Analysis of clinicopathologic prognostic features in patients with gastric adenocarcinoma

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Background. *We evaluated the influence of several clinicopathologic variables on 5-year actuarial survival rate after curative resection of gastric adenocarcinoma.*
Methods. *Clinical characteristics were retrieved from the records of all patients who underwent gastric resection for curative intent between 1965 and 1986 at The University of Chicago Medical Center, and follow-up was obtained from our tumor registry. Pathologic characteristics were determined from a detailed review of all available histopathologic slides.*
Results. *One hundred seventy-eight patients underwent a curative resection during the study period at our institution. Overall 5-year actuarial survival rate was 29%. The relationship between clinicopathologic variables and 5-year survival rate was evaluated by Kaplan-Meier survival curve construction and chi-squared analysis. Lymphatic and/or capillary microinvasion (absent vs present, $p < 0.001$), tumor location (antrum and body vs gastroesophageal junction, $p = 0.05$), local extent of disease (limited to the gastric wall versus involving adjacent organs, $p = 0.003$), stage (absence versus presence of lymph node metastases, $p < 0.001$), Lauren type (intestinal versus diffuse, $p < 0.01$), and Ming type (expanding versus infiltrative, $p < 0.02$) significantly influenced survival. When a multivariate analysis with logistic regression of 5-year survival was performed, lymphatic and/or capillary microinvasion emerged as the only statistically significant, independent prognostic factor associated with long-term survival ($p = 0.039$). If microinvasion was omitted from the analysis, lymph node metastases ($p < 0.05$) and the extension to adjacent organs ($p < 0.04$) became the only statistically significant variables. Multiple correlation analyses suggested that microinvasion is an early histopathologic finding that correlates with a more aggressive natural history.*
Conclusions. *Lymphatic and/or capillary microinvasion is a more powerful predictor of 5-year survival than lymph node metastases or tumor extension to adjacent organs. Correlation among clinicopathologic variables suggests that microinvasion may represent an early finding, serving as a potential marker for a biologically more aggressive tumor. (SURGERY 1994;116:804-10.)*

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DURING THE PAST DECADE efforts have been made to identify prognostic variables in patients affected by cancer, to predict outcome, and recently to help define high-risk patients who may benefit from adjuvant therapy. In 1988 we reviewed our experience with patients who underwent a curative resection for rectal adenocarcinoma and suggested that cancer stage, race, tumor morphology, and lymphatic and/or capillary microinvasion were four independent statistically significant variables influencing 5-year survival.[1] In 1991 we extended these results to patients who had undergone a curative resection for colon adenocarcinoma.[2]

Variables representing pathologic, clinical, and therapeutic characteristics have already been analyzed by other authors in an attempt to identify prognostic indicators in patients affected by gastric cancer. From 1981 to the present, numerous retrospective reports using multivariate analysis of clinical and pathologic features in gastric adenocarcinoma have identified a number of high-risk, independent prognostic parameters.[3-10] Stage and depth of penetration, tumor cell dissociation at the invasion front, nonpyloric site of involvement, microscopically positive gastric resection margins and inade-

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quate lymphadenectomy, extent of surgery, and vascular invasion have all been variously reported to be prognostically important.

The aim of the present investigation was to review the experience at our institution with gastric adenocarcinoma to determine the influence of several clinicopathologic variables on outcome and to identify possible similarities among adenocarcinomas in different sites of the gastrointestinal tract.

MATERIAL AND METHODS

Between January 1965 and December 1986, 178 patients with gastric adenocarcinoma underwent curative resections at The University of Chicago Medical Center. The clinical records of all these patients were reviewed and in 161 (86%) complete follow-up to December 1991 was obtained through our registry of neoplastic diseases. Excluding perioperative deaths, the length of follow-up averaged 4.9 years, with a range from 2.5 months to 23.5 years. Data on age, gender, race, tumor location, structure, and size, evidence of local invasion, the type of operation performed, perioperative mortality, and evidence of local recurrence or distant metastasis were specifically sought in each patient. Operative deaths were defined as those deaths occurring within 60 days from the time of operation.

Histologic slides and archival paraffin blocks were retrieved for confirmation of diagnosis, determination of histologic type (intestinal vs mucinous or signet ring), degree of tumor differentiation (poorly, moderately, well-differentiated), stage, invasion of adjacent structures, presence of vascular and/or lymphatic microinvasion, and evidence of microscopic tumor at the surgical margin by one pathologist (J.H.) who was unaware of the patients' clinical course. Lymphatic microinvasion was defined as the presence of tumor within an endothelial-lined space lacking a smooth muscle coat; the same finding was defined as vascular microinvasion if the endothelial-lined space was surrounded by a smooth muscle layer.

Tumors were also classified according to the Ming[11] and Lauren[12] classifications. In the Ming classification tumors are defined as expanding or infiltrative on the basis of their microscopic pattern of growth. An expanding carcinoma is characterized by an expanding and well-circumscribed invasive border. An infiltrative carcinoma, on the other hand, shows diffuse infiltration by individual tumor cells at the periphery. In the Lauren classification tumors are separated into two groups on the basis of their microscopic architectural arrangement. In the intestinal type the tumor cells are arranged in well-formed glandular patterns; in the diffuse type the tumor cells are arranged singly or in small clusters, without gland formation.

