EXPRESSION OF p53 AND PROLIFERATION INDEX AS PROGNOSTIC FACTORS IN GASTROINTESTINAL SARCOMAS

Medina-Franco H, **Ramos-De la Medina A**, Heslin MJ, Eltoum IE, Baquera J, Nuncio F, Cortés R, Urist MM

Aceptado para publicarse en *Annals of Surgical Oncology*

Publicación que presenta **Antonio Ramos De la Medina** a manera de tesis para obtener el título de especialista en Cirugía General

SUBDIVISION DE ESPECIALIZACION
DIVISION DE ESTUDIOS DE POSGRADO
FACULTAD DE MEDICINA
U. N. A. M.

2002

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

Dr. Luis F. Uscanga Domínguez
Director de Enseñanza
Instituto Nacional de Ciencias Médicas y Nutrición
"Salvador Zubirán"

Dr. Hector Orozco Zepeda
Director de Cirugía
Profesor Titular del Curso de Especialización en Cirugía General
Instituto Nacional de Ciencias Médicas y Nutrición
"Salvador Zubirán"

UNIVERSIDAD NACIONAL AUTÓNOMA DE MÉXICO

FACULTAD DE MEDICINA
DIVISION DE ESTUDIOS DE POSGRADO E INVESTIGACION

SUBDIVISION DE ESPECIALIZACIONES MEDICAS

OFICIO FMED/SEM/1791/2002

ASUNTO: Autorización del trabajo de investigación del Dr. Antonio Ramos de la Medina

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. Antonio Ramos de la Medina**, alumno del curso de especialización en **Cirugía General** en el **Instituto Nacional de Ciencias Médicas y Nutrición,** presenta el trabajo de investigación intitulado ***""Expressión of p53 and Proliferation Index as Prognostic Factors in Gastrointestinal Sarcomas".***

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.

Atentamente
"POR MI RAZA HABLARA EL ESPIRITU"
Cd. Universitaria, D. F. a 11 de septiembre de 2002

JEFE DE LA SUBDIVISION

DR. LEOBARDO C. RUIZ PEREZ

LRP*ajr.

ANNALS OF
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

July 15, 2002

RE: Manuscript #ASO-200203033, "Expression of P53 and Proliferation Index as Prognostic Factors in Gastrointestinal Sarcomas"

Heriberto Medina-Franco, MD
National Institute of Medical Sciences and Nutrition "Salvador Zubiran"
Department of Surgery
Vasci de Quiroga 15,
Tlalpan, Mexico City 14000,
Mexico

Dear Dr. Medina-Franco,

The Editorial Board of the *Annals of Surgical Oncology* has reviewed your manuscript, and I am pleased to inform you that it has been accepted for publication and will be scheduled for an upcoming issue.

When the manuscript has been scheduled for publication, it will be forwarded to Lippincott Williams & Wilkins, and you will receive electronic page proofs via e-mail directly from the publisher. Should you have any questions, please feel free to contact us.

Thank you for your support of the *Annals of Surgical Oncology*.

Sincerely,

Charles M. Balch, MD
Editor in Chief

Mark S. Roh, MD
Senior Editor

EXPRESSION OF p53 AND PROLIFERATION INDEX AS PROGNOSTIC FACTORS IN GASTROINTESTINAL SARCOMAS

Heriberto Medina-Franco MD.*, **Ramos-De la Medina A. MD***, Cortes-Gonzalez R MD.*, Baquera J MD.**, Angeles-Angeles A MD.**, Urist MM MD.#, Eltoum IE MD.##, Heslin M. MD.#

Department of Surgery (*) and Pathology (**). Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán".

Division of General Surgery, Section of Surgical Oncology (#) and the Department of Surgical Pathology (##). The University of Alabama at Birmingham, USA.

Correspondence: Heriberto Medina-Franco M.D. Department of Surgery. Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán". Vasco de Quiroga 15. Tlalpan. México 14000. Phone: 5573-7333/2140. Fax: 5573-9321

Running title: p53 in gastrointestinal sarcomas

Key words: gastrointestinal sarcoma, p53, prognosis

Abstract.

Baackground. Sarcomas of the gastrointestinal tract are rare tumors. Clinicopathologic determinants of survival have been conflictive and there are some data suggestive that molecular markers are associated with prognosis in this type of tumors.

