

Citología Peritoneal en Cáncer Gástrico y sus Implicaciones en la toma de decisiones



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Cáncer gástrico y peritoneo

El Cáncer Gástrico

es una

neoplasia peritoneotropa

Patrón de diseminación (H^a natural)

Patrón de recidiva

Recidiva peritoneal tras tto. adyuvante

	Mediana de seguimiento	Cirugía	Cirugía + adyuvancia
INT 0116 (2001) Mac Donald et al	5 años	72 %	65 %
MAGIC (2006) Cunningham et al	4 años	¿? "local" 20.6 %	¿? "local" 14.4 %

Recidiva peritoneal tras tto. neoadyuvante

VOLUME 22 · NUMBER 14 · JULY 15 2004

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Multi-Institutional Trial of Preoperative Chemoradiotherapy in Patients With Potentially Resectable Gastric Carcinoma

J.A. Ajani, P.F. Mansfield, N. Janjan, J. Morris, P.W. Pisters, P.M. Lynch, B. Feig, R. Myerson, R. Nivers, D.S. Cohen, and L.L. Gunderson

Peritoneal cavity remained a frequent failure site despite laparoscopic screening before protocol therapy.

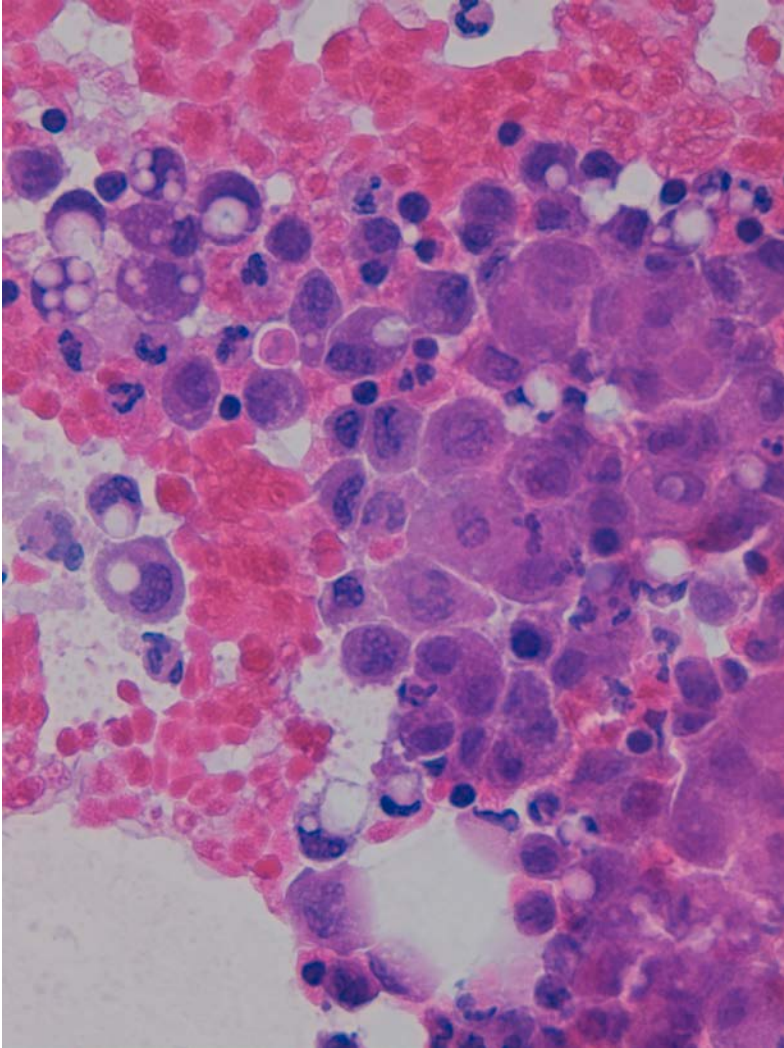
EDITORIAL

Peritoneal Dissemination: A Pending Issue in Gastric Cancer Worth Exploring

Santiago González-Moreno, MD, PhD

El control de la **diseminación peritoneal** es una asignatura pendiente en cáncer gástrico

Células tumorales libres en la cavidad peritoneal



Análisis citológico:

líquido ascítico

lavado peritoneal

Citología lavado peritoneal

Incidencia Cy (+)

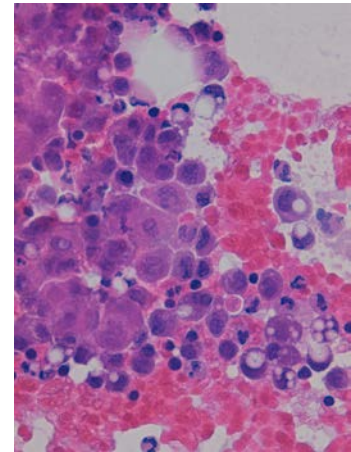
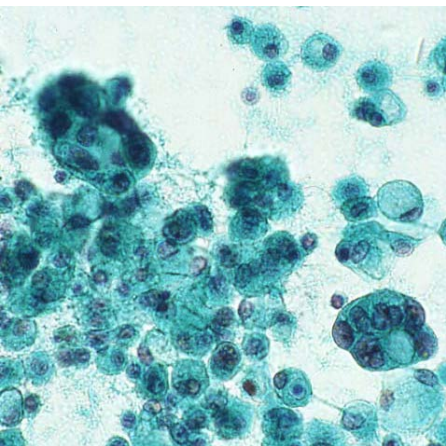
	H & E	Rt-PCR CEA mRNA	Combinación
Hao, 2010	27 / 29 %	32 / 35 %	39 / 43 %
Yonemura, 2001	18 %	17 %	89 %
Muntean, 2009	19 %	-----	-----

Valor pronóstico de la citología en el lavado peritoneal

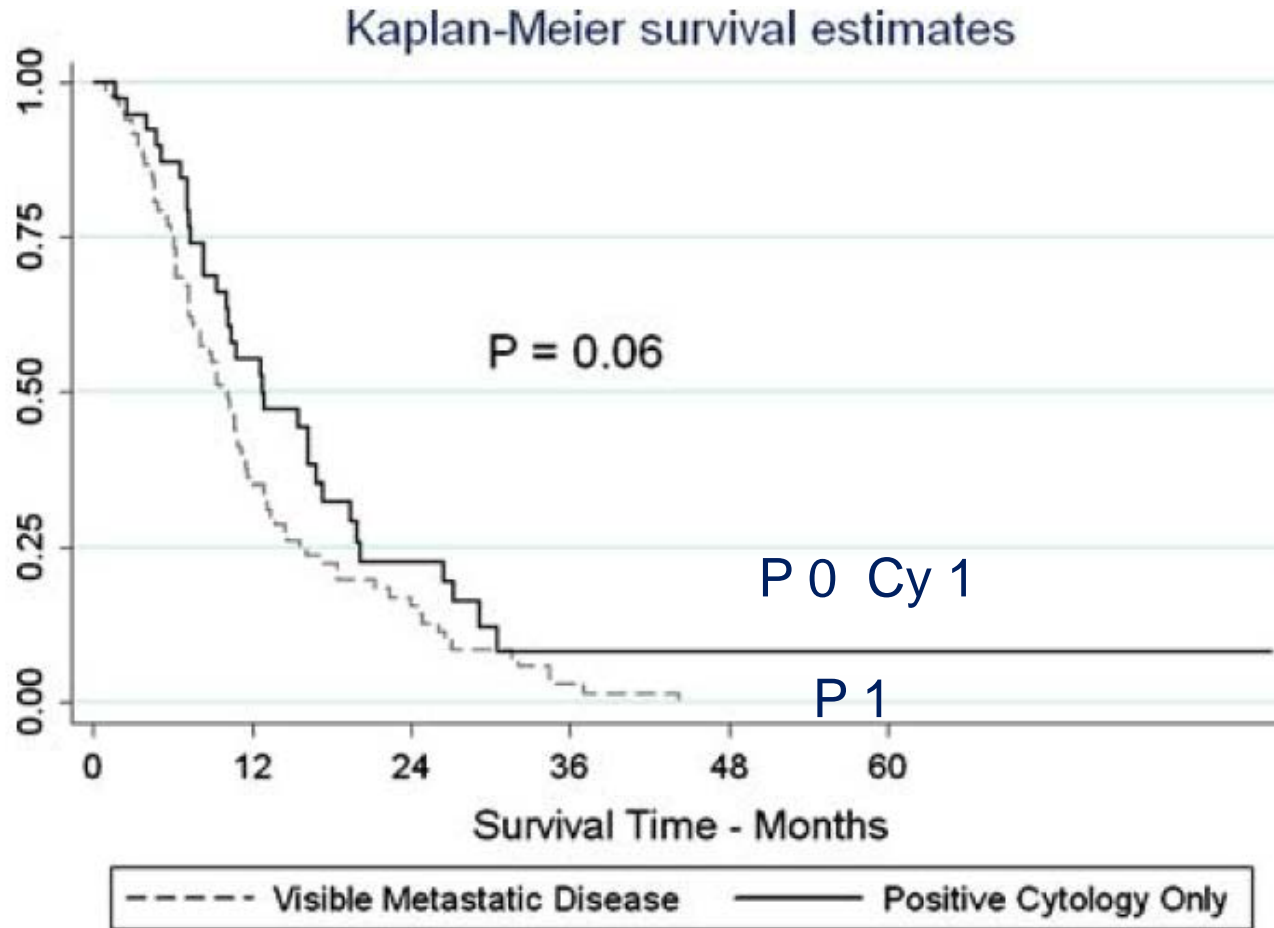
Citología positiva

=

Metástasis a distancia
(ESTADIO IV)

