resection rate of 82.7%.

Lymph node dissection was demonstrated and taught to all participating centers according to the recommendations of the JRSGC. An en bloc resection with dissection of N1 and N2 lymph nodes or compartments I and II was recommended as the surgical procedure of choice. Although all surgeons principally agreed to perform a lymph node dissection of compartments I *and* II, a lymph node dissection of only compartment I was performed as the standard procedure in some of the participating centers. This problem was objectively demonstrated by careful assessment of the removed lymph nodes.

Although the study was not a strict, randomized comparison of D1 versus D2 resection, this situation allowed objective comparison of more extensive and less extensive lymph node dissections in patients with gastric carcinoma. The histopathologic examination, not the description by the surgeon, was used to classify the resection as a standard or an extended procedure. The histopathologic evaluation by the pathologist thus served as a quality control of the extent of the lymph node dissection and the basis for the classification. Each surgeon was allowed to performed the procedure he or she preferred and was most comfortable with.

Based on anatomic and histopathologic investigations, extirpation of more than 25 lymph nodes was defined as a radical lymph node dissection and removal of fewer than 25 lymph nodes was defined as a standard lymph node dissection. Of the 1654 resected patients 558 had a standard dissection and 1096 patients had a radical lymph node dissection. The distribution of the demographic data and the UICC tumor stages did not differ between patients who had a standard and those who had a radical lymph node dissection. The prevalence of lymph node metastases was not dependent on the number of removed lymph nodes provided 15 or more nodes were removed. Because the average number of

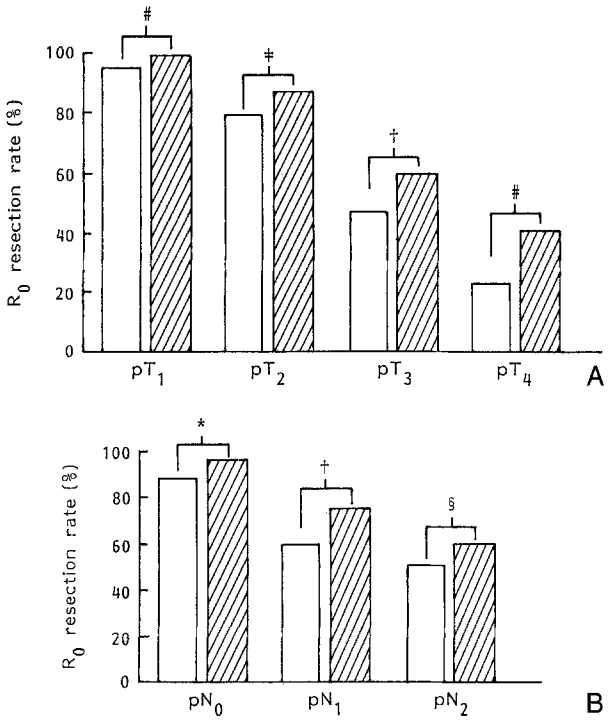

Fig. 3. Frequency of R0 resections in patients with standard and radical lymphadenectomy in relation to pT category (**A**) and pN category (**B**). Reprinted with permission [20].

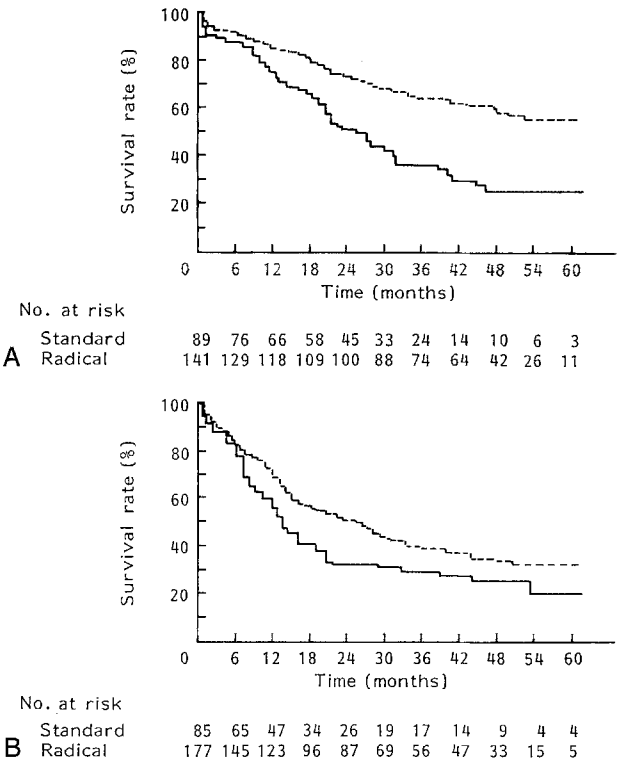

Fig. 4. Survival probability for patients with UICC stages II (**A**) and IIIA (**B**): standard lymph node dissection versus radical lymph node dissection. Reprinted with permission [20].