Methods. Retrospective analysis of adult patients with primary gastrointestinal sarcomas at the National Institute of Medical Sciences and Nutrition in Mexico City and the University Hospital of the University of Alabama at Birmingham. Patient, tumor and treatment factors were analyzed with overall survival as the main outcome variable. Expression of p53 and cellular proliferation antigen Ki-67 was also analyzed. Statistical analysis was performed by log-rank test and Cox regression. Significance was defined as $P<0.05$.

Results. Forty-nine patients with gastrointestinal sarcomas were identified from the Tumor Registry of both institutions. Age ranged from 16 to 82 years with a median of 53 years. Twenty-five patients were women (51%). Hispanics were the predominant race with 22 patients (45%) followed by Caucasians with 18 patients (38%). The stomach was the most common site of presentation (47%) followed by small bowel (37%). Mean tumor size was 14 cm (range 2-46 cm). A complete resection was achieved in 41 patients (83.7%). With a median follow-up of 30 months, actuarial 3-year survival was 65%. Univariate analysis identified overexpression of p53 and Ki-67, high tumor grade, tumor size bigger than 10 cm and incomplete resection as a significant negative prognostic factors. Hispanic race and good performance status were significantly associated with prolonged survival. On multivariate analysis, overexpression of p53 was the only independent negative prognostic factor.

Conclusion. Overexpression of p53 is the strongest predictor of poor prognosis in patients with sarcomas of the gastrointestinal tract.

Gastrointestinal (GI) sarcomas are uncommon tumors accounting for only 0.1 to 3 per cent of all GI malignancies and about 10 per cent of all sarcomas (1). Clinicopathological determinants of survival have been conflictive in some aspects despite several series of smooth muscle tumors of the digestive tract (2-7). Recently, there has been an increasing interest in this type of tumors because they are responsive to a molecularly targeted therapy (8,9). In addition, recent studies with molecular markers have suggested that alterations in p53 activity and the overexpression of the Ki-67 as a proliferation marker are associated with prognosis in high-grade extremity soft tissue sarcomas (10). Most of the published reports of GI sarcomas span long periods of time during which there may have been many changes in diagnostic and therapeutic approaches, and some of them have included benign mesenchymal tumors (11,12).

The purpose of this review was to analyze the clinical presentation, management, histologic variables and factors associated with prognosis with special focus in molecular markers of primary GI sarcomas at the University Hospital, School of Medicine of the University of Alabama at Birmingham, USA and the National Institute of Medical Sciences and Nutrition (NIMSN) in Mexico City.

Patients and methods

Adult patients with diagnosis of primary gastrointestinal sarcoma at both institutions between January 1990 and December 2000 were included. We did not include any tumor classified as benign stromal tumor. Charts and histopathologic slides were reviewed to determine demographic data, clinical presentation, histologic type and grade of the tumor, extent of surgical resection, operative morbidity and mortality rates, the use of adjuvant therapy, patterns of recurrence and overall survival data.

All available histologic material was reviewed by a single pathologist at each institution (I.E.E for UAB and J.B. for the NIMSN). Original hematoxylin and eosin (H&E)-stained slides were reviewed to confirm the presence of the tumor. Histologic type was recorded

Gastrointestinal (GI) sarcomas are uncommon tumors accounting for only 0.1 to 3 per cent of all GI malignancies and about 10 per cent of all sarcomas (1). Clinicopathological determinants of survival have been conflictive in some aspects despite several series of smooth muscle tumors of the digestive tract (2-7). Recently, there has been an increasing interest in this type of tumors because they are responsive to a molecularly targeted therapy (8,9). In addition, recent studies with molecular markers have suggested that alterations in p53 activity and the overexpression of the Ki-67 as a proliferation marker are associated with prognosis in high-grade extremity soft tissue sarcomas (10). Most of the published reports of GI sarcomas span long periods of time during which there may have been many changes in diagnostic and therapeutic approaches, and some of them have included benign mesenchymal tumors (11,12).

The purpose of this review was to analyze the clinical presentation, management, histologic variables and factors associated with prognosis with special focus in molecular markers of primary GI sarcomas at the University Hospital, School of Medicine of the University of Alabama at Birmingham, USA and the National Institute of Medical Sciences and Nutrition (NIMSN) in Mexico City.

