VNIVERSIDAD NACIONAL AVTONOMA DE MEXICO

DIVISION DE ESTUDIOS DE POSGRADO E INVESTIGACION

SUBDIVISION DE ESPECIALIZACIONES MEDICAS

OFICIO FMED/SEM/1845/2002

ASUNTO: Autorización del trabajo de investigación del Dr. Dan Green Renner.

DR. CESAR AUGUSTO COLINA RAMÍREZ
SECRETARIO DE SERVICIOS ESCOLARES
DE LA FACULTAD DE MEDICINA
Presente.

Estimado Dr. Colina Ramírez:

Me permito informar a usted que el **Dr. Dan Green Renner**, alumno del curso de especialización en **Oncología Médica** en el **Instituto Nacional de Ciencias Médicas y de la Nutrición "Dr. Salvador Zubirán,** presenta el trabajo de investigación intitulado ***"Adenocarcinoma of the Stomach: Univariate and multivariate análysis of factors associated with survival".***

De conformidad con el artículo 21 capítulo 5º. de las Normas Operativas del Plan Unico de Especializaciones Médicas (PUEM) se considera que cumple con los requisitos para validarlo como el trabajo formal de Investigación que le otorga el derecho de la diplomación como especialista.

Sin otro particular de momento, reciba un cordial saludo.

INCMNSZ
INSTITUTO NACIONAL
DE CIENCIAS MEDICAS Y NUTRICION
"DR. SALVADOR ZUBIRAN"
DIRECCION DE ENSEÑANZA
México, D.F.

Atentamente
"POR MI RAZA HABLARA EL ESPIRITU"
Cd. Universitaria, D. F. a 23 de septiembre de 2002

JEFE DE LA SUBDIVISION

DR. LEOBARDO C. RUIZ PEREZ

LRP*ajr.

Am J Clin Oncol (CCT) 25(1): 84–89, 2002.

Adenocarcinoma of the Stomach: Univariate and Multivariate Analysis of Factors Associated With Survival

Dan Green, M.D., Sergio Ponce de Leon, M.D., Ph.D., Eucario Leon-Rodriguez, M.D., and Ricardo Sosa-Sanchez, M.D.

Gastric cancer is the most frequent tumor of the digestive tract in Mexico. Most patients are diagnosed at advanced stages, and fatal outcome is expected. One hundred fifty patient charts were retrospectively reviewed. Univariate and multivariate analyses were performed to evaluate the impact of clinicopathologic and treatment variables on survival. Most patients (75%) were at advanced stages, harboring poorly differentiated tumors. Surgery, mostly palliative, was performed on 114 patients. Chemotherapy was administered to 47 patients. On univariate analysis, significant prognostic factors were TNM stage, chemotherapy, surgical attempt, performance status, histology, and tumor site ($p < 0.001$). On multivariate analysis, independent prognostic factors were TNM stage, histology, tumor site, surgical attempt, and chemotherapy ($p < 0.01$). Median survival for patients with palliative or adjuvant chemotherapy was 11.4 and 10.4 months, respectively, compared with ± 3 months for patients with no chemotherapy ($p < 0.03$). Nonsurgical patients receiving chemotherapy survived 5.4 months versus 1.1 months for those without chemotherapy. The favorable influence of chemotherapy persisted after a stratified analysis of subgroups eliminating potential biases. We identified prognostic factors for survival. Chemotherapy should be considered even for advanced-stage patients with either adjuvant or palliative attempts, because we consistently found a favorable impact on the median survival time. However, phase III prospective randomized trials are awaited.

Key Words: Gastric cancer—Chemotherapy—Multivariate analysis—Prognostic factors—Survival—Univariate analysis.