Of the 178 patients operated on for curative intent, 122 were entered in our analysis and form the data base for this report. The remaining 56 patients were excluded because they were lost to follow-up ($n = 17$, 10%), died in the perioperative period ($n = 15$, 9%), or were found to have presence of tumor at the surgical margin on review ($n = 24$, 14%). In all remaining cases but 16, vascular and/or lymphatic microinvasion was directly assessed on review of existing slides or those obtained from archival paraffin blocks. The search for data concerning all other parameters of interest was successful in at least 96% of patients.

Table I. Factors influencing 5-year survival after curative resection of gastric cancer

Variable	*p Value*
Tumor location	0.05
Extent of disease	0.003
Stage	0.001
Lauren type	0.007
Ming type	0.012
Lymphatic/capillary microinvasion	0.001

The relationship between clinical and pathologic variables and 5-year survival was evaluated by Kaplan-Meier survival curve construction[13] and use of the log-rank test.[14] Multivariate logistic regression analysis was then performed to determine which variables were independent prognostic factors. The dependent variable for both the univariate and the multivariate analysis was the 5-year survival rate. The following independent variables were entered in the univariate analysis: gender, race, age (dichotomized at 60 years), tumor location (gastroesophageal junction, body or fundus, antrum), tumor structure (exophytic vs nonexophytic), extent of disease (tumor confined to gastric wall vs invading adjacent organs), histologic type, stage (stage II vs stage III; American Joint Committee on Cancer), degree of differentiation, Lauren and Ming type, and presence of vascular and/or lymphatic microinvasion. The independent variables that achieved statistical significance in the univariate analysis were then entered in the multivariate analysis.

RESULTS

Of the 122 patients studied, 88 (72%) were men and 34 (28%) were women; 89 (73%) were white and 33 (27%) were black. Mean age at the time of operation was 63.2 years, with a range from 32 to 85 years. Tumors were located at the gastroesophageal junction in 50 patients (41%), in the body or fundus of the stomach in 39 (32%), and in the antrum in 33 (27%). The location of the tumor within the stomach influenced the type of operation performed: patients with a tumor at the gastroesophageal junction underwent an esophagogastrec-

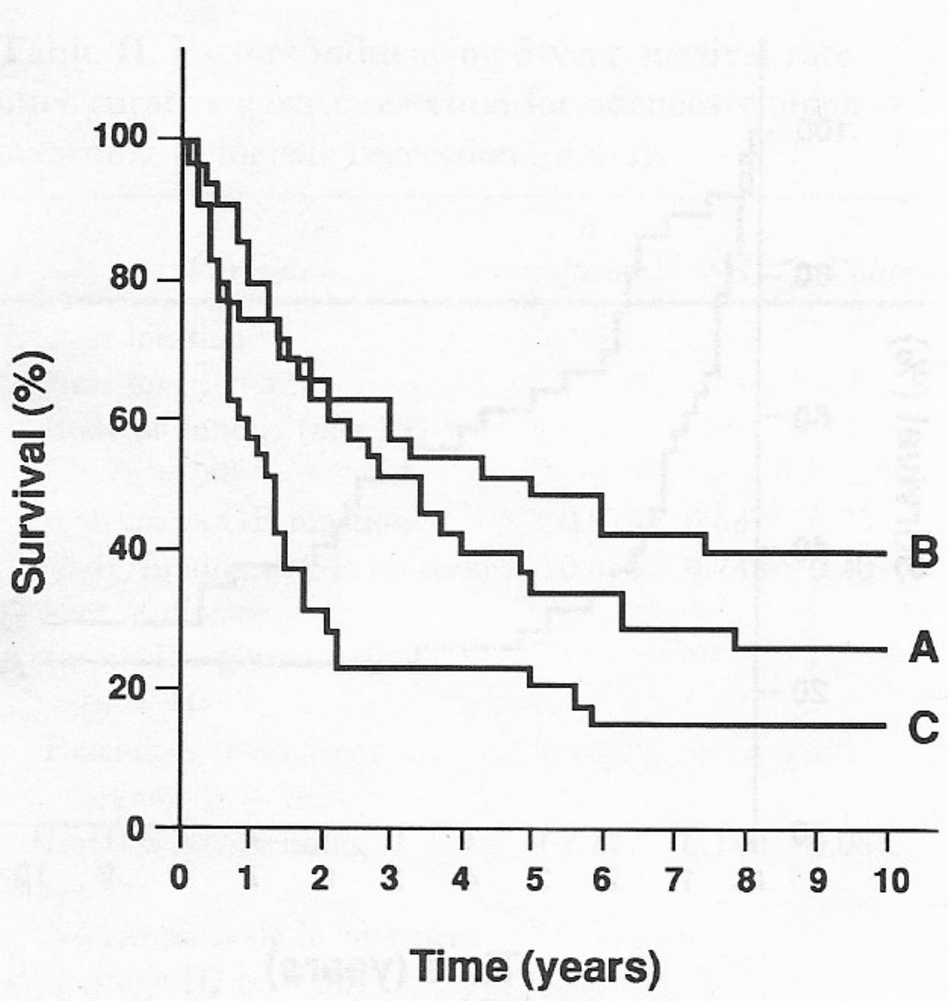

Fig. 1. Influence of tumor location on survival after curative resection of gastric adenocarcinoma. *A*, Antrum; *B*, body; *C*, gastroesophageal junction. Univariate analysis; $p = 0.05$.