Patients and methods

Adult patients with diagnosis of primary gastrointestinal sarcoma at both institutions between January 1990 and December 2000 were included. We did not include any tumor classified as benign stromal tumor. Charts and histopathologic slides were reviewed to determine demographic data, clinical presentation, histologic type and grade of the tumor, extent of surgical resection, operative morbidity and mortality rates, the use of adjuvant therapy, patterns of recurrence and overall survival data.

All available histologic material was reviewed by a single pathologist at each institution (I.E.E for UAB and J.B. for the NIMSN). Original hematoxylin and eosin (H&E)-stained slides were reviewed to confirm the presence of the tumor. Histologic type was recorded

as originally reported. Paraffin-embedded tissue blocks were retrieved and matched to confirm the same tissue block as was used in the original H&E-stained slide. The grade of the tumor was assigned according to size, mitoses, tumor necrosis, nuclear pleomorphism, and cellularity (13).

Immunostains for Ki-67 (clone MM1) and p53 (clone Bp53-11) were done on formalin-fixed and paraffin-embedded material as described by the manufacturer (Ventana, Tucson, AZ). The number of positively staining nuclei was counted per 1000 tumor nuclei in the most intensely stained areas of the tumor. As other authors have suggested (10) we used nuclei with positive staining of 20 per cent or greater to include as categorically positive.

For the purpose of this review resection was considered complete if all gross disease was removed. Partial resection included removal of the bulk of tumor but with gross disease remaining.

Actuarial survival was measured by the Kaplan-Meier method beginning at the date of surgery. Univariate analysis to identify factors associated with survival was performed by the log-rank test and multivariate analysis was done with the Cox proportional hazards model. $P < 0.05$ was considered as statistically significant.

Results

During the study period, 49 adult patients with primary GI sarcomas were identified from the Tumor Registry from both institutions. Twenty-seven patients (55.1%) were from the UAB database and 22 (44.9%) from the NIMSM. Demographic characteristics are shown in Table 1. There were 25 female and 24 male patients. Ages ranged from 16 to 82 years with a median of 53 years. Most patients were Hispanic (45%). The stomach (49%) and small bowel (41%) were the most common site of tumor origin. Other tumor locations are depicted in Figure 1. Two patients had a history of other types of

as originally reported. Paraffin-embedded tissue blocks were retrieved and matched to confirm the same tissue block as was used in the original H&E-stained slide. The grade of the tumor was assigned according to size, mitoses, tumor necrosis, nuclear pleomorphism, and cellularity (13).

Immunostains for Ki-67 (clone MM1) and p53 (clone Bp53-11) were done on formalin-fixed and paraffin-embedded material as described by the manufacturer (Ventana, Tucson, AZ). The number of positively staining nuclei was counted per 1000 tumor nuclei in the most intensely stained areas of the tumor. As other authors have suggested (10) we used nuclei with positive staining of 20 per cent or greater to include as categorically positive.

For the purpose of this review resection was considered complete if all gross disease was removed. Partial resection included removal of the bulk of tumor but with gross disease remaining.

Actuarial survival was measured by the Kaplan-Meier method beginning at the date of surgery. Univariate analysis to identify factors associated with survival was performed by the log-rank test and multivariate analysis was done with the Cox proportional hazards model. $P < 0.05$ was considered as statistically significant.

Results

During the study period, 49 adult patients with primary GI sarcomas were identified from the Tumor Registry from both institutions. Twenty-seven patients (55.1%) were from the UAB database and 22 (44.9%) from the NIMSM. Demographic characteristics are shown in Table 1. There were 25 female and 24 male patients. Ages ranged from 16 to 82 years with a median of 53 years. Most patients were Hispanic (45%). The stomach (49%) and small bowel (41%) were the most common site of tumor origin. Other tumor locations are depicted in Figure 1. Two patients had a history of other types of

malignancies: a female patient with a history of breast cancer and a male patient with history of bladder carcinoma.

Abdominal pain (67%) and/or abdominal mass (57%) were the most common presenting symptoms. Other frequent complains were GI bleeding (43%) and symptoms of obstruction (42%). Three quarters of patients presented with two or more symptoms, and only three patients were asymptomatic at diagnosis and the neoplasm was identified during a celiotomy for other reasons. The mean duration of symptoms was 7 months (range 1-40 months).