Gastric cancer in Mexico is a major health problem. With other tumors of the gastrointestinal tract, it represents 32.5% of the malignant neoplasms with a mortality rate of 5.1 per 100,000 population.[1] It is the most frequent tumor (33%) of the digestive tract.[2] In the United States, there is a trend toward decreasing incidence; however, it still has a death rate of 14,000 per year.[3] In other countries, mainly Japan, gastric cancer is the major cause of death from malignant neoplasms.[4,5] Unfortunately, at the time of diagnosis the majority of patients are in advanced stages, and a fatal outcome will be expected.[6,7] Different clinical and anatomopathologic factors affect prognosis, treatment response, and survival: TNM stage,[8,9] histologic type,[10,11] tumor differentiation,[12] and the site of the primary tumor.[13–15]

Surgical resection is the only curative treatment;[16,17] however, the resectability rate is low, with curative resection rates reported between 30% and 40%.[18] In Mexico, the resectability rate is even lower (10–15%), probably related to advanced stages at diagnosis.[2,19] The extension of the surgical procedure may influence survival,[20,21] but even in patients with curative resections, the relapse rate and mortality from metastatic disease are high.[22] To improve the survival rate, systemic chemotherapy, either adjuvant or palliative, has been attempted.[23,24] Combined modality treatments with the fluorouracil, doxorubicin (Adriamycin), and methotrexate (FAM),[2,25] fluorouracil, doxorubicin, methotrexate,[24] and etoposide, doxorubicin, and cisplatin (EAP)[26] regimens have shown response rates between 33% and 55%, but with a minimum impact on survival.[7,9,27]

The purpose of this study was to evaluate, in a retrospective univariate and multivariate analysis, the role of chemotherapy and other factors with prognostic impact on survival for gastric cancer patients treated in a single Mexican institution.

MATERIALS AND METHODS

The charts of 150 patients with gastric adenocarcinoma proved by biopsy, admitted to our institution between December 1987 and May 1993, were retrospectively reviewed. Clinical and histopathologic data, and details of the surgical and chemotherapy procedures, were recorded. General performance status was registered according to the Eastern Cooperative Oncology Group scale.[28] Clinical and pathologic staging was determined according to the TNM staging system.[29] Early, intermediate, and advanced stages were defined as TNM stages IA-IB, II-IIIA, and IIIB-IV, respectively, according to several

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reports in which the 5-year survival rate shows a clear separation (average 20%) in these subsets, so defined.[30–32] Tumor localizations considered were: proximal third—gastroesophageal junction and gastric fundus, middle third—gastric body and curvatures, and distal third—the antropyloric region.[33] Tumor grade was defined as well, moderate, and poorly or undifferentiated neoplasms,[30] and histologic type was according to Lauren.[34] Extreme disease was defined as the evidence of metastatic disease to the peritoneal cavity, liver, or lung.

The surgical procedures were defined as follows: *subtotal gastrectomy*—as proximal or distal depending on preservation of the antrum or fundus and resection of regional proximal lymph nodes; *total gastrectomy*—similar to subtotal gastrectomy but including complete resection of the stomach; and *radical gastrectomy*—similar to total gastrectomy but including resection of distal regional lymph nodes, distal pancreatectomy, splenectomy, and omentectomy. "Palliative surgery" was defined as a partial resection of the tumor and/or a bypass procedure. "Exploratory laparotomy" was defined as the opening of the abdominal cavity for biopsy sampling without tumor resection or bypass procedure.[10,35] "Surgical attempt" was defined as curative only if there was no evidence of residual tumor. Chemotherapies used were either the FAM[25] or EAP[26] regimens (Table 1). Chemotherapy was considered palliative when given to patients without curative resections and adjuvant when surgery was performed with a curative purpose. Chemotherapy-induced toxicity was scored according to the World Health Organization scale.[36]