removed lymph nodes by far exceeded 15 nodes in each center, stage migration can thus be excluded as a reason for the observed differences in survival between standard and extended lymph node dissection.

When analyzed according to the UICC pT and UICC pN categories, radical lymph node dissection significantly increased the rate of UICC R0 resections in patients with pT2, pT3, or pT4 tumors and patients with pN0, pN1, and pN2 lymph node status (Fig. 3). On multivariate analysis radical lymph node dissection had an independent prognostic impact on survival in patients with UICC tumor stages II and IIIA (Fig. 4). Radical lymph node dissection had no statistical survival advantage over standard lymph node dissection in patients with UICC tumor stages IA or IB and for patients with pN2 lymph node status or distant metastases (i.e., UICC stages IIIB and IV). There was no difference in morbidity and mortality between the two procedures (Table 5).

Table 5. Morbidity and mortality of radical and standard lymph node dissection in the German Gastric Carcinoma Study.

Morbidity/mortality	Standard lymph node dissection (n = 558) (%)	Extended lymph node dissection (n = 1096) (%)
Anastomotic leakage	8.2	8.0
Bleeding	1.8	1.9
Wound infection	3.9	3.8
Abscess	3.2	4.7
Cardiopulmonary complication	9.5	9.3
Other complications	2.3	2.7
30-Day mortality	5.2	5.0

Dutch Gastric Cancer Trial

The Dutch Gastric Cancer Trial was initiated to evaluate whether the documented benefit of D2 over D1 resection in Japanese series represents a true survival advantage and not just an improvement in pathologic classification [21, 22]. To achieve this goal a collaborative research program was started between the Leiden University Hospital in The Netherlands and the NCC Hospital in Tokyo.

From September 1990 until July 1993, a total of 1078 patients were recruited of whom 996 (92%) were eligible for analysis. Of these patients 711 (71%) were operated on with curative intent, and 285 (29%) underwent a noncurative procedure. Procedures were performed in 33 hospitals by more than 70 surgeons. Extensive quality control was implemented to achieve standardization of surgical procedures. Although complete survival analysis could not be expected before 1995, details of quality control within this trial are worth discussion.

At the beginning of the trial, few Dutch surgeons were familiar with the D2 resection. Therefore a Japanese surgeon experienced in the treatment of gastric cancer was invited to The Netherlands. He attended all operations and performed most of the D2 resections during the initial months and instructed the coordinator and eight consulting surgeons, who continued the supervision of D2 resections in their assigned regions after the instruction period. Although gastrectomy with limited lymph node dissection was routinely performed in The Netherlands, variations in surgical technique and extent of lymphadenectomy were apparent in daily

practice, and D1 resection according to the rules of the JRSGC was therefore introduced as the standard procedure in the control arm.

To prevent misunderstanding of the complex surgicopathologic techniques involved with lymphadenectomy according to the Japanese criteria, the original definitions of the JRSGC were introduced as the gold standard. Although these definitions seemed unambiguous, deviations were noted in the course of the trial.

To qualify these deviations, two parameters were introduced: *noncompliance* (no proof of lymph nodes of indicated stations at pathologic examination) and *contamination* (detection of lymph nodes at pathologic examination that belonged to stations that were not indicated for that particular dissection). Noncompliance of at least one station occurred in 84% of the D1 and D2 dissections, whereas contamination of at least one station occurred in 48% of the D1 and in 52% of the D2 procedures. Contamination in D1 and noncompliance in D2 carry the risk of minimizing the distinction between these dissections and subsequently underestimating a possible beneficial effect of D2 dissection.