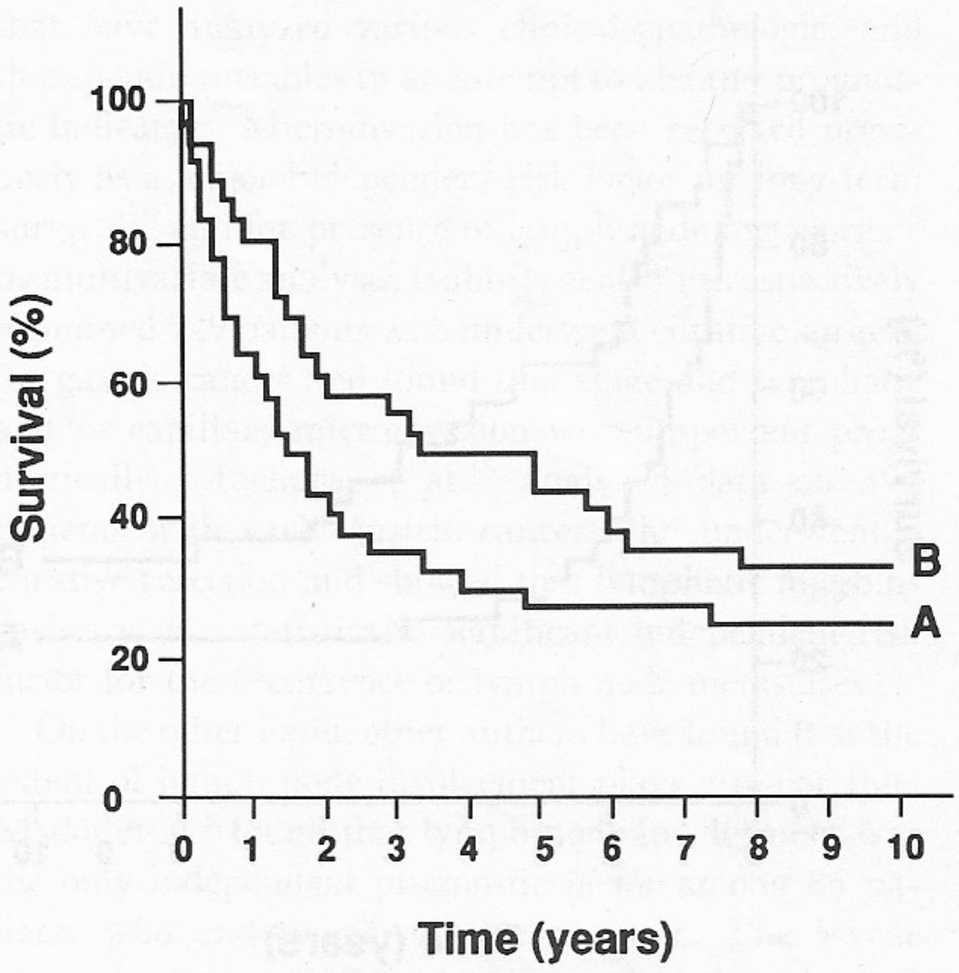

Fig. 3. Influence of stage on survival rate after curative resection of gastric adenocarcinoma. *A*, Stage III; *B*, stage II. Univariate analysis; $p = 0.001$.