Forty-two patients had preoperative CT scan that was suspicious for GI sarcoma in 31 patients. Eight patients underwent a preoperative biopsy, all of them from UAB. In three cases it was performed during GI endoscopy and in five patients the biopsy was obtained percutaneously. In seven of these patients there was a correct pathologic diagnosis. All patients were initially treated surgically. Forty-one patients (83.7%) underwent resection with curative intent; in other words all tumor was removed with negative gross surgical margins. In 40 of these cases microscopic margins were reported free of tumor also. Five patients had a debulking procedure in order to palliate symptoms; two patients had only tumor biopsy because of extensive and/or unresectable disease and one patient had a colostomy for palliation of unresectable rectal tumor. Of 46 patients who underwent resection, adjacent organs were resected in 17 in addition to the primary site. The most common organs resected were pancreas (twelve patients), spleen (six patients), and colon (four patients). Eleven patients had two or more organs resected. There was no operative (30-day) mortality.

Twelve patients received doxorrubicin-based chemotherapy. In eight cases it was administered in an adjuvant setting after gross tumor resection and four patients received treatment in presence of macroscopic disease. Four patients received radiation therapy, all of them in presence of macroscopic disease.

Leiomyosarcoma was the predominant histologic diagnosis (n=23) followed by GI stromal tumor (GIST) (n=20). Four cases of autonomic nerve tumor (GANT) and isolated cases of rhabdomyosarcoma and primitive neuroectodermal tumor (PNET) were identified. Twenty-five tumors were classified as high grade (51%) and 24 as a low grade (49%). There were no regional nodes involved by tumor in any case. The tumor size was known in 45 of the 49 cases. The mean tumor size in these cases was 13.6 cm (range 2-46 cm). Twenty-two tumors (49%) were $\geq$ 10 cm.

Immunohistochemistry for expression of p53 or Ki-67 could be performed in 30 cases. They were considered positive in 14 cases (28.6%) each of them. In 11 cases (36.6%) both molecular marker were both positive. Ki-67 and p53 were more frequently expressed in high grade (69%), than in low-grade (21%) tumors (p=0.01); and in big (>10 cm) (77%) than in smaller (<10 cm) tumors (25%) (P=0.001).

Of the 41 patients who were resected with curative intent, there were 12 recurrences, two local and ten distant. There was no statistical difference in possibility of recurrence according to histologic diagnosis. The most common site of distant failure was the liver (7 cases) followed by peritoneum (three patients). The mean time to recurrence was 11 months (range 4-30 months). Seventy-four per cent of recurrences occurred in patients with high-grade tumors.

Overall actuarial 3 and 5-year survival was 65 and 56 percent, respectively. The median follow-up was 30 months (range 1-112 months). The prognostic factors analyzed and their impact on survival are shown in Table 2. On multivariate analysis, the only factor associated with an adverse outcome was the positivity for p53 (P=0.04). The Kaplan-Meier curves for p53, tumor grade and completeness of resection are presented in Figures 2, 3 and 4, respectively.

Discussion

Gastrointestinal sarcomas occur infrequently accounting for only 0.1 to 3 per cent of all GI malignancies and 10 per cent of all sarcomas (1). Recently, it has been shown to be responsive to molecular targeted therapy. Most of this tumors are now known to be derived from the interstitial cells of Cajal and are characterized by expression of the proto-oncogene c-kit and often harbor gain-of-function KIT mutations leading to ligand-independent kinase activation. GI sarcomas are unresponsive to standard sarcoma chemotherapy, but in two recent Phase II studies, STI571, that selectively inhibits BCR-ABL, KIT and PDGFR tyrosine kinases, showed activity in patients with this type of neoplasms (8,9). Those reports have renewed the interest in this kind of malignancies. In the present report we combined the experiences of two large referral centers in two countries, so we can analyze the biology of this tumors in different populations.

Of anatomic sites of the digestive tract the stomach is the most common location of primary malignant stromal tumors: 38 to 65 per cent of all GI sarcomas in most series (3,5-7) and 49 per cent in our series. Although somewhat less common in the small bowel (41% in our series), sarcomas represent the second most common small bowel malignancy with an incidence one-third to one-half that of adenocarcinoma (6). Other locations are less common and are represented by four cases of colorrectal sarcomas and an isolated case of gallbladder rhabdomyosarcoma, which is extremely rare (14).

Mean tumor diameter in our series was 14 cm (range 2-46), which is bigger than that reported by Mc Grath et al (5) (11 cm) and Conlon et al (15) (9 cm). Ng et al (16) noted that 60 per cent of GI sarcomas were > 10 cm at presentation (49% in our series). There was almost an even distribution between high and low-grade tumors in the present series.