Overall survival was determined from the date of histologic diagnosis to the last follow-up or death. The influence of each variable on survival was determined. The clinicopathologic variables studied were gender, age, Eastern Cooperative Oncology Group status, site of primary tumor, TNM stage, histologic type, and tumor grade. Treatment variables were type of surgery, postsurgical residual disease, and chemotherapy. Initial data analysis included relative frequencies, median, and range values. Survival distributions were calculated according to Kaplan-Meier.[37] Log-rank statistics were used to compare subsets of patients.[38] To identify independent variables that influenced survival, the Cox model of proportional hazards was used.[39] From this, "dummy" variable indicators were generated to better appreciate data originally analyzed at nominal and ordinal levels (site of primary tumor, type of surgery, TNM stage, and Eastern Cooperative Oncology Group). Data analysis was carried out with the software STATA 4.0 (Stata Corp., College Station, Texas, U.S.A.). At this point, to allow a more meaningful examination of the efficacy of chemotherapy and its prognostic influence on survival, those patients considered as having extreme disease, postsurgical complications or death, or grade IV chemotherapy toxicity were excluded from further analysis because a selection bias might have been introduced because of their poor associated prognosis potentially favoring the chemotherapy subsets of patients.

TABLE 1. *Chemotherapy regimens*

		Day							
		1	2	3	4	5	6	7	8
EAP									
Etoposide	100–120 mg/m²				•	•	•		
Doxorubicin	20–30 mg/m²	•						•	
Cisplatin	50 mg/m²		•						•
FAM									
5-FU	400–600 mg/m²	•	•	•	•	•			
Doxorubicin	30–40 mg/m²	•							
Mitomycin	10 mg/m²	•							

EAP, etoposide, doxorubicin, cisplatin; FAM, fluorouracil, doxorubicin, methotrexate; 5-FU, 5-fluorouracil.

RESULTS

Patient Characteristics

Follow-up was complete for 91% of the 150 patients. One hundred eighteen patients subsequently died of gastric cancer–related events. At 5 years, only 17 patients (11.3%) were alive. Median follow-up for the study was 5.5 months (range: 0.5–61). Clinical charac-

TABLE 2. *Clinical characteristics*

Characteristics	No. (%)*	Characteristics	No. (%)*
Gender		Site of primary tumor	
Male/female	81/69 (1.2:1)	Proximal third	45 (30)
Age		Middle third	35 (23)
Median (range)	57 (21–89)	Distal third	46 (31)
ECOG at diagnosis		Entire stomach	24 (16)
0	3 (2)	TNM stage	
1	66 (44)	IA	6 (4)
2	39 (26)	IB	2 (1.3)
3	29 (19)	II	9 (6)
4	13 (9)	IIIA	17 (11.3)
Tumor grade		IIIB	16 (10.7)
Good	15 (10)	IV	96 (64)
Moderate	29 (19)	Not determined	4 (2.7)
Poor	72 (48)	Histologic type	
Undifferentiated	8 (5)	Intestinal	53 (35)
Not determined	26 (18)	Diffuse	97 (65)

ECOG, Eastern Cooperative Oncology Group.
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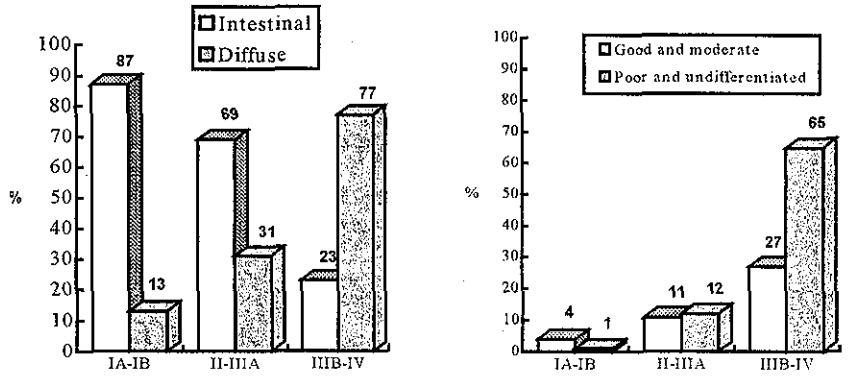

FIG. 1. Histologic type and tumor differentiation grade by early, intermediate, and advanced TNM stage.