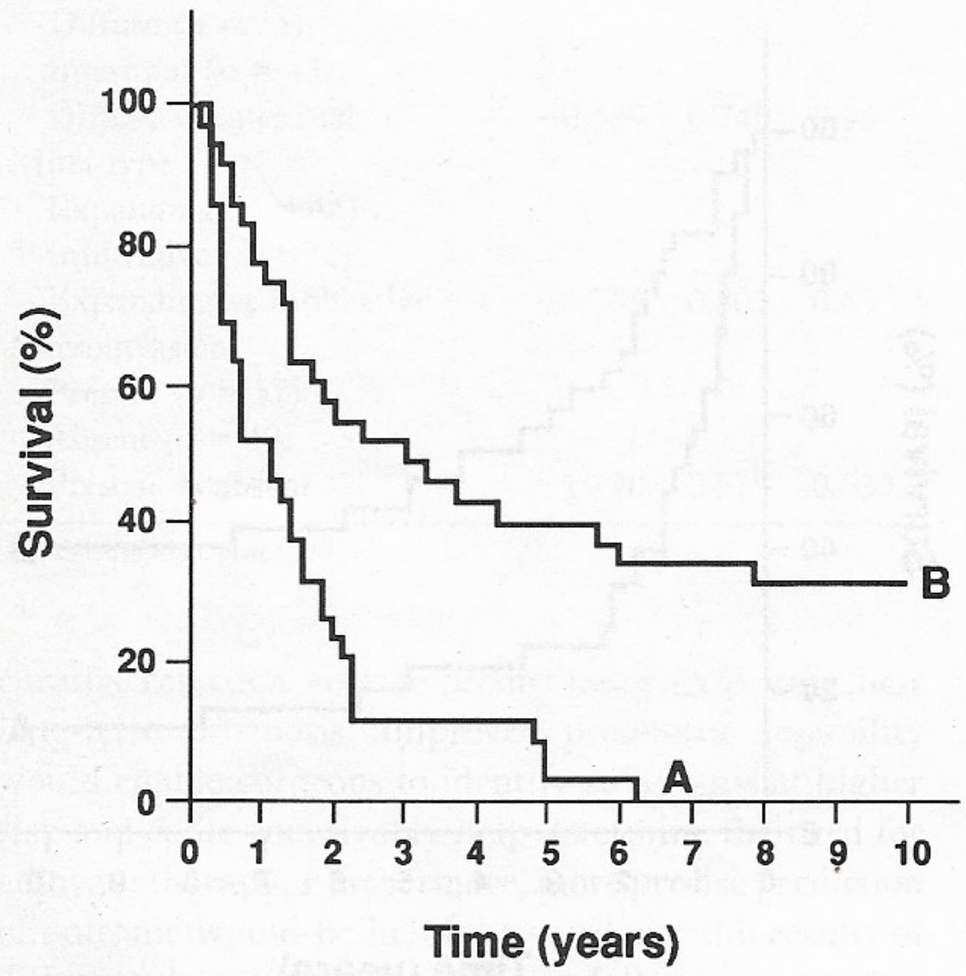

Fig. 2. Influence of extent of disease on survival rate after curative resection of gastric adenocarcinoma. *A*, Invasion into adjacent organs; *B*, limited to gastric wall. Univariate analysis; $p = 0.003$.

tomy, patients with a tumor in the body or fundus of the stomach underwent a total gastrectomy, and a distal subtotal gastrectomy was performed for patients with a distal or antral tumor.

Follow-up analysis revealed that the overall 5-year actuarial survival rate, exclusive of perioperative deaths, was 29%. Univariate analysis was performed to evaluate significant relationships between clinicopathologic features and patient survival. Of the 13 clinical and pathologic variables entered in the analysis (see Methods), six were found to have a significant influence on survival. Table I summarizes the results of the analysis. Unfavorable prognostic factors included tumor location at the gastroesophageal junction, involvement of adjacent organs, lymph node involvement, Lauren diffuse type, Ming infiltrative type, and presence of lymphatic and/or capillary microinvasion. To present our results in a more clinically useful manner, demonstrating the magnitude of the difference in outcome observed with each significant variable in our study population, 10-year survival rate curves were calculated for each of the six variables. Figs. 1 to 6 graphically display these results.

The difference in 5- and 10-year survival rates on the basis of tumor location is depicted in Fig. 1. It is noteworthy that independent of the location of the primary tumor several patients died of recurrent disease between 5 and 10 years. In addition, no patient with a gastric tumor invading an adjacent organ survived past 6 years from the time of the gastrectomy (Fig. 2). Patient outcome at 5 years was also found to differ significantly with respect to lymph node involvement (Fig. 3). Patients with lymph node involvement had a worse long-term prognosis than patients with no lymph node