An interim analysis of the morbidity and mortality associated with the D1 or D2 resection shows a rather high rate of complications in patients who had extensive resections and a substantial postoperative mortality in peripheral hospitals. The high complication rate probably reflects the large number of surgeons performing the resections without adequate training. Whereas these complications could be managed in experienced centers without an increase in mortality, the limited resources and know-how for dealing with postoperative complications may have contributed to the higher mortality in peripheral hospitals.

MRC Trial

In 1986 a randomized controlled trial was initiated in Great Britain by the Medical Research Council (MRC) to identify patients who would benefit from a D2 rather than a D1 resection. The trial was designed to study D1 versus D2 gastrectomy in patients with stage I and II disease. Morbidity, mortality, long-term survival, cause of death, local cancer recurrence, and systemic metastases were chosen as endpoints. All participating centers agreed to the definitions of a D1 and D2 resection proposed by the JRSGC.

A total of 725 patients were registered, but only 390 patients were randomized after intraoperative staging. A D1 resection was performed in 192 patients and a D2 resection in 198 patients. Long-term survival data are not yet available, and pathologic assessment of the removed specimen is so far incomplete.

Although no final statistical analysis is yet available, surgically related complications such as infection and anastomotic leakage and the total number of complications (which includes cardiorespiratory problems and pulmonary emboli) were more frequent in the D2 resection group. These complications contributed to a higher mortality rate after D2 resection. Serious complications were more common after total gastrectomy than after a subtotal gastrectomy independent of a D1 or D2 resection. Distal pancreatectomy doubled the morbidity and increased the mortality in the D2 arm. Although the incidence of serious postoperative complications appeared to decrease as the participating surgeons gained more experience, there was no concomitant decrease in the mortality rate as the study matured.

Median survival time in the entire population is in the order of 30 months. Because of the short follow-up a potential beneficial effect of extended lymphadenectomy on locoregional recurrences and long-term survival cannot yet be assessed.

Conclusion

The controversy over the value of extended lymph node dissection for treatment of gastric cancer patients is fiercely debated. Proponents, mostly in the Eastern world, believe that locoregional tumor spread is the limiting factor for survival. They regard the improvements in survival rates observed after the introduction of the D2 resection as sufficient evidence to accept this technique as standard procedure. Critics, however, believe that benefits attributed to extended lymphadenectomy in Japanese studies merely result from differences in patient- and tumor-related selection criteria or upstaging of tumors with extensive lymph node dissection (i.e., so-called stage migration).

A comparison of the prevalence of patient- and tumor-dependent prognostic factors in large Eastern and Western series shows some imbalances of the prognostic factors between patients with advanced gastric cancer in Japanese and Western series (Table 3) [17]. This imbalance, however, does not explain the observed differences in long-term survival rates, as the Japanese patients generally had worse prognostic features than patients in the German or Dutch Gastric Carcinoma study.

Variability in the extent of lymphadenectomy and the number of lymph nodes examined per N level may affect nodal staging by inducing stage migration, a situation also known as the Will Rogers phenomenon [23]. This phenomenon consists of the migration of patients to a more advanced tumor stage by demonstrating lymph node metastases that remain unidentified with conventional surgical treatment. Because the prognosis of those who migrated, although worse than that for other members of the "good-stage group," is better than for members of the "bad-stage group," survival rates rise in each group with no change in individual outcomes. Thus stage migration may influence stage-specific survival rates and explain some of the beneficial effect observed with extended lymphadenectomy. The German Gastric Carcinoma Study, however, shows that the prevalence of patients with lymph node metastases does not depend on the number of removed lymph nodes provided 15 or more nodes were removed. In addition, the distribution of tumor stages in this study did not differ between those who underwent a standard dissection and those who had an extensive lymph node dissection. This finding suggests that stage migration plays a rather small role if more than 15 nodes are removed in each of the assessed groups of patients.

Because no single institution sees enough patients within a reasonable period, multicenter trials such as the still ongoing MRC and Dutch trials are essential. Such trials, however, are usually associated with inconsistencies, which is clearly shown in the Dutch and German trials. There was a clear tendency to perform intermediate-type dissections and to retrieve insufficient numbers of lymph nodes in both trials. This point underlines the crucial need for standardization and quality control when assessing the role of lymphadenectomy. A meticulous evaluation of the removed lymph nodes should be used as an objective quality control of the extent of lymph node dissection performed.