teristics of patients are shown in Table 2. No significant differences were found in age distribution. A discrete predominance of male subjects (81 versus 69) was observed. The majority of patients were at advanced TNM stages (IIIB and IV); metastatic disease was evident in most of them. Most frequent primary sites were the middle and distal thirds. Tumor grade was predominantly poor; diffuse-type tumors were the most frequent (Fig. 1). Treatment modalities used are shown on Table 3. One hundred and fourteen patients were submitted to surgery, with a low rate of curative attempts. Perioperative mortality (30 days) occurred in 26 patients (23.6%) mainly on advanced stages and with palliative procedures. Forty-seven patients received systemic chemotherapy, being the EAP regimen the most frequently used.

Univariate and Multivariate Analysis of Prognostic Factors

On the univariate analysis variables influencing survival were TNM stage (Fig. 2), chemotherapy, curative surgical attempt, Eastern Cooperative Oncology Group, histologic type and site of primary tumor (Table 4). No significant associations were found with gender, age, tumor grade, type of surgical resection and chemotherapy regimen employed. Of the surgical factors, the type of surgery and the presence of residual postsurgical disease showed an independent prognostic effect when measured separately in models adjusted for TNM stage, histologic type and site of primary tumor; however, when combined, they lost significance since their information is not independent of each other. Also, the separate prognostic influence of these variables was no longer significant when the effect of chemotherapy was added to the analysis.

Results of the multivariate analysis (Table 5) of the total patient population on a model including TNM stage, histologic type, site of primary tumor and postsurgical residual disease, showed an independent prognostic effect for each of those variables. The addition of the variable "chemotherapy administration" substantially increased the significance of this model. The proportional hazard associated to this variable was 0.18 ($p < 0.0001$) pointing out a potential protective effect on survival. This effect persisted even after the exclusion of patients

TABLE 3. *Treatment data*

Surgery	No. (%)	Chemotherapy	No. (%)
Patients	114 (76)	Patients	47 (31)
Surgical attempt		Regimen	
Curative	43 (38)	EAP	29 (62)
Palliative	71 (62)	FAM	18 (38)
Type of surgery and attempt		Chemotherapy attempt	
Subtotal gastrectomy	22 (19)	Palliative	25 (53)
Curative	15	Adjuvant	22 (47)
Palliative	7	Regimen used and attempt	
Total gastrectomy	30 (26)	EAP	29 (62)
Curative	20	Palliative	17
Palliative	10	Adjuvant	12
Radical gastrectomy	17 (15)	FAM	18 (38)
Curative	8	Palliative	8
Palliative	9	Adjuvant	10
Bypass	12 (11)		
Laparotomy only	33 (29)		

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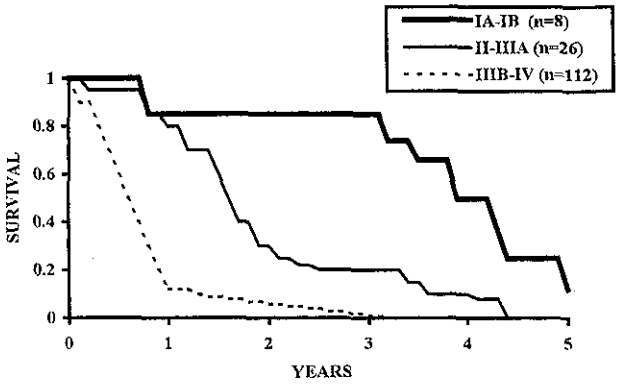

FIG. 2. Total study overall survival curve by early, intermediate, and advanced TNM stage.

not receiving chemotherapy due to unfavorable factors such as poor clinical postsurgical condition, extreme disease or chemotherapy toxicity.