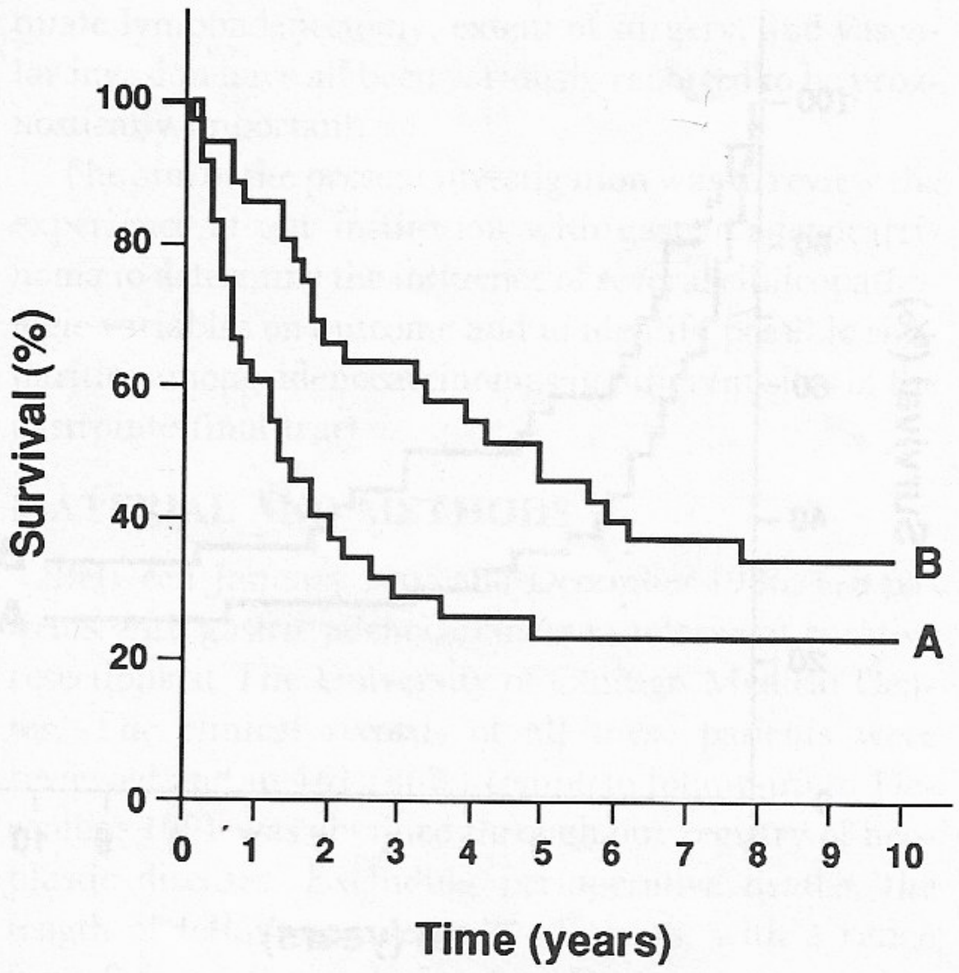

Fig. 4. Influence of Lauren type on survival rate after curative resection of gastric adenocarcinoma. *A*, Diffuse; *B*, intestinal. Univariate analysis; $p = 0.007$.

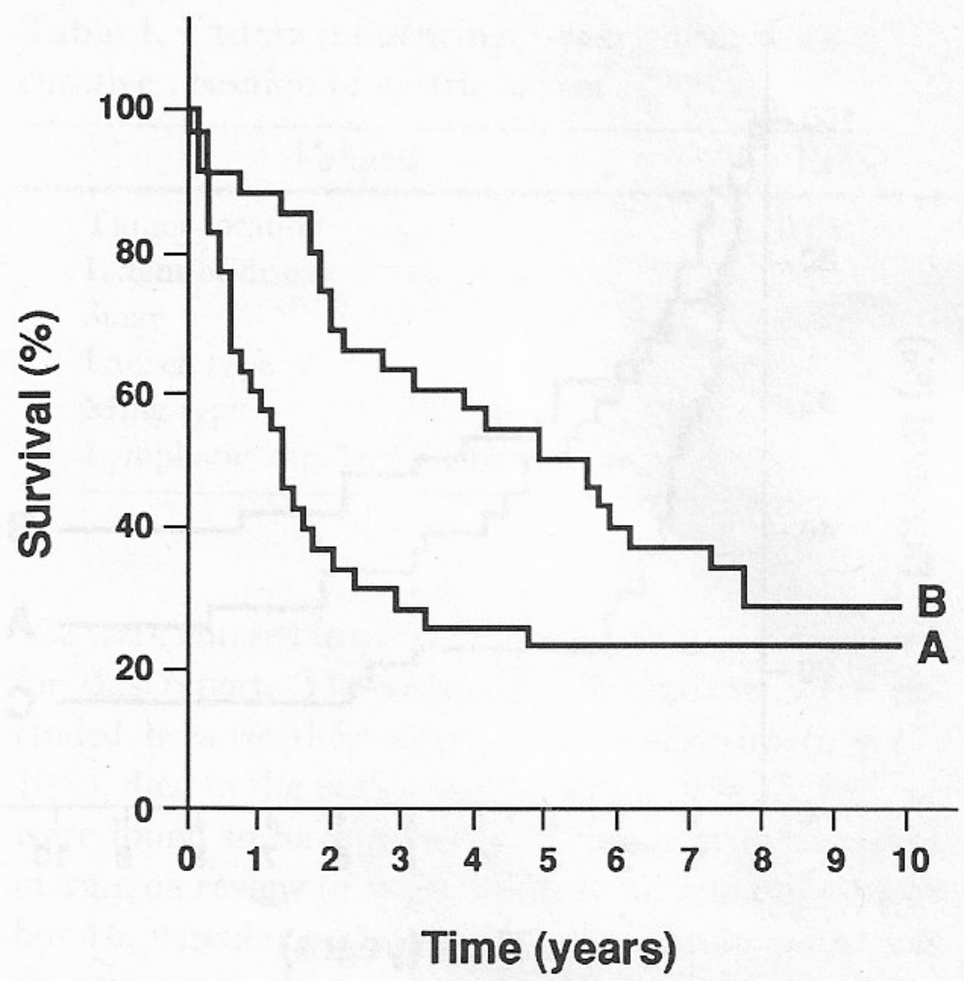

Fig. 5. Influence of Ming type on survival rate after curative resection of gastric adenocarcinoma. *A*, Infiltrative; *B*, expanding. Univariate analysis; $p = 0.012$.

involvement (23% survival at 5 years vs 56%, respectively), although this difference almost disappeared at 10 years because of further deaths from recurrent disease in the group of patients with uninvolved lymph nodes. Figs. 4 and 5 display the different long-term survival rates according to the Lauren and Ming histologic types. Lauren diffuse and Ming infiltrative types were associated with worse 5-year survival rates than Lauren intestinal and Ming expanding types (25% and 27% versus 52% and 49%, respectively). Finally, the presence of vascular and/or lymphatic microinvasion was associated with lower long-term survival rates: 23% of patients with this histologic characteristic survived for 5 years compared with 51% of patients without such microinvasion (Fig. 6).