Consistent with other reports of the literature (5-7) this analysis demonstrated that completeness of resection; tumor grade and size are significant prognostic factors on

univariate analysis. Performance status was statistically significant related to prognosis too. Race was not considered prognostic factor in previous reports (7,15), but African-American and Hispanics have been found to have worse prognosis in other neoplasms as breast cancer (17,18). Those differences have been attributed to socioeconomic status and tendency to more advanced tumors in minorities (19). Strikingly, in the present series, Hispanics were found to have better prognosis than Caucasian or African-American, with no difference between tumor grade, size or completeness of resection between populations of the two institutions included in the present series (data not shown). At present we do not have an explanation for this relationship.

Other factor analyzed was the positivity for Ki-67, which is an antigen expressed throughout the majority of the cell cycle and is a good measure of dividing cells (20). Drobnjak et al examined 174 fresh frozen primary and recurrent soft tissue sarcomas from a variety of sites and correlated this with overall survival (21). In approximately 40% of the tumors, $\geq$ 20% of the cells expressed nuclear staining, with the higher percentage in synovial sarcomas (78%) and the lowest in liposarcomas/fibrosarcomas (27%). Similar to the present study, high proliferation index ($\geq$ 20% nuclear expression) was associated with high grade tumors and correlated with poor outcome, but they did not retain independent prognostic significance when grade was taken into account. Choong et al examined 182 paraffin embedded, primary extremity and superficial trunk soft tissue sarcomas for overexpression of Ki-67 (overexpression defined as > 10% nuclear staining) and demonstrated a significant correlation with size, grade, necrosis, vascular invasion, S-phase fraction, and metastasis (22). In the present series we were able to show a statistically significant relationship between grade and size and the expression of Ki-67, and similar to the study of Choong et al, when subjected to multivariate analysis, overexpression of Ki-67 did not retain independent prognostic significance after other prognostic factors were taken into account.

Nuclear accumulation of the p53 protein indicates a longer half-life of the protein, suggests mutations in the DNA (23), and has been correlated with poor outcome in a number of tissue types, including soft tissue sarcoma (24). The majority of studies have been performed with fresh frozen tissue and have revealed nuclear accumulation of p53 on the order of 23-33% (24-26). The current study utilized paraffin embedded tissue and revealed nuclear accumulation in 29% of the tumors analyzed. On multivariate analysis, p53 overexpression retained its significance as a marker of poor outcome. In the study of Heslin et al, p53 was not associated with outcome, however, only 9% of the tumors analyzed in this study showed overexpression of p53 (10).

In conclusion, this study has demonstrated that overexpression of p53 is an independent prognostic factor associated with increased risk of recurrence and death in a group of patients with primary GI sarcomas. With clinical/radiologic size, grade, Ki-67 index and expression of p53 available, patients can be better stratified by risk, now that there are promising molecular targeted therapies available.

References.

1. Medina-Franco H, Eltoum IE, Urist MM, Heslin MJ. Primary gastrointestinal sarcomas. Am Surg 2000; 66: 1-5.
2. Akwari OE, Dozois RR, Weiland LH, Beahrs OH. Leiomyosarcomas of the small and large bowel. Cancer 1978; 42:1375-84.
3. Evans HL. Smooth muscle tumors of the gastrointestinal tract. Cancer 1985; 58:2242-50.
4. Zollinger RM, Sternfeld WC, Schreiber H. Primary neoplasms of the small intestine. Am J Surg 1986; 151:654-8.
5. McGrath PC, Neifield JP, Lawrence W Jr. et al. Gastrointestinal sarcomas: Analysis of prognostic factors. Ann Surg 1987; 206:706-10.
6. Dougherty MJ, Compton C, Talbert M, Wood WC. Sarcomas of the gastrointestinal tract: separation into favorable and unfavorable prognostic groups by mitotic count. Ann Surg 1991; 214:569-74.
7. DeMatteo RP, Lewis JJ, Leung D, Mudan SS, Woodruff JM, Brennan MF. Two hundred gastrointestinal stromal tumors. Recurrence patterns and prognostic factors for survival. Ann Surg 2000; 231: 51-8.
8. Blanke CD, von Mehren M, Joensuu H, et al. Evaluation of the safety and efficacy of an oral molecularly-targeted therapy, STI571, in patients with unresectable or metastatic gastrointestinal stromal tumors (GISTS) expressing c-kit (CD117). Abstract Meeting Summaries ASCO 2001; 2.
9. Van Oosterom AT, Judson I, Verweij J, DiPaola E, van Glabbeke M, Dimitijevic S, Nielsen O. STI571, an active drug in metastatic gastrointestinal stromal tumors (GIST), an EORTC Phase I Study. Abstract Meeting Summaries ASCO 2001; 2.