The available trials show that an extension of lymphadenectomy is not without risk. In the trials from Cape Town and Hong Kong, complication rates, hospital stay, and blood transfusion requirements

were higher after extensive resection than after a conventional D1 resection [18, 19]. Preliminary results from the prospective Dutch and MRC trials indicate a similar trend. Of note is that these centers have not been routinely performing extended dissections and so required special training. In contrast, morbidity and mortality rates are similar with standard and extensive lymph node dissection in centers with experience in extensive resection (i.e., the German Gastric Carcinoma Study [20], Memorial Sloan Kettering Cancer Center in New York [13], and the NCC in Tokyo [4]). The experience and training of the surgeon and his or her personal attitude toward lymph node dissection may therefore be a major factor influencing the morbidity associated with the procedure.

A final point is that the extent of lymph node dissection may have to be guided by the location of the primary tumor. Clearly, lymphatic drainage of tumors of the cardia is different from the lymphatic drainage of antral carcinoma. The concept of a tailored lymphadenectomy for gastric carcinoma is only now emerging but should be considered when planning new trials.

Résumé

La controverse concernant le curage ganglionnaire étendu dans le traitement du cancer gastrique est vivement débattue. Alors que les chirurgiens japonais clament que la survie est améliorée justement à cause de l'étendue de la résection (dite D2), beaucoup d'experts de l'Occident croient que cette apparente supériorité reflète seulement la différence dans la prévalence des facteurs pronostiques, les différences des systèmes de classification entre l'Occident et l'Orient ainsi que le phénomène de <<migration de stade>> qui est une conséquence des résections étendues. Deux essais randomisés provenant de Hong Kong et du Cap ont démonté une tendance vers une morbidité élevée en cas de dissection plus poussée mais sans supériorité de survie. En contraste, l'étude prospective allemande nommée <<German Gastric Carinoma Study>> a démontré une nette amélioration de survie par la résection D2 pour les tumeurs de stade II et IIIa sans augmentation de la morbidité ou de la mortalité périopératoires. Les résultats à long terme d'autres essais randomisés, toujours en cours, des groupes MRC et Hollandais, sont attendus avec impatience.

Resumen

La controversia sobre el valor de la disección ganglionar radical en el tratamiento del cáncer gástrico es motivo de fiero debate. En tanto que los cirujanos japoneses proclaman que sus mejores tasas de sobrevida se deben a la resección radical (resección D-2), muchas autoridades de Occidente creen que ello sólo refleja diferencias en la prevalencia de factores de pronóstico, inconsistencias entre los sistemas de estadificación del Japón y de Occidente y el fenómeno de la "migración del estadío" que se observa con las resecciones más extensas. Dos pequeños ensayos clínicos prospectivos y randomizados provenientes de Hong Kong y de la Ciudad del Cabo han demostrado una tendencia hacia una más alta morbilidad con la disección radical y ningún beneficio en cuanto a sobrevida. En contraste, el reciente Estudio Prospectivo Alemán sobre cáncer gástrico demostró clara ventaja con la resección D-2 para los estados II y IIIa sin incremento de la morbilidad y la mortalidad perioperatorias. Los resultados a largo plazo del estudio randomizado MRC y del estudio holandés, que están en progreso, son esperados con gran expectativa.