Although these life-table results make the differences in outcome associated with a specific variable readily apparent, they do not account for the interrelationship between variables. To account for the interrelationships among the six variables on 5-year outcome, a multivariate analysis was performed. With logistic regression microinvasion emerged as the only statistically significant prognostic parameter associated with long-term survival ($p = 0.039$; Table II). If microinvasion is omitted from the analysis, then lymph node metastasis and the extent of adjacent organ involvement become the only two statistically significant independent prognostic variables ($p < 0.05$ and $p < 0.04$, respectively).

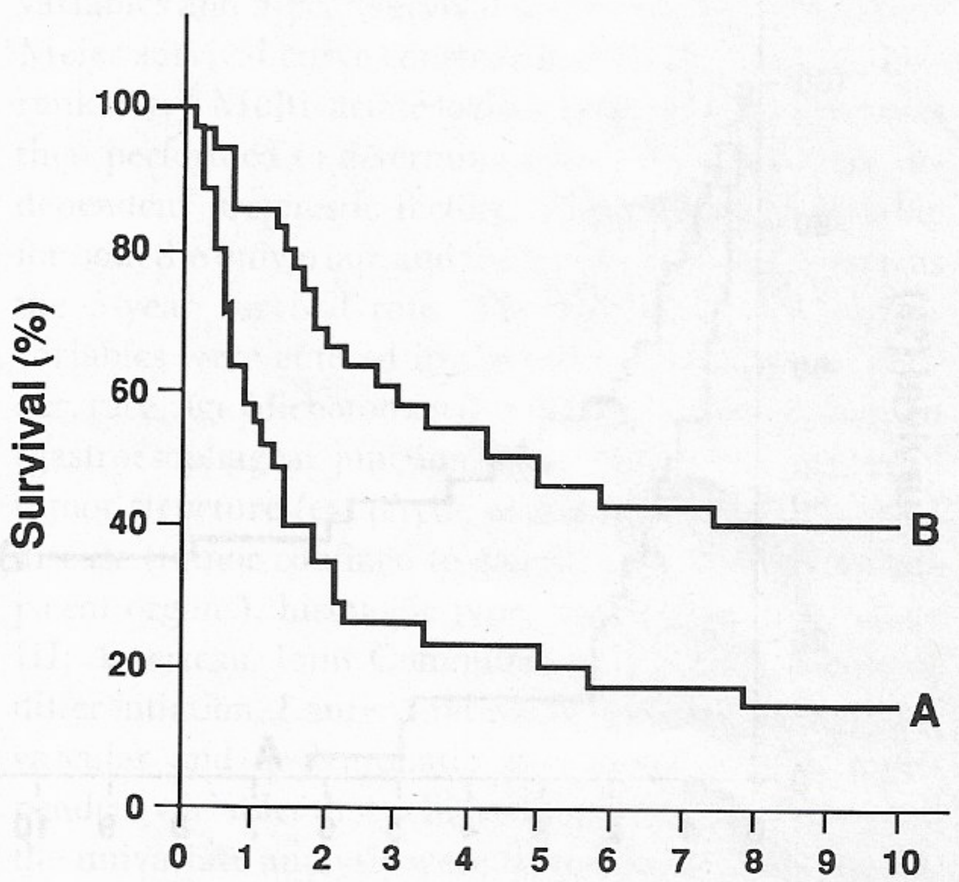

Fig. 6. Influence of lymphatic and/or vascular microinvasion on survival rate after curative resection of gastric adenocarcinoma. *A*, Present; *B*, absent. Univariate analysis; $p = 0.001$.

DISCUSSION

One of the purposes of this study was to identify clinical or pathologic characteristics that influence the prognosis of patients with gastric carcinoma after a

Table II. Factors influencing 5-year survival rate after curative gastric resection for adenocarcinoma according to logistic regression analysis

Variable	*β coefficient*	*SE*	*p Value*
Tumor location			
Antrum (n = 32)			
Body or fundus (n = 38)			
GE (n = 50)			
Antrum vs GE junction	0.873	0.687	0.20
Body/fundus vs GE junction	0.636	0.748	0.40
Extent of disease			
Limited to gastric wall (n = 94)			
Extending to adjacent organs (n = 26)			
Limited vs extending	−2.137	1.140	0.061
Stage			
No lymph node involvement (stage II) (n = 36)			
Lymph node involvement (stage III) (n = 83)			
Negative vs positive nodes	−0.874	0.628	0.16
Lauren type			
Diffuse (n = 73)			
Intestinal (n = 43)			
Diffuse vs intestinal	−0.689	0.740	0.35
Ming type			
Expanding (n = 44)			
Infiltrative (n = 72)			
Expanding vs infiltrative	−0.365	0.801	0.65
Microinvasion			
Present (n = 57)			
Absent (n = 49)			
Present vs absent	−1.190	0.575	0.039

GE, Gastroesophageal.

curative resection, so as to predict more accurately their long-term prognosis. Improved prognostic capability would enable surgeons to identify subgroups at higher risk and could conceivably help determine the need for adjuvant therapy. Furthermore, more precise prediction of outcome would be helpful to evaluate the results of different therapies and to allocate follow-up resources more effectively and efficiently.