10. Heslin MJ, Cordon-Cardo C, Lewis JJ, Woodruff JM, Brennan MF. Ki-67 detected by MIB-1 predicts distant metastasis and tumor mortality in primary, high-grade extremity soft tissue sarcoma. Cancer 1998; 83:490-7.

11. Sanders L, Silverman M, Rossi R, Braasch J, Munson L. Gastric smooth muscle tumors: diagnostic dilemmas and factors affecting outcome. World J Surg 1996; 20:992-5.

12. Ludwig DJ, Traverso LW. Gut stomal tumors and their clinical behavior. Am J Surg 1997; 173:390-4.

13. Lewin KJ, Riddel RH, Weinstein WM eds. Gastrointestinal Pathology and its Clinical Implications. New York: Igaku-Shoin Medica Publishers, 1992, pp299-301.

14. Al-Jaberi TM, Al-Masri N, Tubukhi A. Adult rhabdomyosarcoma of the gallbladder: case report and review of published works. Gut 1994; 35:854-6.

15. Conlon KC, Casper ES, Brennan MF. Primary gastrointestinal sarcomas: analysis of prognostic factors. Ann Surg Oncol 1995; 2:26-31.

16. Ng EG, Pollock RE, Munsell MF, et al. Prognostic factors influencing survival in gastrointestinal leiomyosarcomas. Ann Surg 1992; 215:68-77.

17. Daly MB, Clark GM, McGwire WM. Breast cancer prognosis in mixed Caucasian-Hispanic population. J Natl Cancer Inst 1985; 74:753-6.

18. Elledge RM, Clark GM, Chamness GC, et al. Tumor biologic factors and breast cancer prognosis among white, Hispanic and black women in the United States. J Natl Cancer Inst 1994; 86:705-9.

19. Gordon NH, Crowe JP, Brumberg DJ, et al. Socioeconomic factors and race in breast cancer recurrence and survival. Am J Epidemiol 1992; 135:609-15.

20. Gerdes J. Ki-67 and other proliferation markers useful for immonohistological diagnostic and prognostic evaluations in human malignancies. Semin Cancer Biol 1990; 1:199-206.

21. Drobnjak M, Latres E, Pollack D, et al. Prognostic implications of p53 nuclear overexpression and high proliferation index of Ki-67 in adult sof tissue sarcomas. J Natl Cancer Inst 1994; 86: 549-54.

22. Choong PF, Akerman M, Willen H, et al. Prognostic value of Ki-67 expression in 182 soft tissue sarcomas. Proliferation-a marker of metastasis? APMIS 1994; 102:915-24.

23. Reich NC, Oren M, Levine AJ. Two distinct mechanisms regulate the levels of a cellular tumor antigen. P53. Mol Cell Biol 1983; 3:2143-50.

24. Cordon-Cardo C, Lares E, Drobnjak M, et al. Molecular abnomalities of mdm2 and p53 genes in adult soft tissue sarcomas. Cancer Res 1994; 54:794-9.

25. Leach FS, Tokino T, Meltzer P, et al. p53 mutation and MDM2 amplification in human soft tissue sarcomas. Cancer Res 1993; 53 (Suppl):2231-4.

26. Andreassen A, Oyjord T, Hovig E, et al. p53 abnormalities in different subtypes of human sarcomas. Cancer Res 1993; 53:468-71.