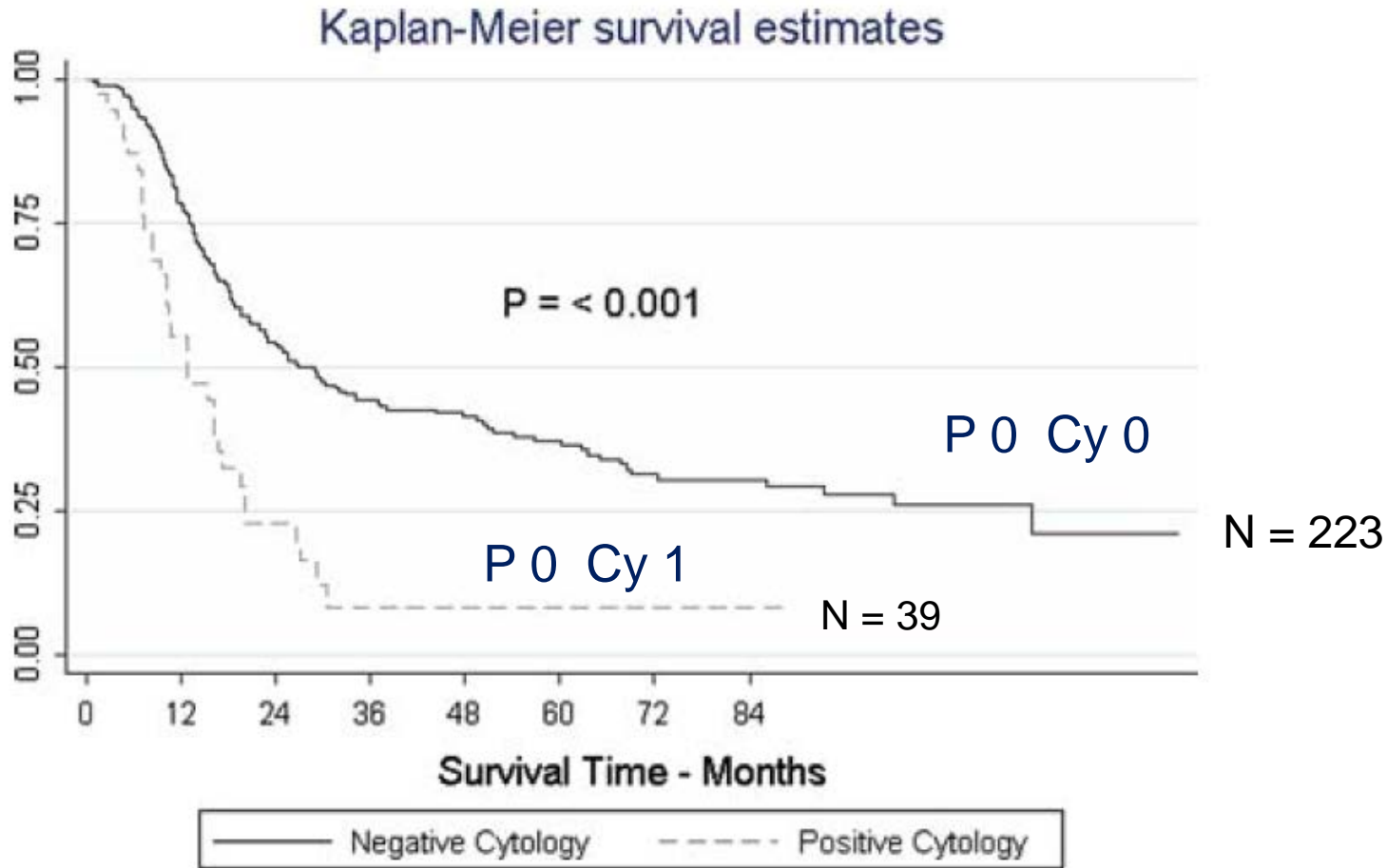


Valor pronóstico de la citología peritoneal



*Badgwell B T et al. Ann Surg Oncol 2008; 15(10): 2684-91
Does neoadjuvant treatment for gastric cancer patients with positive peritoneal cytology at diagnostic laparoscopy improve survival?*

Valor pronóstico de la citología peritoneal



Badgwell B T et al. Ann Surg Oncol 2008; 15(10): 2684-91
Does neoadjuvant treatment for gastric cancer patients with positive peritoneal cytology at diagnostic laparoscopy improve survival?

Valor pronóstico de la citología peritoneal

Table 7 5-Year overall survival for curative gastric cancer patients positive and negative for IFCCs

Study	N of M0 patients	TNM classification	Overall survival for IFCC + patients (%)	Overall survival for IFCC – patients (%)	Statistical significance (P)
Euanorasetr and Lertsithichai [23]	97	T1-4;NX;M0	0 ^b	75 ^b	<0.001 ^b
Kodera et al. 2001 [32]	34	T1-4;N0-3;M0	0 ^a	30 ^a	0.0380 ^b
Li et al. [33]	64	T1-4;NX;M0	15.4 ^a	60.5 ^a	<0.05 ^b
Nekarda et al. [37]	118	T1-4;N0-2;M0	8 ^b	60 ^b	0.0001 ^b
Ribeiro et al. [39]	220	T1-3;N0-2;M0	0 ^a	50 ^a	0.00001 ^b
Rosenberg et al. [40]	346	T1-4;N0-2;M0	35 ^b	71.9 ^b	<0.001 ^b

IFCCs intraperitoneal free cancer cells, N number, + positive, – negative

^a Estimated based on survival curves

^b Calculations published in original manuscript

Leake P-A et al. A systematic review of the accuracy and utility of peritoneal cytology in patients with gastric cancer. *Gastric Cancer* DOI 10.1007/s10120-011-0071-z. (online Aug 2, 2011)

Valor pronóstico de la citología peritoneal

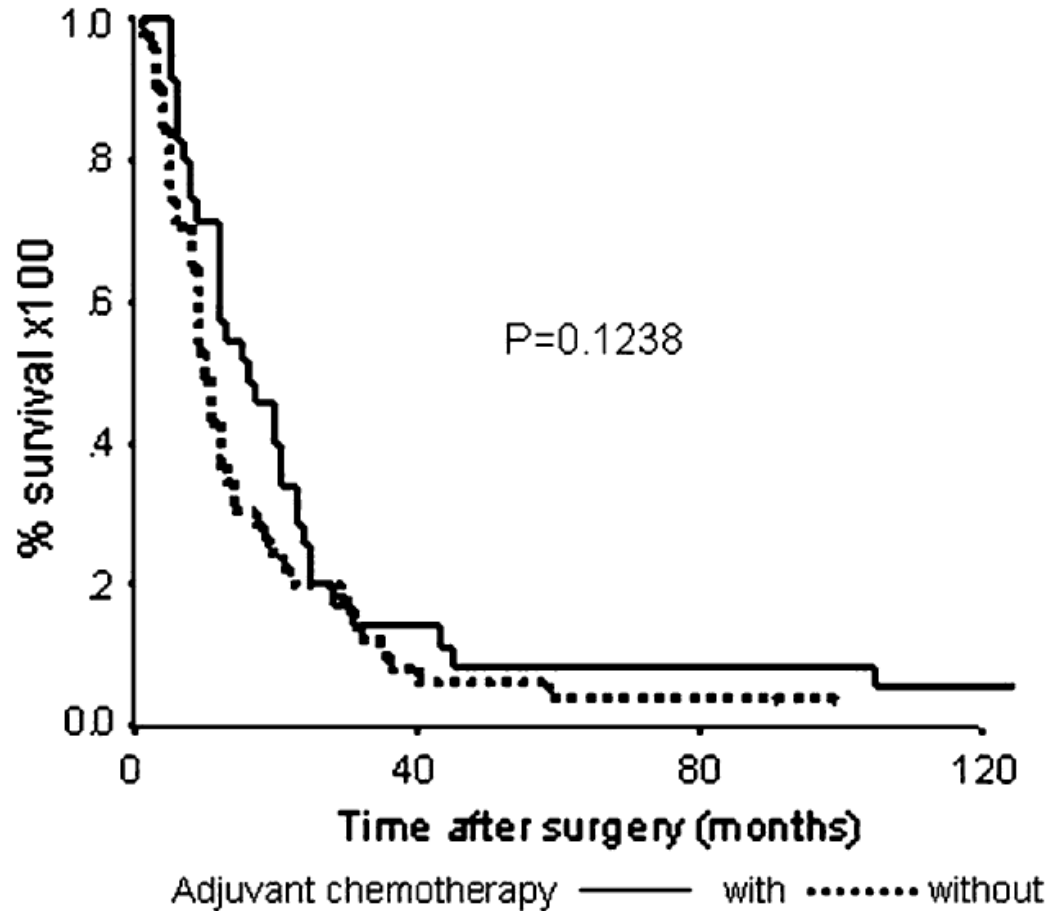
Independiente del estadio de la enfermedad

Suzuki T, Ochiai T, Hayashi H et al. Sem Surg Oncol 1999; 17: 103-107

Independiente de la radicalidad del tratamiento quirúrgico

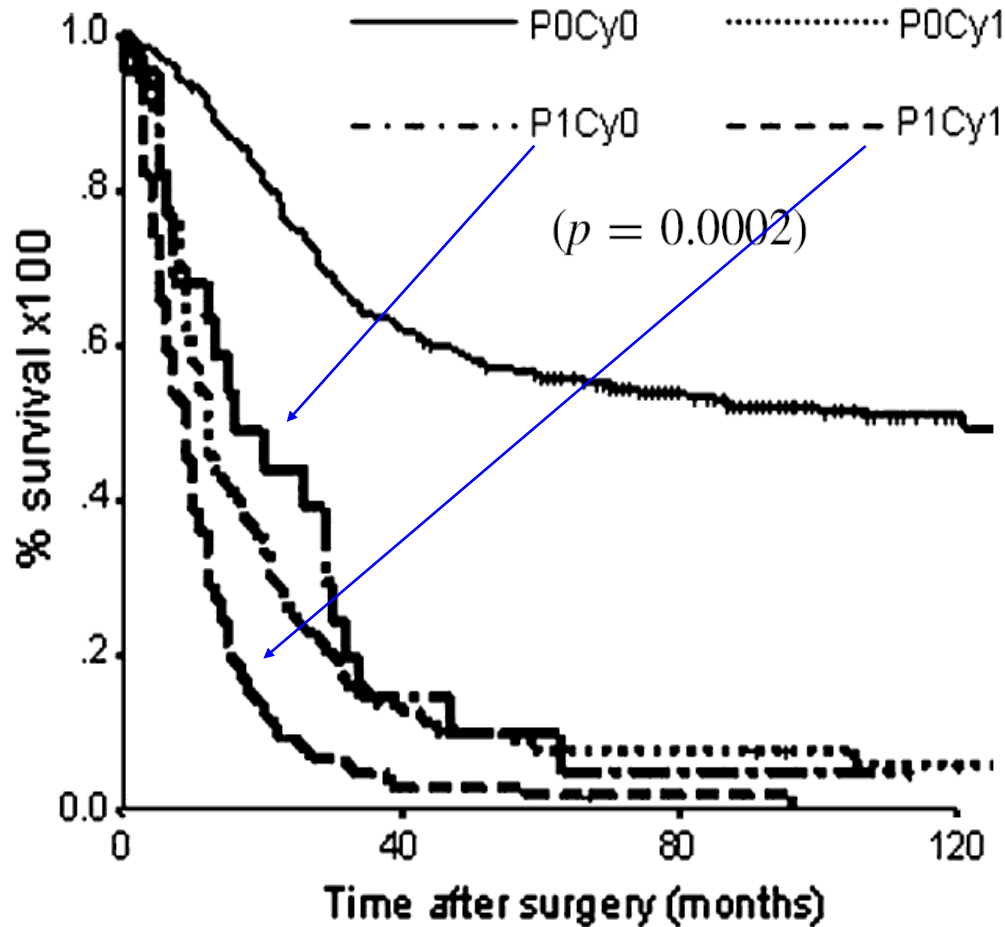
Bonenkamp J, Songun I, Hermans L et al. Br J Surg 1996; 83: 672-4

Valor pronóstico de la citología peritoneal



Fukagawa T et al. World J Surg 2010; 29: 1131-4
Significance of Lavage Cytology in Advanced Gastric Cancer Patients

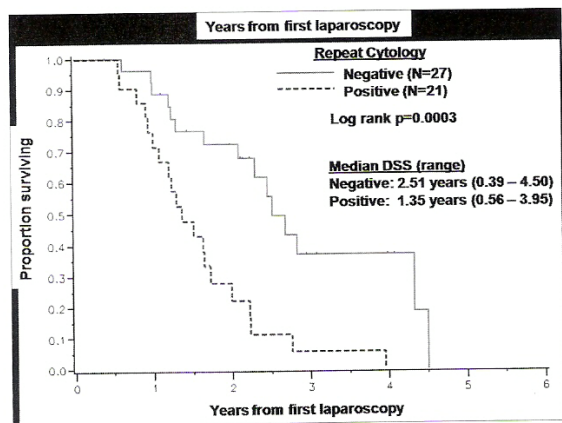
Valor pronóstico de la citología peritoneal