Acknowledgments

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References

1. Allum, W.H., Powell, D.J., McConkey, C.C., et al.: Gastric cancer: a 25-year review. Br. J. Surg. *76*:535, 1989
2. Akoh, J.A., MacIntyre, I.M.C.: Improving survival in gastric cancer: review of 5-year survival rates in English language publications from 1970. Br. J. Surg. *79*:293, 1992
3. Wanebo, H.J., Kennedy, B.J., Chmiel, J., Steele, G., Winchester, D., Osteen, R.: Cancer of the stomach: a patient care study by the American College of Surgeons. Ann. Surg. *218*:583, 1993
4. Maruyama, K., Okabayashi, K., Kinoshita, T.: Progress in gastric cancer surgery and its limits of radicality. World J. Surg. *11*:418, 1987
5. Nakamura, K., Ueyama, T., Yao, T., Xuan, Z.X., Ambe, K., Adachi, Y.: Pathology and prognosis of gastric carcinoma: findings in 10,000 patients who underwent primary gastrectomy. Cancer *70*:1030, 1992
6. UICC: TNM Classification of Malignant Tumours (4th ed.), P. Hermanek, L.H. Sobin, editors. Berlin, Springer, 1987
7. Kajitani, T., Japanese Research Society for the Study of Gastric Cancer: The general rules for gastric cancer study in surgery and pathology. Jpn. J. Surg. *11*:127, 1981
8. Gall, F.P., Hermanek, P.: Die systematische erweiterte Lymphkontendissektion in der kurative Therapie des Magenkarzinoms. Chirurg *64*:1024, 1993
9. Roder, J.D., Böttcher, K., Siewert, J.R., et al.: Prognostic factors in gastric carcinoma. Cancer *72*:2089, 1993
10. Jaehne, J., Meyer, H.J., Maschek, H., Geerlings, H., Bruns, E., Pichlmayer, R.: Lymphadeenctomy in gastric carcinoma: a prospective and prognostic study. Arch. Surg. *127*:290, 1992
11. Böttcher, K., Becker, K., Busch, R., Roder, J.D., Siewert, J.R.: Prognosefaktoren beim Magenkarzinom: Ergebnisse einer uni-und multivariaten Analyse. Chirurg *63*:656, 1992
12. Maruyama, K.: The most important prognostic factors for gastric cancer patients: a study using univariate and multivariate analyses. Scand. J. Gastroenterol. *22*:63, 1987
13. Shiu, M.H., Moore, E., Sanders, M., Huvos, A., Freedman, B., Goodbold, J.: Influence of the extent of resection on survival after curative treatment of gastric carcinoma. Arch. Surg. *122*:1347, 1987
14. Baba, H., Korenaga, D., Okamura, T., Saito, A., Sugimachi, K.: Prognostic factors in gastric cancer with serosal invasion: univariate and multivariate analysis. Arch. Surg. *124*:1061, 1989
15. Bozzetti, F., Bonfanti, G., Morabito, A., Bufalino, R., Menotti, V., Andreola, S.: A multifactorial approach for the prognosis of patients with carcinoma of the stomach after curative resection. Surg. Gynecol. Obstet. *162*:229, 1986
16. UICC: TNM Classification of Malignant Tumours (3rd ed.), M. Harmer, editor. UICC, Geneva, 1978
17. Bonenkamp, J.J., van de Velde, C.J.H., Kampschöer, G.H.M., et al.: A comparison of factors influencing the prognosis of Japanese and Western gastric cancer patients. World J. Surg. *17*:410, 1993
18. Dent, D.M., Madden, M.V., Price, S.K.: Randomized comparison of R1 and R2 gastrectomy for gastric cancer. Br. J. Surg. *75*:110, 1988
19. Robertson, C.S., Chung, S.C.S., Woods, S.D.S., et al.: A prospective randomized trial comparing R1 subtotal gastrectomy with R3 total gastrectomy for antral cancer. Ann. Surg. *220*:176, 1994
20. Siewert, J.R., Roder, J.D., Böttcher, K., Busch, R., Hermanek, P., Meyer, H.J.: Prognostic relevance of systematic lymph node dissection in gastric carcinoma. Br. J. Surg. *80*:1015, 1993
21. Bonenkamp, J.J., van de Velde, C.J.H., Sasako, M., Hermans, J.: R2 compared with R1 resection for gastric cancer: morbidity and mortality in a prospectice, randomised trial. Eur. J. Surg. *158*:413, 1992
22. Sasako, M., Maruyama, K., Kinoshita, T., et al.: Quality control in a

multicenter, prospective randomized controlled study on the surgical treatment of gastric cancer. Jpn. J. Clin. Oncol. *22*:41, 1992
23. Feinstein, A.R., Sosin, D.M., Wells, C.K.: The Will Rogers phenomenon: stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. N. Engl. J. Med. *312*:1604, 1985

Invited Commentary

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The place of lymphadenectomy for surgical treatment of gastric cancer has not yet been determined. Despite several ongoing trials—prospective and retrospective—an interim balance appears warranted.

The Japanese results regarding the prognostic value of lymphadenectomy are convincing [1]. Despite epidemiologic differences [2] and different staging systems, the prognostic differences in patterns with tumor stages II and III between Japanese and Western studies remain a fact. Lymphadenectomy is the most attractive explanation for this phenomenon. In addition, early postoperative administration of cytotoxic agents (e.g., mitomycin) is a parameter that differs between Japanese and Western series and should be drawn into our considerations.