Table 1. Demographic characteristics of patient population (n=49)

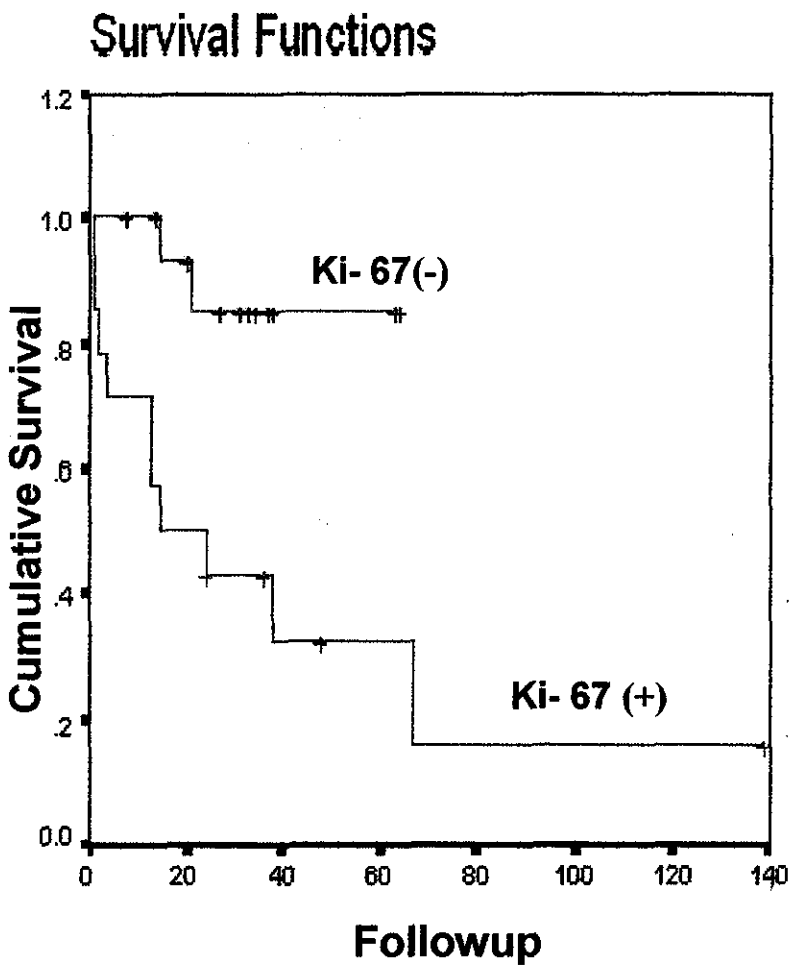
	Number	**Percentage**
Gender	24	49
Male	25	51
Female		
Race		
Hispanic	22	45
Caucasian	18	37
African-American	9	18
Age, years		
10-19	2	4.1
20-29	0	--
30-39	5	10.2
40-49	10	20.4
50-59	17	34.7
60-69	8	16.3
$\geq$ 70	7	14.3

Table 2. Factors associated with overall survival in primary GI sarcomas (Univariate analysis)

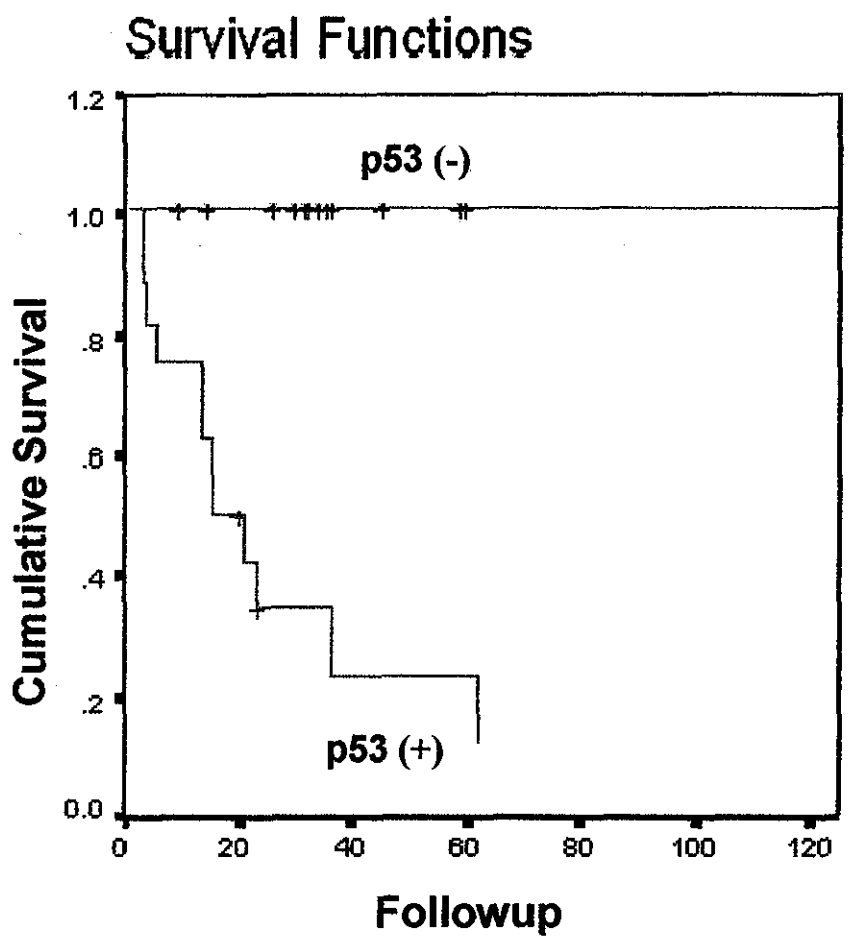
Factor		Median survival (mo)	P
Gender:	Male	47	0.3
	Female	79	
Age:	< 50	76	0.5
	> 50	49	
Race:	Hispanic	NR	**0.01**
	Caucasian	38	
	African-American	6	
Karnofski:	≥ 90	NR	**0.0002**
	<90	23	
Site:	Stomach	NR	0.5
	Other	67	
Tumor grade:	Low	NR	**0.00001**
	High	20	
Tumor size:	< 10 cm	NR	**0.004**
	> 10 cm	38	
Complete resection:	Yes	NR	**0.00001**
	No	10	
p53:	Positive	15	**0.00001**
	Negative	NR	
Ki-67:	Positive	18	**0.007**
	Negative	NR	