Fukagawa T et al. World J Surg 2010; 29: 1131-4
Significance of Lavage Cytology in Advanced Gastric Cancer Patients

Impact of Positive Peritoneal Cytology on Outcome in 291 Patients with Gastric Cancer J.J. Mezhir,* D.C. Coit, L.M. Jacks, M.A. Shah, M.F. Brennan, V.E. Strong. *Memorial Sloan Kettering Cancer Center, New York, NY.*

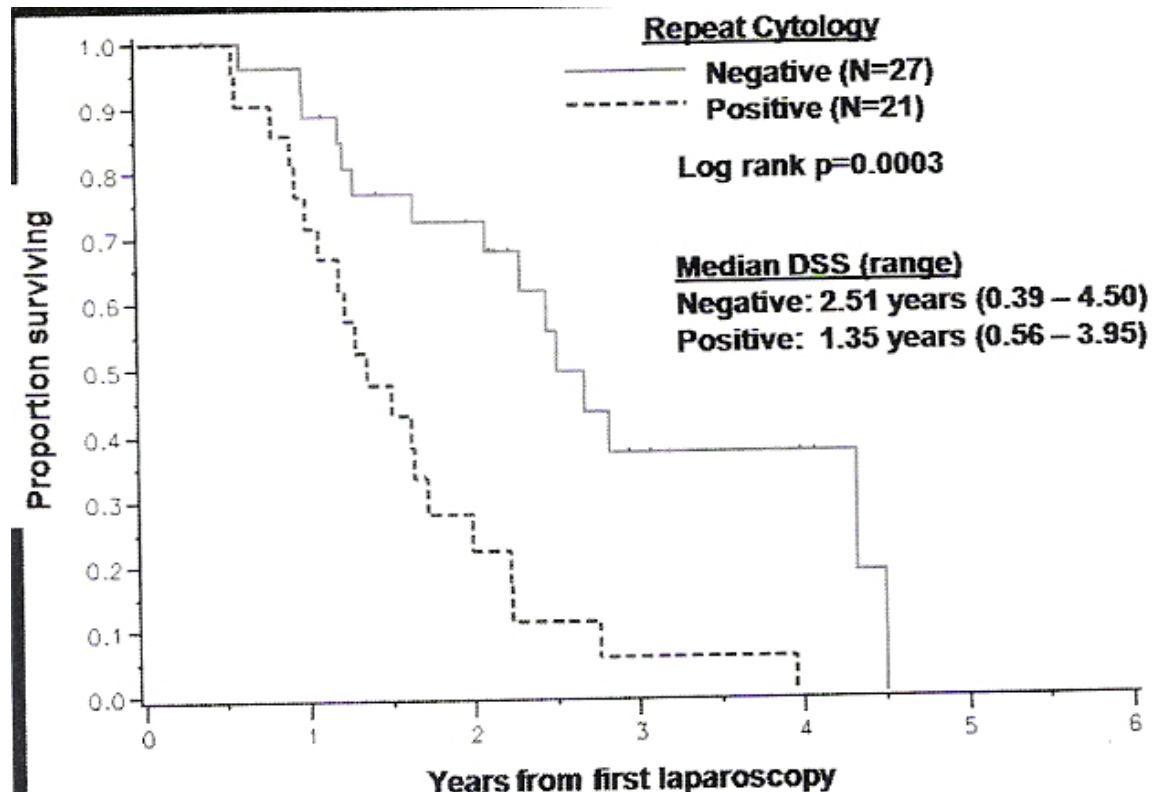
Introduction: Positive peritoneal cytology is a predictor of poor survival in patients with gastric cancer. Our aim is to more clearly define the natural history of this cohort. **Methods:** From 1993 to 2009, 1,241 patients with gastric cancer underwent staging laparoscopy with peritoneal washings; 291 (23%) had positive cytology. Multivariable Cox regression was performed to determine factors predictive of disease specific survival (DSS) at the time of initial staging laparoscopy. **Results:** There were 198 patients who had either peritoneal or visceral metastases discovered at laparoscopy and are designated M1-Cyt+. The remaining 93 patients had M0-Cyt+ disease (defined as cytology positive but no visible visceral or peritoneal metastases). The median DSS was 1 year (CI 0.9 to 1.1) for the entire cohort; all but one patient had died of disease by 58 months after initial diagnosis. Independent predictors of worse DSS were tumor location (antrum best, diffuse worst) and M-status (M1-Cyt+ median DSS 0.8 years versus M0-Cyt+ 1.3 years, $p < 0.0001$). Poor performance status predicted worse DSS (HR 2.78, CI 1.9–3.9, $p < 0.0001$). Seventy-two patients (25%) were selected for resection of primary tumor: T1/2=11(15%), T3=55(76%), T4=6(8%), 86% had nodal metastases. Resected patients were more often M0 (72% vs. 19%, $p < 0.0001$). Of the 261 patients who were treated initially with chemotherapy, 48 (18%) underwent repeat laparoscopy. Of these, 21 patients had persistent positive cytology and had significantly worse DSS than the 27 patients who converted to negative cytology (Figure). **Conclusions:** Patients with M0-Cyt+ disease exhibit significantly longer DSS than those with M1-Cyt+ disease; tumor location and performance status further predict DSS in advanced gastric cancer. Although long-term survival in patients with positive cytology is extremely uncommon, those who convert to negative cytology after chemotherapy exhibit significant improvement in DSS.



Valor pronóstico de la citología peritoneal tras quimioterapia

N=1241

23 % Cy1



Mezhir JJ et al. *Impact of Positive peritoneal cytology on outcomes in 291 patients with gastric cancer*

Ann Surg Oncol 2010; 17 (Supl1): S10

SSO 2010 Abstract

La Citología Peritoneal en las Clasificaciones de Cáncer Gástrico

- **Clasificación Japonesa (JGCA)**

Cy+ P- = Estadio IV

- **7ª Edición TNM:**

Citología Positiva = M1 (estadio IV)

- **NCCN (guidelines 2009):**

“peritoneal seeding (including peritoneal cytology) is a criteria of unresectability for cure”