A stratified analysis of the impact of chemotherapy on survival showed no significant differences for patients on early and intermediate TNM stages (probably due to the limited number of patients), although some favorable trends were observed. On the other hand, the effect of chemotherapy on advanced stages was observed to be favorable at several levels. Median survival for patients with palliative or adjuvant chemotherapy was 11.4 and 10.4 months respectively, compared with 3.8 months for patients with no chemotherapy ($p < 0.03$). Non-surgical patients receiving chemotherapy survived 5.4 months, compared to 1.1 months for those not receiving chemotherapy (Table 6).

DISCUSSION

This retrospective study is necessarily limited in its statistical power; however, it clearly identified prognostic factors for survival in gastric cancer patients usually with poor prognosis for survival and very limited treatment options due to advanced stages at diagnosis. We confirmed a discrete predominance of male patients as reported.[40] Age at presentation showed a trend to appear 5 to 8 years earlier than in other series.[12,31,41] It is important to mention the predominance of the diffuse histologies (65%) as compared with 35% to 50% of other reports,[12,21,42] probably reflecting changes in tumor biology and a possible influence of carcinogens on diet as described by Correa,[11] and/or a suggested potential immunologic association with *Helicobacter pylori* infection.[43–46] Tumor grade was similar to other reports, and we observed a trend for a progressive loss of differentiation with more advanced tumor stages (Fig. 1).[6] The pathologic findings and the significant prognostic factors observed in our series are difficult to interpret, because the reported distributions are widely variable.[12,16,19–21,32–35,40–48]

Even though there is an unquestionable improvement in surgical techniques and perioperative management, the 5-year survival rate for patients with gastric cancer has remained practically unchanged in a range between 10% and 15%.[40] In our study, the extent of surgery initially showed significant differences on univariate analysis, with better survival rates for patients with radical gastrectomies; however, this effect was lost when compared on multivariate analysis against TNM stage, a circumstance already pointed out.[31] The extent of surgery has been considered to be more in accordance with tumor extension found on surgery and having no significant impact on survival curves;[40] on this ground, it would appear that the routine use of radical gastrectomies is not to be recommended, because it does not seem to lengthen survival and significantly affects postoperative mortality. Conversely, some authors agree that radical surgery in selected patients[20,49] or extended lymphadenectomies[35] may have a significant curative or palliative impact, improving survival and quality of life even in advanced stages. Unfortunately, in our series it

TABLE 4. *Univariate analysis of clinical, pathologic, and treatment factors*

	Pts.	Sv*	p		Pts.	Sv*	p
TNM stage			<0.0001	Histology (Laurén)			<0.0001
Early (IA-IB)	8	58.4		Intestinal	53	10.2	
Intermediate (II-IIIA)	26	23.9		Diffuse	97	3.6	
Advanced (IIIB-IV)	112	3.5		ECOG at diagnosis			<0.001
Not determined	4	—		0	3	—	
Chemotherapy			<0.0001	1	66	8.0	
No	103	2.8		2	39	6.4	
Yes	47	12.4		3	29	2.5	
Site of primary tumor			<0.01	4	13	0.9	
Proximal third	45	4.4		Postsurgical residual disease			<0.0001
Middle third	35	10.7		Absent	43	25.9	
Distal third	46	6.4		Present	71	3.9	
All the stomach	24	1.9					

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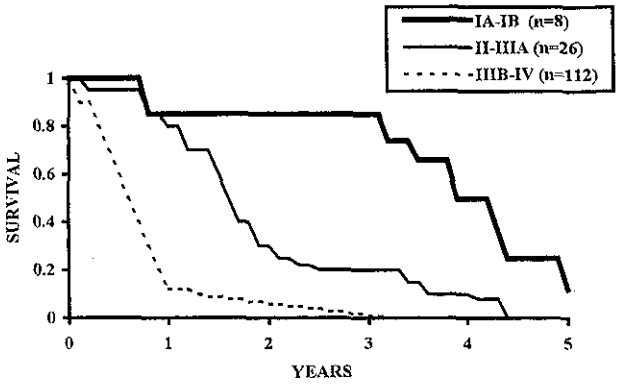
* Median survival (months).