Multivariate analysis of our institutional experience with patients who underwent curative resection for gastric carcinoma during a 21-year period revealed that the only variable to influence 5-year survival rate was lymphatic and/or capillary microinvasion. When microinvasion was omitted from the regression analysis, lymph node involvement and the extent of adjacent organ involvement became statistically significant.

These results are in agreement with previous reports that have analyzed various clinical, pathologic, and therapeutic variables in an attempt to identify prognostic indicators. Microinvasion has been reported previously as a major independent risk factor for long-term survival[10] and for presence of lymph node metastasis[15] by multivariate analysis. Gabbert et al.[10] retrospectively examined 529 patients who underwent curative surgery for gastric cancer and found that stage and lymphatic and/or capillary microinvasion were important prognostically. Machara et al.[15] analyzed data on 396 patients with early gastric cancer who underwent a curative resection and showed that lymphatic microinvasion was a statistically significant independent risk factor for the occurrence of lymph node metastases.

On the other hand, other authors have found that the extent of lymph node involvement plays a major role. Msika et al.[3] found that lymph node involvement was the only independent prognostic factor among 86 patients who underwent curative resection. The 5-year survival rate was 75% with negative lymph nodes and decreased to 28% with proximal and 7% with distal lymph node involvement. Shiu et al.[7] undertook a retrospective study of 210 patients treated with curative intent and found two pathologic variables predictive of death from recurrent gastric cancer: nonpyloric site of primary tumor and metastases in more than three lymph nodes. Both authors failed to consider and analyze the influence of lymphatic and/or capillary microinvasion. It is interesting that when microinvasion was omitted from our analysis, lymph node involvement was one of two variables to assume statistical significance with regard to long-term survival.

Baba et al.[8] included lymphatic microinvasion as a possible prognostic factor in a study of 142 patients who had undergone curative resection for advanced adenocarcinoma of the stomach, that had invaded into or through the gastric subserosa. The multivariate analysis indicated that stage, lymph node metastasis, and depth of penetration were the significant prognostic factors influencing long-term survival. Lymphatic invasion did not attain statistical significance. It is possible that in advanced tumors microinvasion, an earlier finding than full-thickness penetration and lymph node metastases, loses its predictive value.

A second aim of the present investigation was to identify possible similarities among adenocarcinomas occurring in different sites of the gastrointestinal tract. The finding that the presence or absence of microinvasion influences 5-year actuarial survival rate in gastric adenocarcinoma parallels a similar result obtained by us in a retrospective analysis of rectal[1] and colon[2] adenocarcinoma. In rectal adenocarcinoma the presence or absence of lymphatic and/or capillary microinvasion significantly influenced patient outcome together with

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Dukes stage, race, and tumor morphology. The same results were obtained after a similar analysis for colonic adenocarcinoma.[2]

Microinvasion may represent an early finding in the metastatic spread of hollow organ gastrointestinal tumors. Lymphatic microinvasion may predispose to lymph node metastasis, whereas capillary microinvasion may predispose to distant, blood-borne metastasis. The detection of microinvasion may therefore have potential clinical usefulness as a marker for biologically more aggressive tumors.

Recently reported results from our laboratory indicate a significant correlation between loss of heterozygosity on chromosome 8p and the presence of lymphatic and/or capillary microinvasion in 15 colorectal cancers.[16] Now that our data suggest an important role of microinvasion in the long-term outcome of patients after curative resections of gastric adenocarcinoma, it remains to be seen whether the same chromosomal alterations are at the basis of the microinvasion in gastric cancers. In the future preoperative detection of chromosomal alterations in tumors may identify tumors with a propensity for microinvasion, thus defining a patient group that may benefit from more aggressive therapy.

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DISCUSSION

Dr. James A. Madura (Indianapolis, Ind.). I think there are two ways to look at this paper.

One way to view it is as another small American retrospective study of less than five or six cases a year of gastric cancer, with relatively good results either because of the highly selective nature of these patients or to the expertise of surgeons at the University of Chicago. If you do that, it is easy to minimize the importance of the paper and say that compared with an Asian or South American series of 5000 or 7000 cases, a more secure conclusion can be drawn from a larger series than from the current study.

The other way to look at this study is as a continuum of the Chicago group's recent efforts in looking first at their patients with colon cancer and becoming more and more molecular and genetic in their reviews. You heard the brief reference to the loss of heterozygosity of the 8p chromosome in more aggressive lesions. Is this going to become an important prognostic factor? Will this become part of our staging when we see patients with gastrointestinal malignancies?