Factores de riesgo para P0 Cy 1

Valor predictivo positivo de una citología positiva

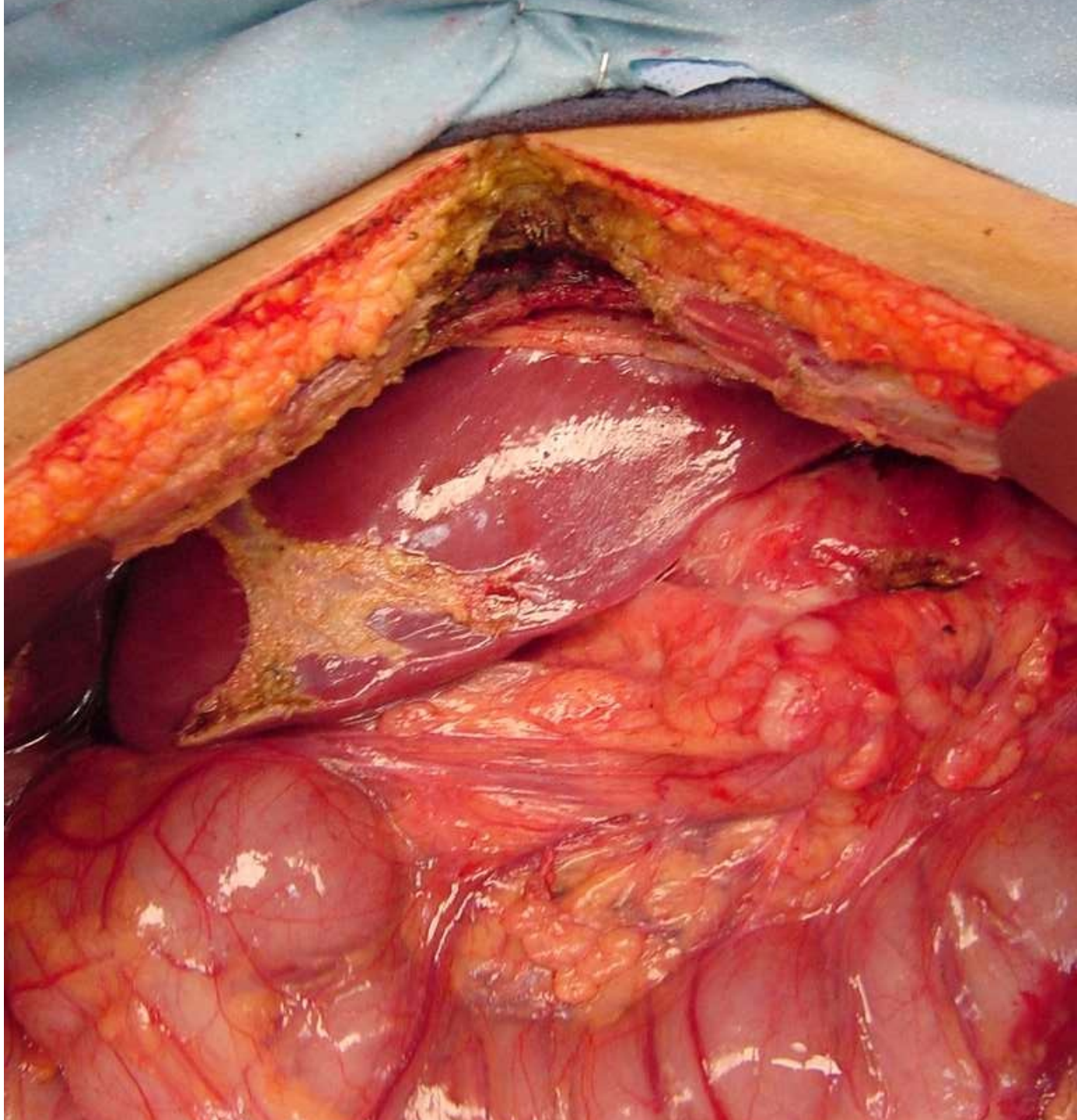
Invasión serosa

0'95

Adenopatías positivas

0'9

Bonenkamp J, Songun I, Hermans L et al. Br J Surg 1996: 83: 672-4



Factores de riesgo para P0 Cy 1

Predictores independientes de citología positiva

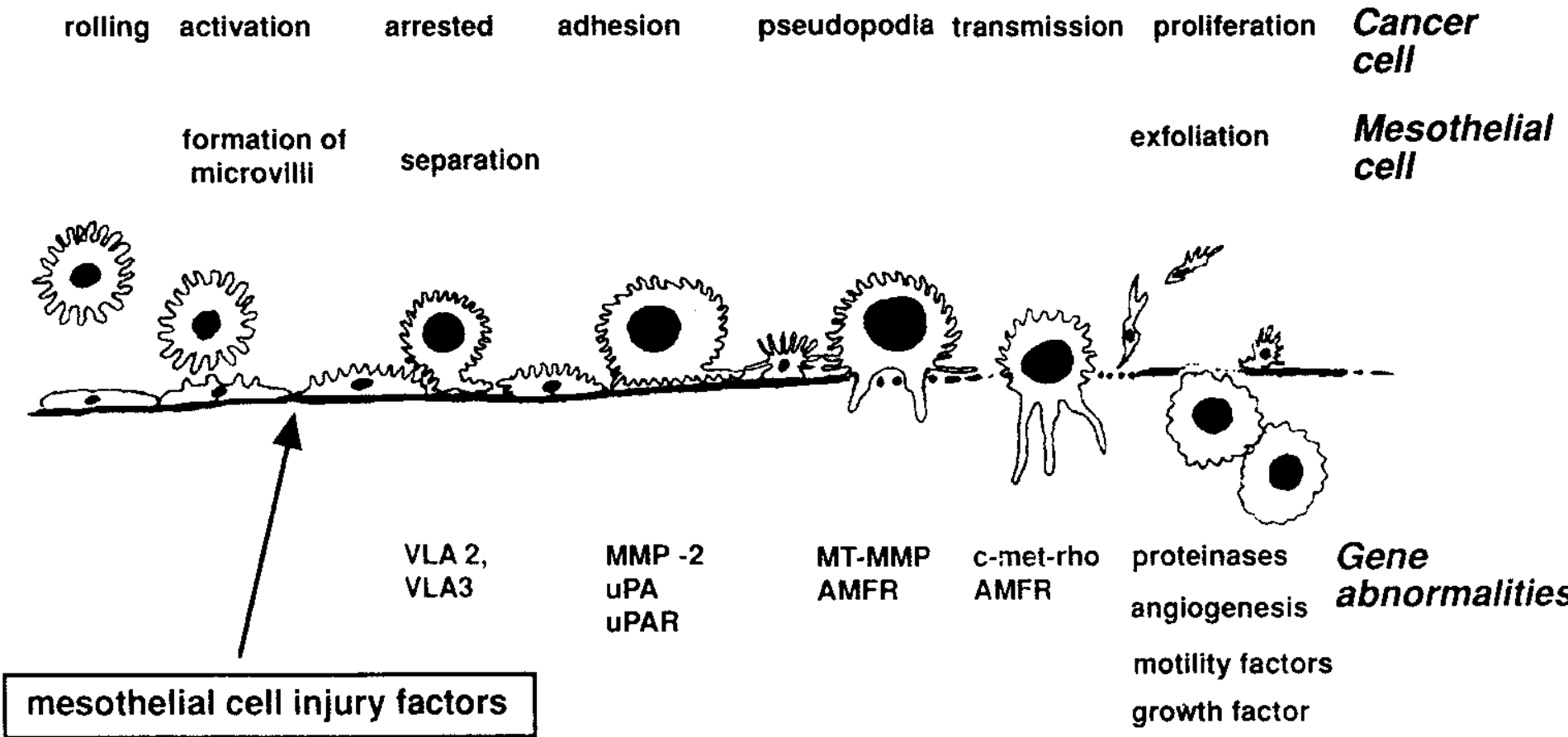
- Invasión serosa macroscópica (pT)
- Afectación linfática (pN)
- Histotipo (Lauren)

Predictores independientes de supervivencia

- Invasión serosa macroscópica
- Citología peritoneal positiva

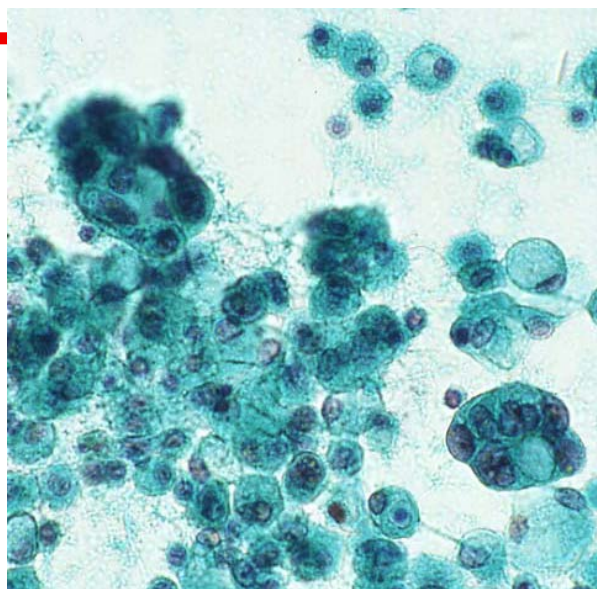
Zhe Sun, Ying-ying Xu, Zhen-ning Wang et al. Macroscopic Serosal Classification Predicts Peritoneal Recurrence for Patients with Gastric Cancer Underwent Potentially Curative Surgery
Ann Surg Oncol (2011) 18:1068–1080

Eficiencia metastásica de las células tumorales libres en la cavidad peritoneal

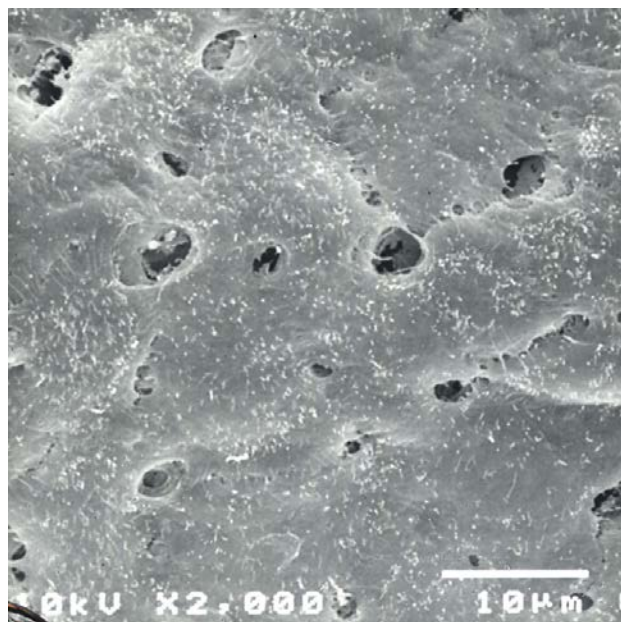
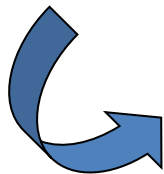


proteinasas, EGF, HGF, TGFβ, IL6?

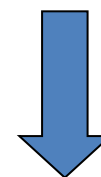
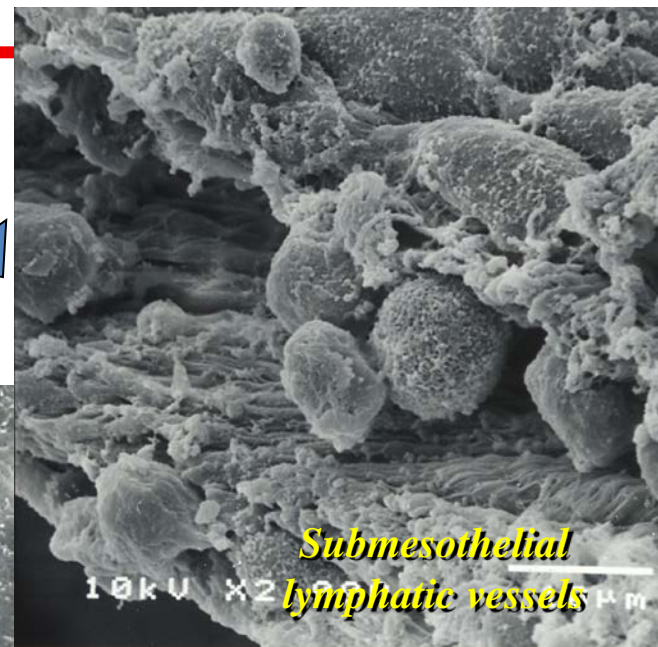
Mechanisms of peritoneal dissemination through lymphatic stomata on diahragm (translymphatic metastasis)



**Peritoneal free
Cancer cells**



**Diaphragmatic
lymphatic stomata**



Historia Natural P0 Cy1

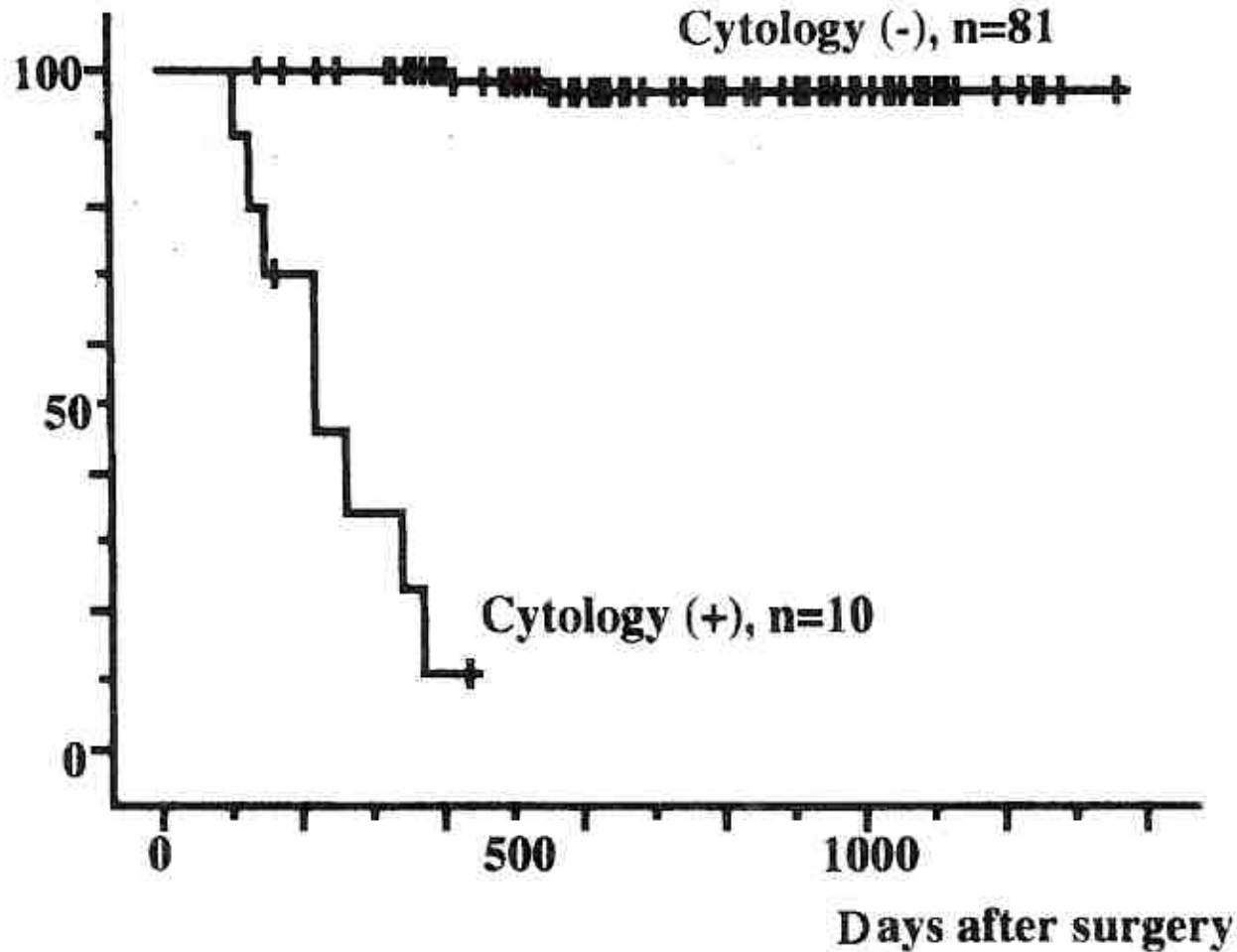
Recidiva peritoneal en citología (+)