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Distal third	46	6.4		Present	71	3.9	
All the stomach	24	1.9					

ECOG, Eastern Cooperative Oncology Group.
* Median survival (months).

TABLE 5. *Independent prognostic variables identified by Cox proportional hazards model (n = 144)*

Variables in the model	Without chemotherapy*		With chemotherapy†	
	Proportional hazards	p	Proportional hazards	p
TNM stage	1.6	0.03	3.0	<0.001
ECOG	1.1	0.2	1.1	0.3
Histologic type	0.6	0.01	0.5	0.001
Site of primary tumor				
Proximal third	0.3	0.004	2.2	<0.001
Middle third	0.4	0.004	0.3	<0.001
Distal third	0.3	0.0001	0.3	<0.001
All the stomach	0.7	0.3	0.6	0.09
Postsurgical residual disease	2.1	0.005	1.4	0.2
Chemotherapy			0.2	0.000

ECOG, Eastern Cooperative Oncology Group.
* Chi-square (9) = 63.24 p = 0.0000 pseudo r^2 = 0.0736.
† Chi-square (10) = 111.5 p = 0.0000 pseudo r^2 = 0.1298.

was not possible to define the number and localization of resected lymph nodes to classify them as N1 or N2 and establish adequate comparisons.

In our study, the use of chemotherapy was shown to be an independent factor with consistent favorable impact on survival, unrelated to the regimens used. Similar results have already been found in a phase II trial and retrospective reviews at our institution.[2] Our findings differ from other results reported.[50–52] In a meta-analysis of 11 prospective studies including more than 2,000 patients including several adjuvant chemotherapy regimens, no favorable results were obtained.[53] However, in most of the studies it is difficult to find standard criteria for analysis of prognostic factors such as TNM stage, extent of surgery, residual disease, selection methods of patients for chemotherapy, selection of a standard chemotherapy regimen, and some of them did not report univariate and multivariate analysis, making difficult to interpret their data. Even though our study is retrospective and with a limited number of patients, we examined factors potentially contributing to selection bias and established uniform criteria for comparison, i.e., the inclusion of patients only in advanced stages and the exclusion of individuals with extreme disease, postoperative complications, or chemotherapy toxicity potentially favoring the chemotherapy subset. Our results suggest that chemotherapy is likely to prolong the overall survival of patients after surgical resection of the tumor; however, phase III randomized trials are needed to establish chemotherapy as the standard treatment. So far, there is no conclusive evidence on the role of adjuvant or palliative chemotherapy in the management of patients with gastric carcinoma. Future survival analyses would need appropriate stratification criteria for staging and prognostic factors. Even though phase III randomized clinical trials are needed to establish the actual role of chemotherapy in gastric cancer, difficulties in conducting prospective trials with adequate number of patients make retrospective studies useful.

TABLE 6. *Stratified analysis of chemotherapy in advanced stages (TNM IIIB-IV)*

	Pts.	Sv.*	p
Total number of patients (n = 112) without exclusion of factors for potential bias			<0.0001
With chemotherapy	33	10.1	
Without chemotherapy	79	2.5	
Palliative resections (n = 71) excluding 22 patients with perioperative mortality			<0.0001
With chemotherapy	21	10.4	
Without chemotherapy	28	3.8	
Patients without surgery (n = 31)			†
With chemotherapy	5	5.4	
Without chemotherapy	26	1.1	
Exclusion of 58 patients with unfavorable conditions and perioperative mortality			
Remaining patients (n = 54)			<0.0001
With chemotherapy	33	10.1	
Without chemotherapy	21	3.6	
Palliative resections (n = 41)			<0.001
With chemotherapy	21	10.4	
Without chemotherapy	20	3.6	
Patients without surgery (n = 5)			†
With chemotherapy	5	5.4	
Without chemotherapy	0	—	

* Median survival (months).
† Number too small for statistical analysis.

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