NR= Not reached

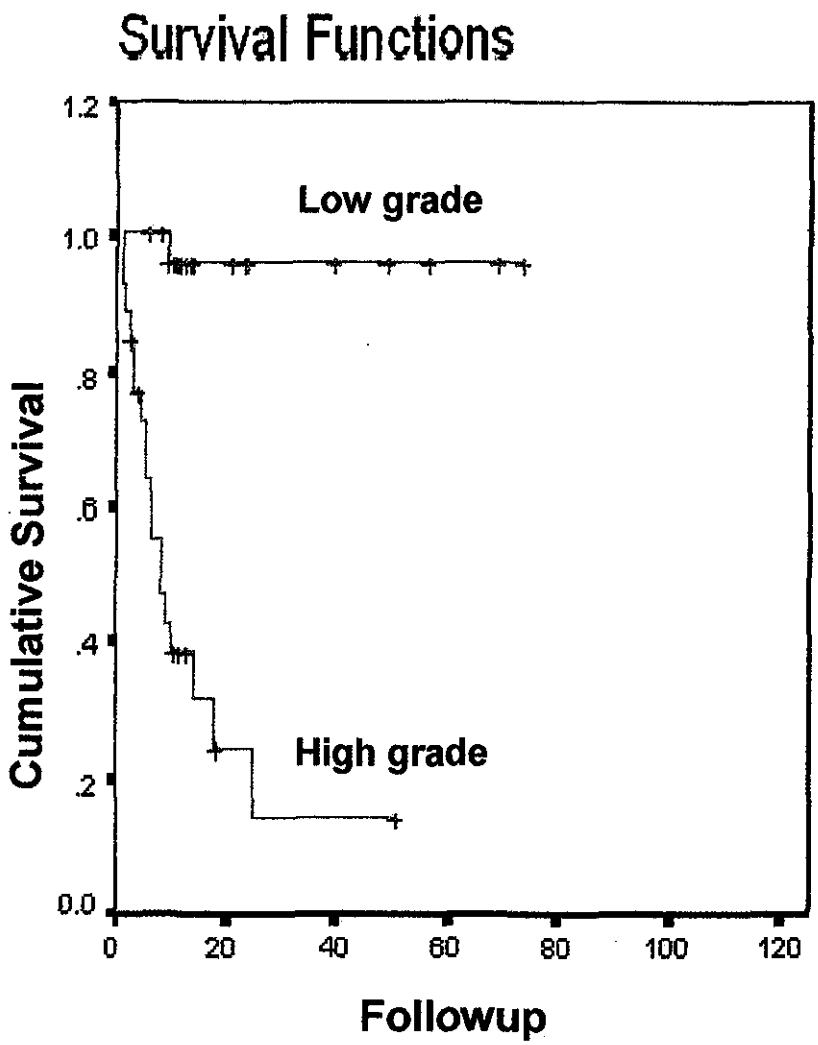
Ki-67



p53



Tumor Grade



Surgical Resection