81%

Suzuki T, Ochiai T, Hayashi H et al. Sem Surg Oncol 1999; 17: 103-107

Historia Natural P0 Cy1

% Survival without peritoneal dissemination



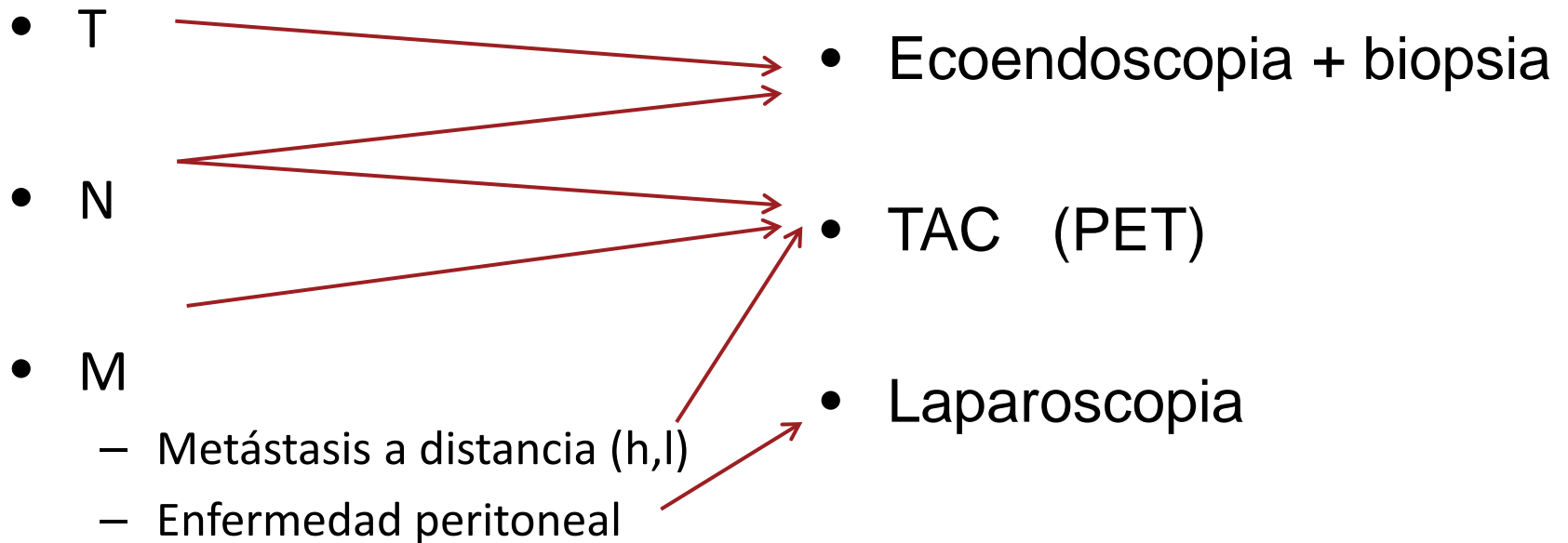
Valor pronóstico de la citología peritoneal

La Citología Peritoneal es un dato
IMPRESINDIBLE en la
estadificación del cáncer gástrico

Estadificación cáncer gástrico

PARÁMETROS

PRUEBAS DIAGNÓSTICAS



Recomendaciones sobre el uso de citología peritoneal

	ORGANISMO / DOCUMENTO	AÑO Journal	RECOMENDACIÓN
JGCA	<i>Japanese Classification of Gastric Carcinoma, 3rd English Edition</i>	2011 Gastric Cancer	Incluida en estadificación (OBLIGADA)
SAGES	<i>Diagnostic Laparoscopy Guidelines</i>	2008 Surg Endosc	Recomendada
ESMO	<i>Clinical Practice Guidelines for Diagnosis, Treatment and Follow-Up</i>	2010 Ann Oncol	Opcional
NCCN	Gastric Cancer	2010 J NCCN	No aparece en algoritmo terapéutico

Estadificación peritoneal en estudios de neoadyuvancia

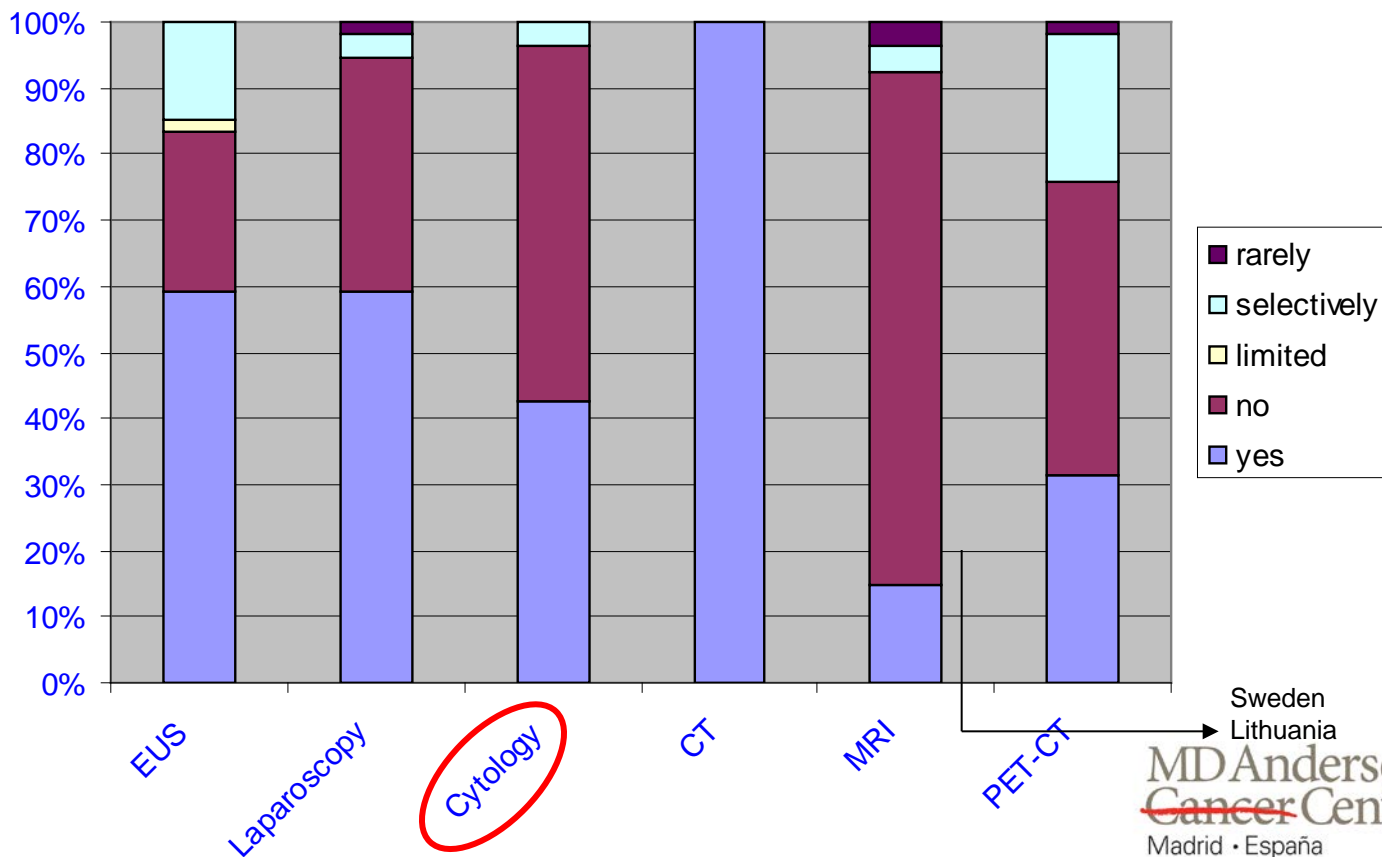
AUTOR	AÑO	INSTITUCIÓN	LAPAROSCOPIA ESTADIFICACIÓN	CITOLOGÍA PERITONEAL
Ajani et al. (n=33/41)	2004 / 5	MDACC	SI	NO / SI
Cunningham et al. (n=250)	2006	MRC (MAGIC)	NO	NO



EUNE Gastric Cancer Survey

(55 participants from 15 European countries)

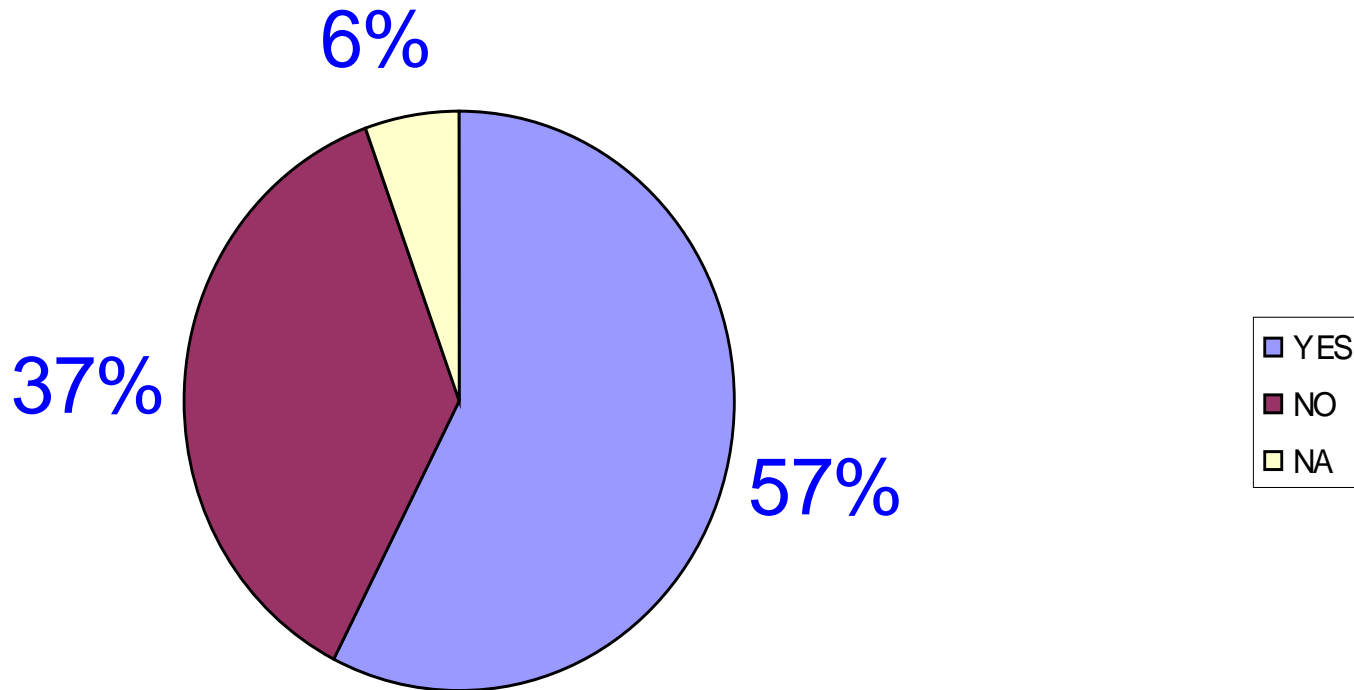
3. Regarding preoperative staging in clinically localized gastric cancer, which methods are used? (say yes or no for each method)





EUNE Gastric Cancer Survey

4. Upon request to your pathologist, can you have an intraoperative reading/report of a peritoneal cytology lavage specimen ?