The German trial describes precisely the group of patients who benefit from lymphadenectomy: those with lymph node metastasis at an early stage (N0 and N1) [3]. In this group of patients lymphadenectomy extends tumor resection to the area of lymphatic drainage and includes an adequate safety margin. Based on these data lymphadenectomy can be seen as a reasonable way to achieve local tumor resection rather than thinking of it as an independent therapeutic principle.

The independent prognostic factor "lymph node ratio" (i.e., the ratio between the number of excised and involved lymph nodes) allows calculation of the extent of the safety margin [4]. The number of removed lymph nodes should exceed the number of involved lymph nodes by a factor of 4. Why is that? More sophisticated analyses of excised lymph nodes have shown a high number of so-called micrometastases in the apparently tumor-free lymph nodes.

These data agree perfectly with the finding that the prognosis of gastric cancer is correlated with the absolute number of involved lymph nodes. If more than seven or eight lymph nodes are involved, the prognosis is dismal [5–7]. Keeping in mind that after an adequate D2 lymph node dissection the specimen includes 35 to 40 lymph nodes, it becomes clear that the lymph node ratio of 0.2 is an important landmark.

About 25% to 30% of all patients with gastric cancer in Germany belong to the group with early lymph node metastasis [3]. The prognostic benefit is 20% to 25% in these groups. The prognostic benefit for all patients with gastric cancer can be calculated to be approximately 5%, which is the expected prognostic difference. This figure must be the basis for calculating the minimal size of groups required to prove statistically a prognostic impact of lymphadenectomy.

What can we expect from the ongoing prospective trials? With the precondition of an expected prognostic difference of 5% with lymphadenectomy, a significance can be only expected if the groups are large enough (more than 300 patients each). As we can realize from the preliminary results of ongoing trials, morbidity and mortality may be higher in the D2 lymph node dissection group in hospitals with surgeons who are not as well trained. This higher mortality can overshadow the prognostic benefit that may be achieved with D2 lymphadenectomy. Moreover, postoperative morbidity is an independent prognostic factor [4]. Increased morbidity can by itself have a negative impact on long-term survival. The remaining prognostic gain for the total group of patients with gastric cancer is therefore lower than 5% if lymphadenectomy results in increased morbidity. Whether positive results can be expected from the ongoing trials under these circumstances is unclear.

In conclusion, the experiences of the Japanese centers and the theoretic and practical arguments in the literature convincingly suggest that lymphadenectomy is necessary to achieve tumor clearance in areas of lymphatic drainage at the end of the operation. If this goal can be reached, lymphadenectomy can have a prognostic benefit for the patient. It is possible to reach a tumor-free state in patients with early lymph node metastasis (up to N1). The available data show, moreover, that D2 lymphadenectomy is more difficult than the standard gastrectomy; hence a well trained surgeon is essential. In the future gastric cancer should be treated in experienced centers, which is the best way to improve the prognosis of patients with gastric cancer.

References

1. Maruyama, K., Okabayashi, K., Kinoshita, T.: Progress in gastric cancer surgery in Japan and its limits of radicality. World J. Surg. *11*:418, 1987
2. Bollschweiler, E., Böttcher, K., Hölscher, A.H., et al.: Is the prognosis for Japanese and German patients with gastric cancer really different? Cancer *71*:2918, 1993
3. Siewert, J.R., Böttcher, K., Roder, J.D., et al.: Prognostic relevance of systematic lymph node dissection in gastric carcinoma. Br. J. Surg. *80*:1015, 1993
4. Roder, J.D., Böttcher, K., Siewert, J.R., et al.: Prognostic factors in gastric carcinoma. Cancer *72*:2089, 1993
5. 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. *81*:414, 1994
6. Böttcher, K., Becker, K., Busch, R., Roder, J.D., Siewert, J.R.: Prognosefaktoren beim Magenkarzinom - Ergebnisse einer uni- und multivariaten Analyse. Chirurg *63*:656, 1992
7. Böttcher, K., Roder, J.D., Busch, R., et al.: Epidemiologie des Magenkarzinoms aus chirurgischer Sicht. Dtsch. Med. Wochenschr. *118*:729, 1993