The staging factors that you looked at yielded no big surprises. The conclusion that I reached from reading the manuscript was that the biologically aggressive tumors do poorly and that the less biologically aggressive, those that do not have the microinvasion, positive nodes, or adjacent organ invasion, carry a survival rate twice that of the patients who do have these poor prognostic factors. So I do not think there are any major surprises there.

I do have some technical questions. Were protocols carried out for lymphadenectomy? Did you do extensive lymphadenectomy in these more aggressive tumors, or did you not know that these tumors were more aggressive ahead of time? What about the preoperative staging? What would you recommend for those of us who are going to go to the operating room next week? Should we do multiple biopsies first and then decide what procedure we are going to do? For those tumors that are not invasive, should we do simple resection? For those that are more invasive, should we do more radical resections and lymphadenectomies? Should we take a wider margin of the esophagus for aggressive lesions? How far should the margins be cleared in these cases? Was there a chemotherapeutic ad-

vantage? You did not mention this at all. Were several adjunctive therapeutic protocols used or none, and did this affect the outcome?

I think the factors addressed in the paper are going to be important factors when we have only small numbers of such cases with which to deal. I think these are major questions to ask, and I hope that your continued investigation into what I assume is the entire gastrointestinal tract, looking at these genetic factors, may be helpful to all of us.

Finally I would like for you to comment on the following. The last half dozen cases or so of gastric cancer that I have seen and managed have been in younger people. The last patient was 28 years old. In addition, most of our tumors are now proximal or at the gastroesophageal junction. As you have shown from your specimen photos from the operating room, you have done fairly major procedures here. Is that going to be enough, or are we dealing with a changing neoplasm that needs preoperative adjunctive chemotherapy as we do in other lesions?

This is a provocative study, and the Association awaits further progress and advice from your group.

Dr. Gerald M. Fried (Montreal, Quebec, Canada). I am concerned about the patients who were excluded from your analysis. Perhaps there is some way that these patients can be looked at; the message from this may allow us somehow to improve their outcome.

Fourteen percent of patients were excluded from the analysis because they had positive margins at the time of the final pathologic diagnosis. This group of 14% of patients are therefore excluded from a possibility of cure despite their other histopathologic features as analyzed in your series.

Can you make any recommendations regarding evaluation of the patients either before or during operation? What is the role of frozen sections in reducing the rate of positive margins? We need to be sure that this 14% of patients is in the pool that is then going to be considered potentially curative.

Dr. G. Aranha (Maywood, Ill.). You have an appreciable number of gastroesophageal junction tumors, and some investigators believe that those tumors behave more as esophageal than as gastric tumors. Did you break down your analysis of variables by site, that is, compare the gastroesophageal junction lesions with body and antral lesions?

Dr. Jay L. Grosfeld (Indianapolis, Ind.). Twelve years ago we performed a vagotomy and antrectomy on a 10-year-old boy for a failed ulcer operation (drainage procedure) that had been done elsewhere. When he was 22 years of age, adenocarcinoma of the stomach developed in the gastric stump and he eventually died.

I wonder whether the University of Chicago group has had an opportunity to study this particular subset of patients in whom adenocarcinoma of the remaining portion of stomach develops after previous gastric resection. Is loss of heterozygosity also observed, and is the spread of tumor similar to that noted in primary cases of gastric cancer with an intact stomach?

Dr. James B. Peoples (Dayton, Ohio). I think it is important to keep in mind that only roughly one third of the patients in whom adenocarcinoma of the stomach was actually diagnosed underwent curative resection and that in fact the 5-year survival rate for all patients was less than 10%.

Because you were able to study these patients for such a long period, have you noted any trends in the more recent portion of the study toward earlier diagnosis of this disease?

Dr. Michelassi (closing). Surgery for gastric cancer should be based on principles of oncologic radicality. When a curative resection is possible, the resection should be done with adequate margins and with a lymphadenectomy all the way to the origin of the vessels. Most often this is an R2 dissection. In expert hands the R2 dissection does not carry higher morbidity and mortality rates than an R1 dissection. In terms of the margins, at the time of operation the duodenal and gastric or esophageal margin should be sent for frozen section studies.

To date no chemotherapy for gastric cancer has been shown to be efficacious. During the course of the 20 years of the study, several protocols of chemotherapy were used in slightly less than 50% of patients. Knowing now that none of this was really helpful, I did not consider chemotherapy as an independent variable.

The location of the tumor was an important prognostic variable in the univariate analysis, and the gastroesophageal cancers indeed had a worse prognosis than the antral and body of the stomach cancers. But when all variables that were statistically significant in the univariate analysis were entered in the multivariate analysis, location lost significance. Microinvasion was indeed the only statistically significant variable influencing 5-year survival.

During the course of the study we have not noticed a shift to earlier stages of cancers. Regarding cancers in the gastric stump, we indeed see about one or two of these tumors per year, but I have not looked at their genetic alterations and cannot answer whether they also show 8p allele loss.