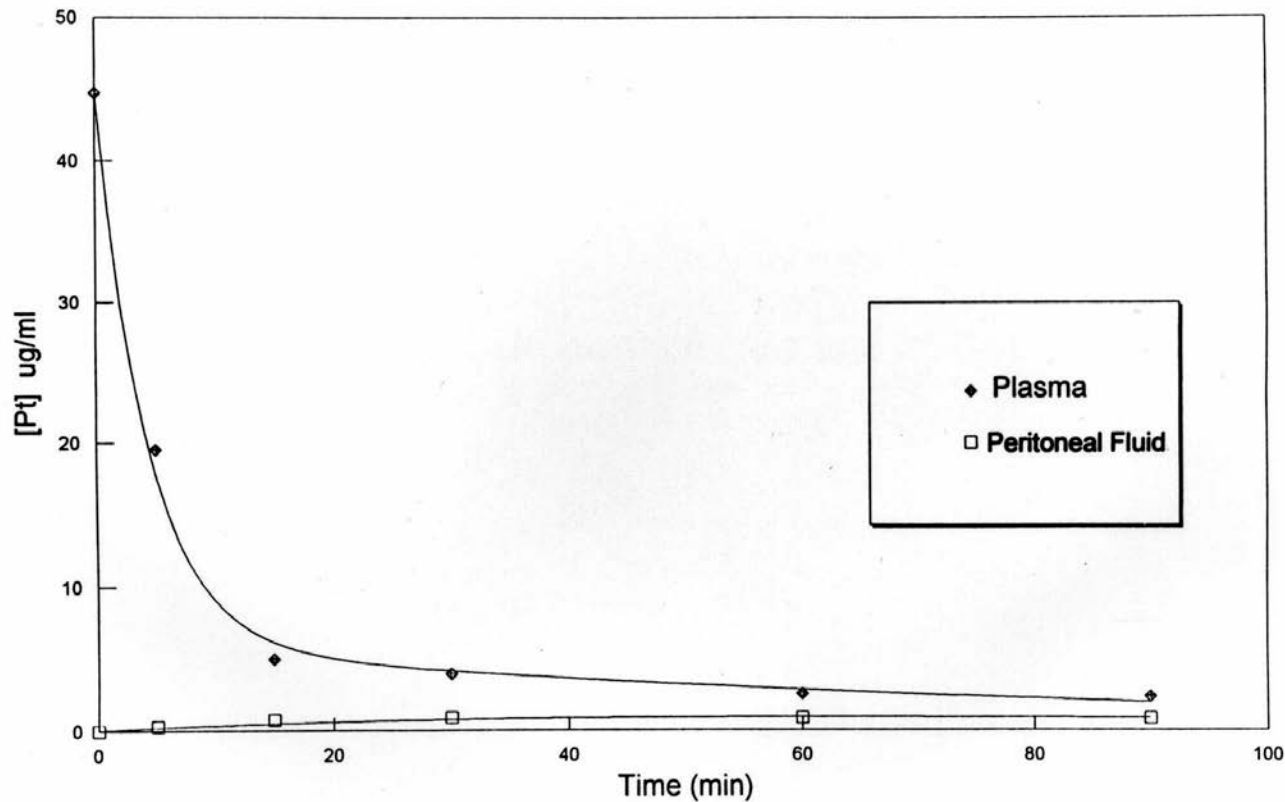
Cáncer gástrico

Determinante de supervivencia:

CONTROL DE LA ENFERMEDAD

PERITONEAL MICROSCÓPICA

Farmacocinética Quimioterapia IV

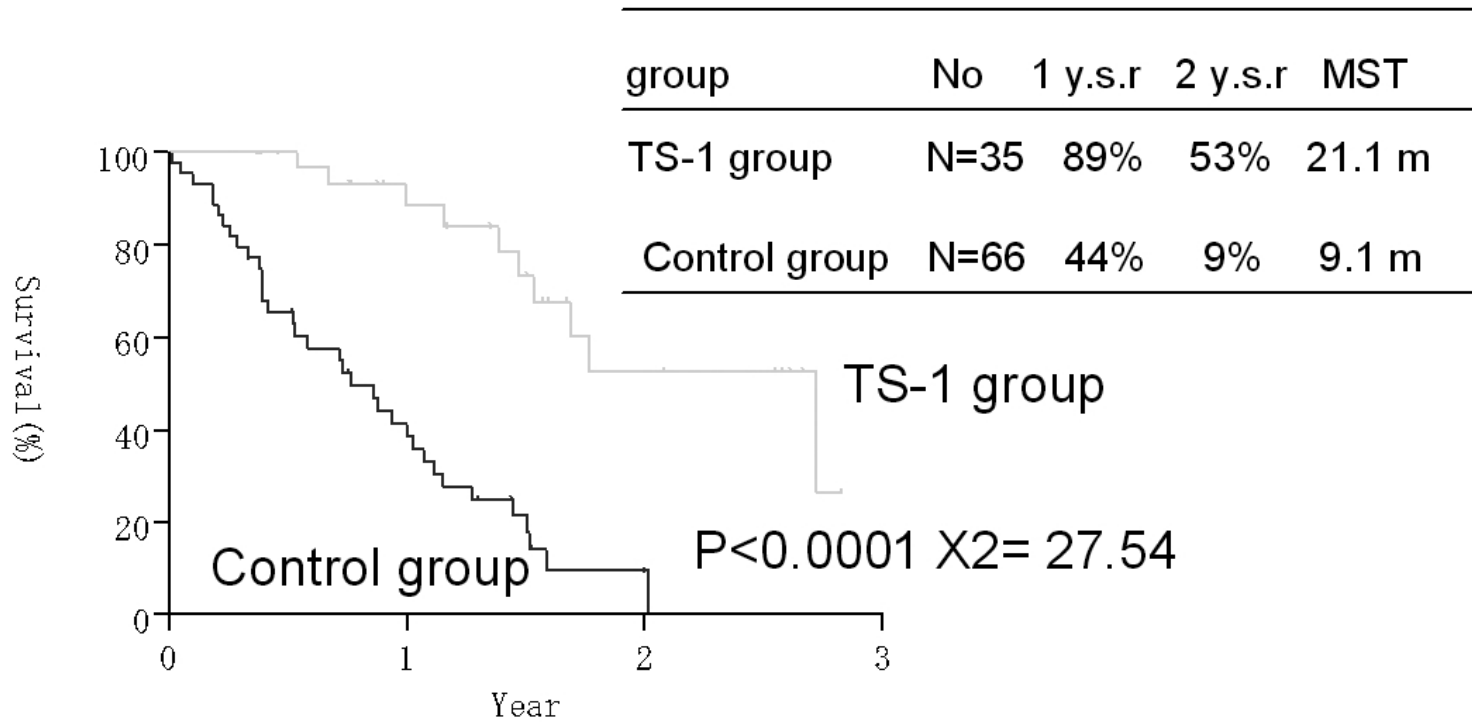


Efecto de la quimioterapia sistémica sobre células libres en la cavidad peritoneal

CITOLOGÍA (+) (Laparoscopia)			CITOLOGÍA (+) (laparotomía)
N	11	QUIMIOTERAPIA NEOADYUVANTE (CDDP + 5FU + LV)	15
%	31%		43 %
INT	0/10	Positivización n=5	1 / 10
DIF	11/25	—————→ Negativización n=1	14 / 25

*Nekarda H, Schenk U, Sendler A et al.
4th IGCC. New York (USA), Mayo 2001*

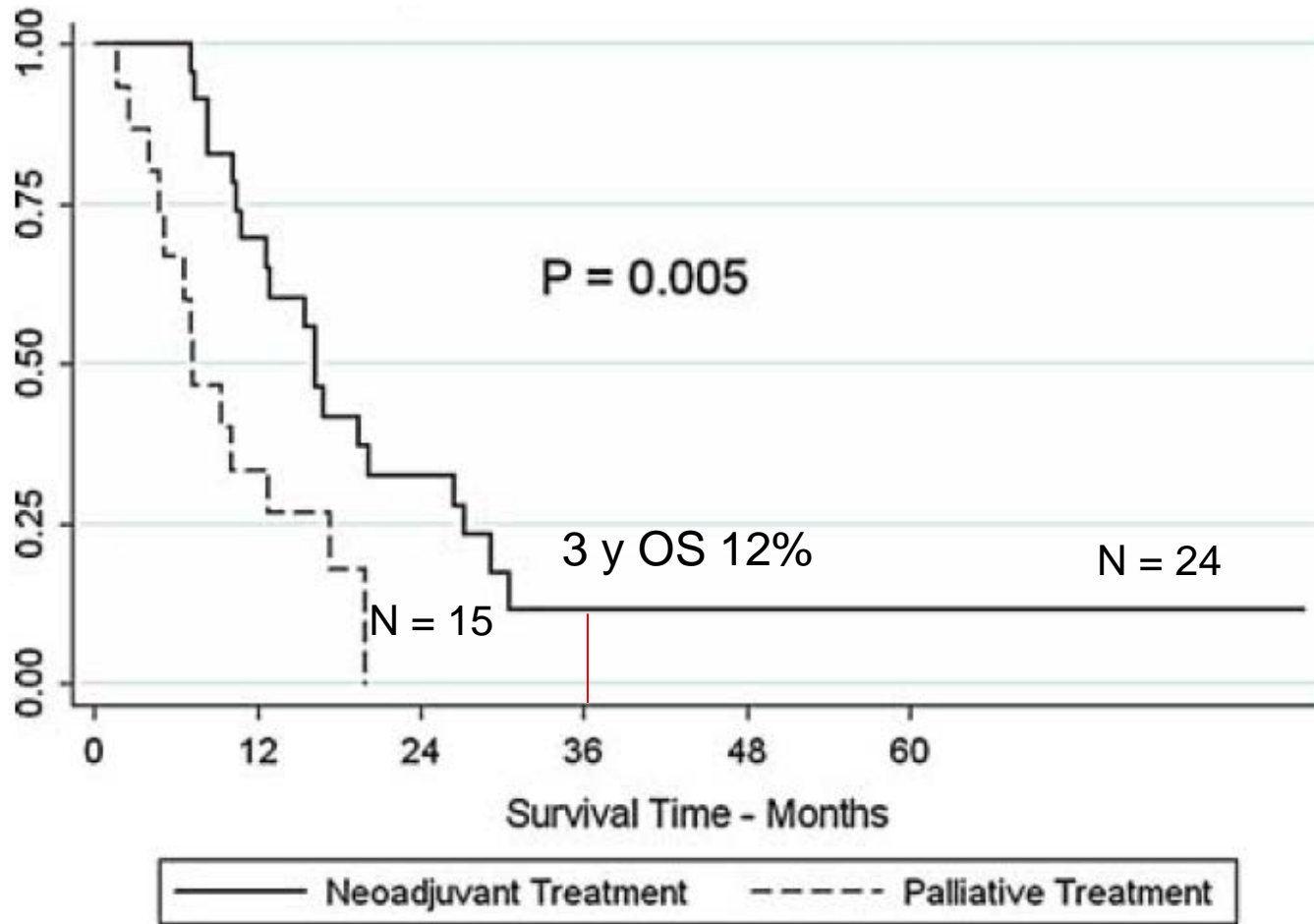
Figure 9: Survival of patients with potentially curable gastric cancer and peritoneal free cancer cells, who were treated with post-operative oral administration of 80 mg/m² of TS-1 at the respective dose for 28 days, followed by a 2-week rest. This schedule was repeated every 6 weeks until the occurrence of recurrence, unacceptable toxicities or patients' refusal.



Yonemura et al- Cancer Treat 2007

The usefulness of oral TS-1 treatment for potentially curable gastric cancer patients with intraperitoneal free cancer cells

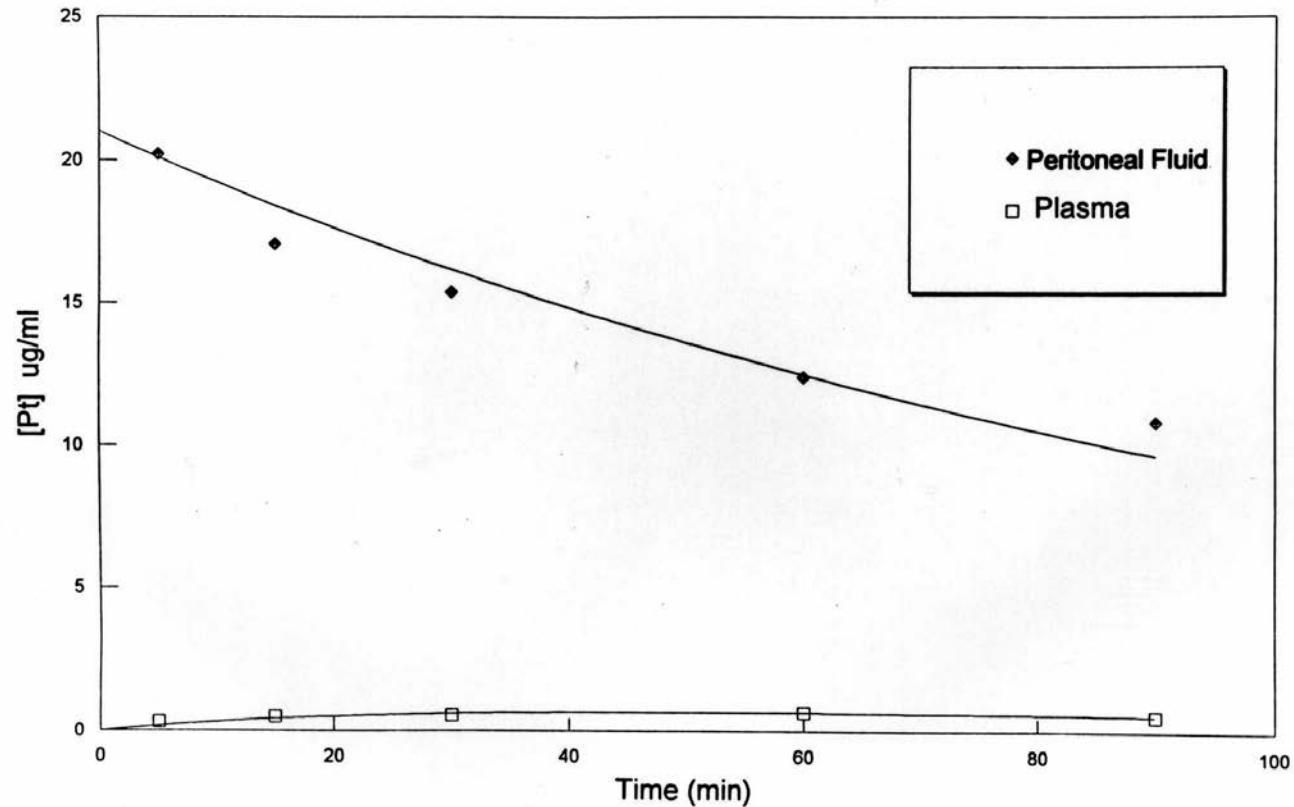
Efecto de la quimioterapia sistémica



P 0 Cy 1

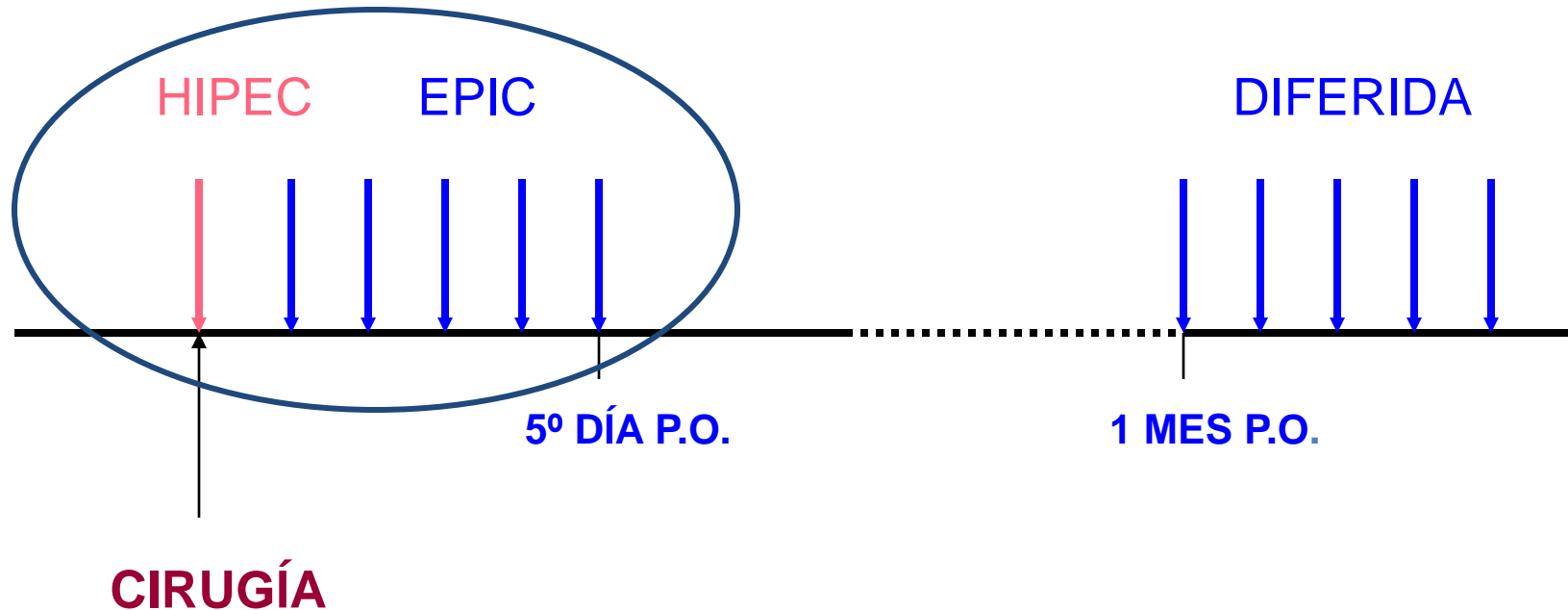
*Badgwell B T et al. Ann Surg Oncol 2008; 15(10): 2684-91
Does neoadjuvant treatment for gastric cancer patients with positive peritoneal cytology at diagnostic laparoscopy improve survival?*

Farmacocinética Quimioterapia IP



Quimioterapia Intraperitoneal: Modos de administración

PERIOPERATORIA



Ca. gástrico resecable P0 Cy 1

Opciones terapéuticas

- 1.-Lavado repetido + EPIC
- 2.- EPIC
- 3.- HIPEC
- 4.- Ensayo clínico – GASTRICHIP

RANDOMIZED CONTROLLED TRIALS

Extensive Intraoperative Peritoneal Lavage as a Standard Prophylactic Strategy for Peritoneal Recurrence in Patients with Gastric Carcinoma

Masafumi Kuramoto, MD, PhD,* Shinya Shimada, MD, PhD,* Satoshi Ikeshima, MD,*
Akinobu Matsuo, MD, PhD,* Yasushi Yagi, MD, PhD,† Masakazu Matsuda, MD, PhD,†
Yutaka Yonemura, MD, PhD,‡ and Hideo Baba, MD, PhD§

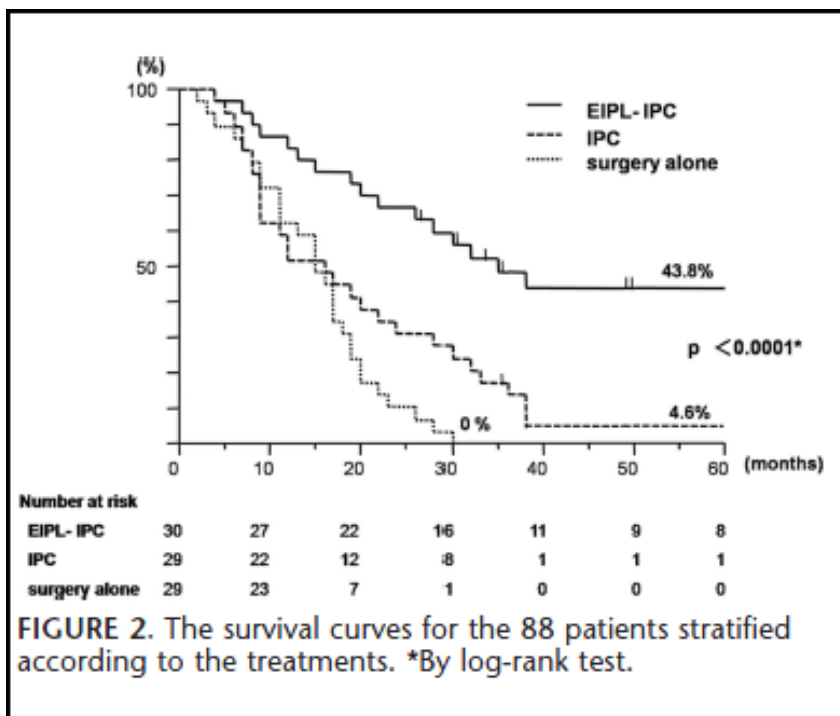


FIGURE 2. The survival curves for the 88 patients stratified according to the treatments. *By log-rank test.

TABLE 3. Comparison of Patterns of Recurrent Site

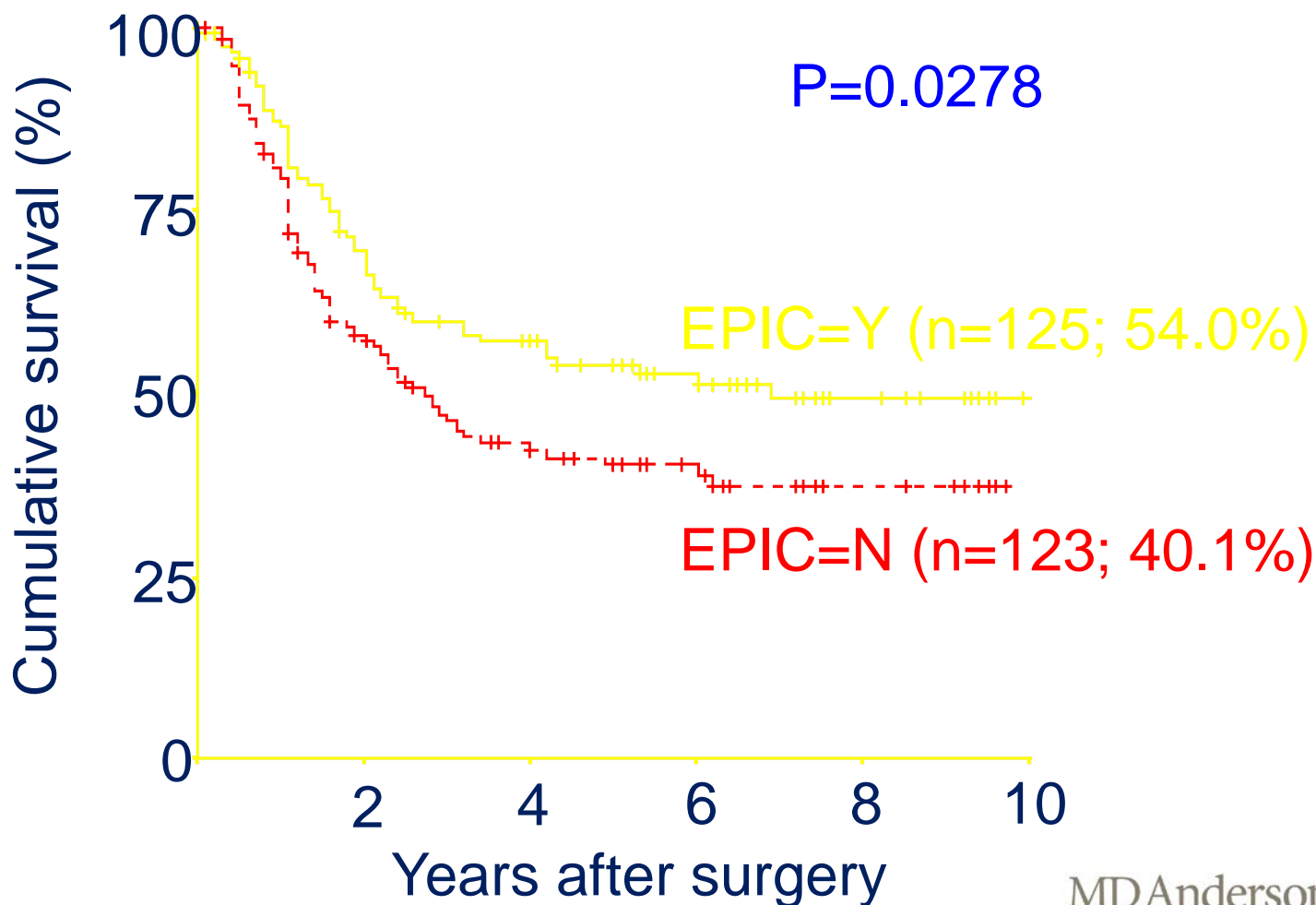
Site of Recurrence	EIPL-IPC (n = 30)	IPC (n = 29)	Surgery Alone (n = 29)	P
Peritoneum	12 (40.0%)	23 (79.3%)	26 (89.7%)	<0.0001*
Lymph node	2 (6.7%)	3 (10.3%)	2 (6.9%)	0.8495
Liver	2 (6.7%)	1 (3.4%)	1 (3.4%)	0.7991
Lung	1 (3.3%)	1 (3.4%)	0 (0.0%)	0.4445
Total	17 (56.7%)	28 (96.6%)	29 (100%)	<0.0001*

Values are number of patients (%).

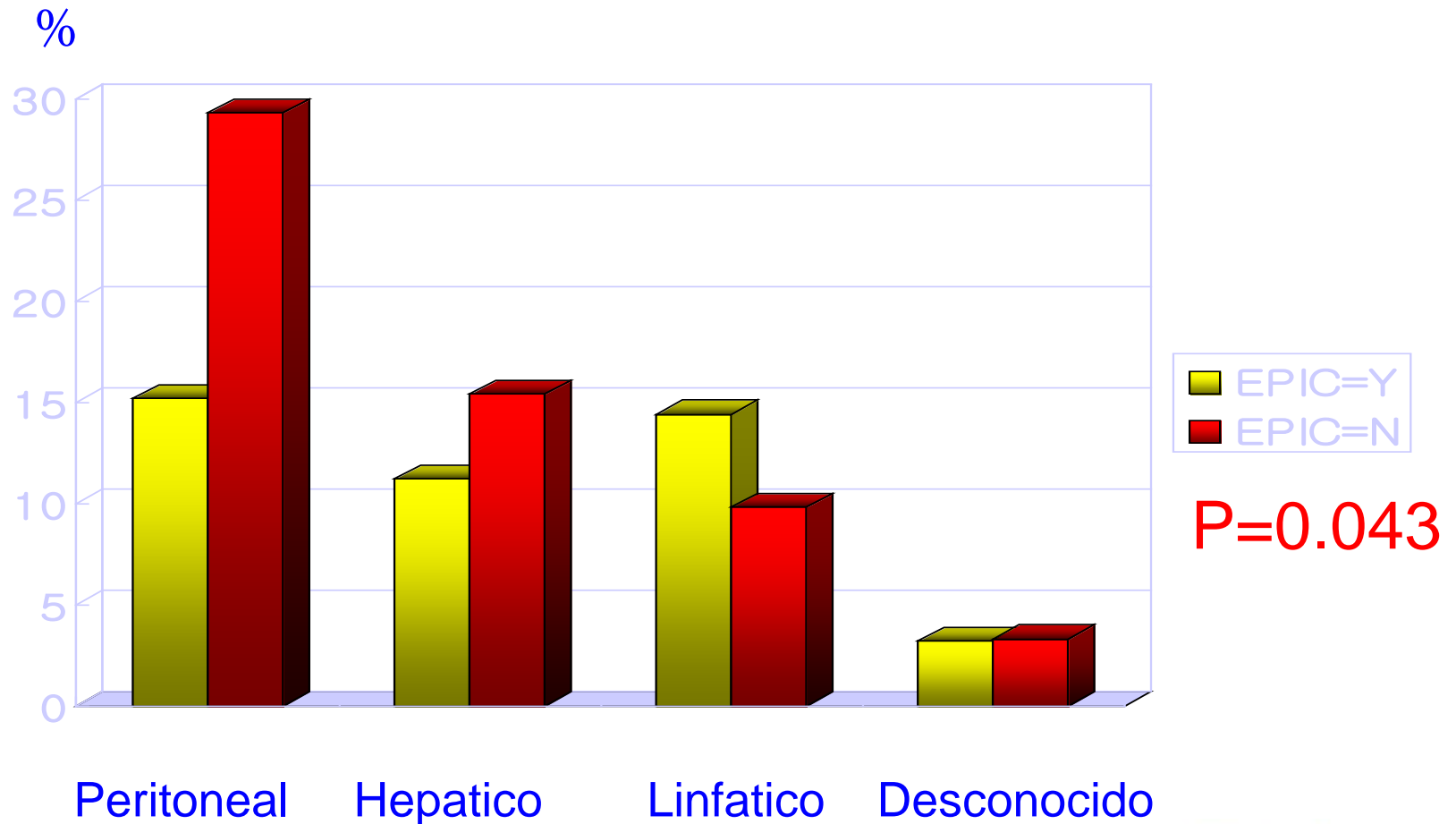
*Statistically significance.

EIPL indicates extensive intraoperative peritoneal lavage; IPC, intraperitoneal chemotherapy.

Supervivencia global



Patrón de recidiva

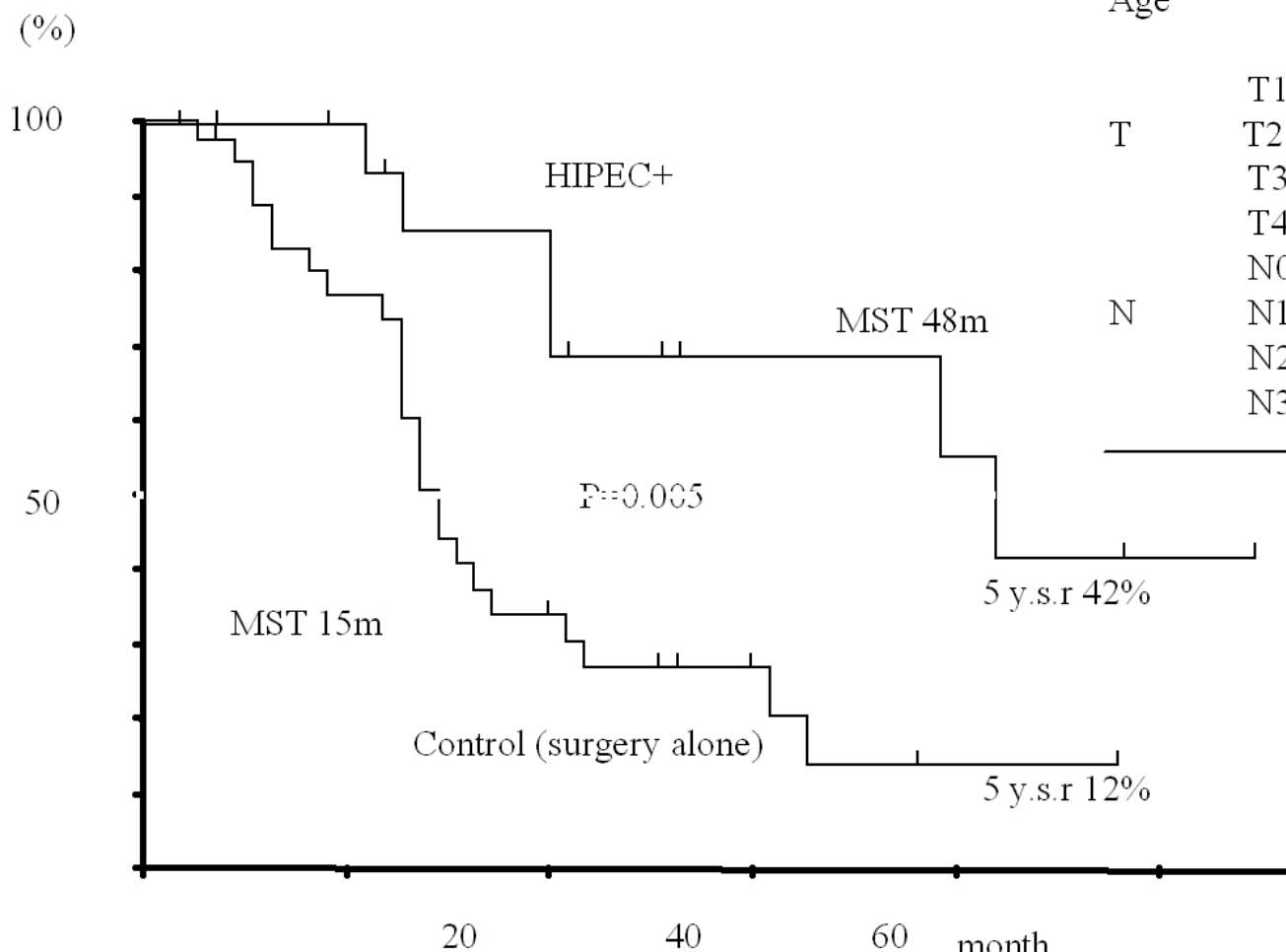


Yu W, Whang I, Ho YC et al. *World J Surg* 2001; 25: 985-90

Recidiva peritoneal en estudios de adyuvancia

	Mediana de seguimiento	Cirugía	Cirugía + adyuvancia
INT 0116 (2001) Mc Donald et al.	5 años	72 %	65 %
MAGIC (2006) Cunningham et al.	4 años	¿? "local" 20.6 %	¿? "local" 14.4 %
(1998, 2001, 2006) Yu et al.	10 años	26.9 %	8.7 %

Figure 10) Survival of patients with potentially curable gastric cancer and peritoneal free cancer cells, who were treated with HIPEC and without HIPEC (Kiyosaki H et al. Ref. 48)

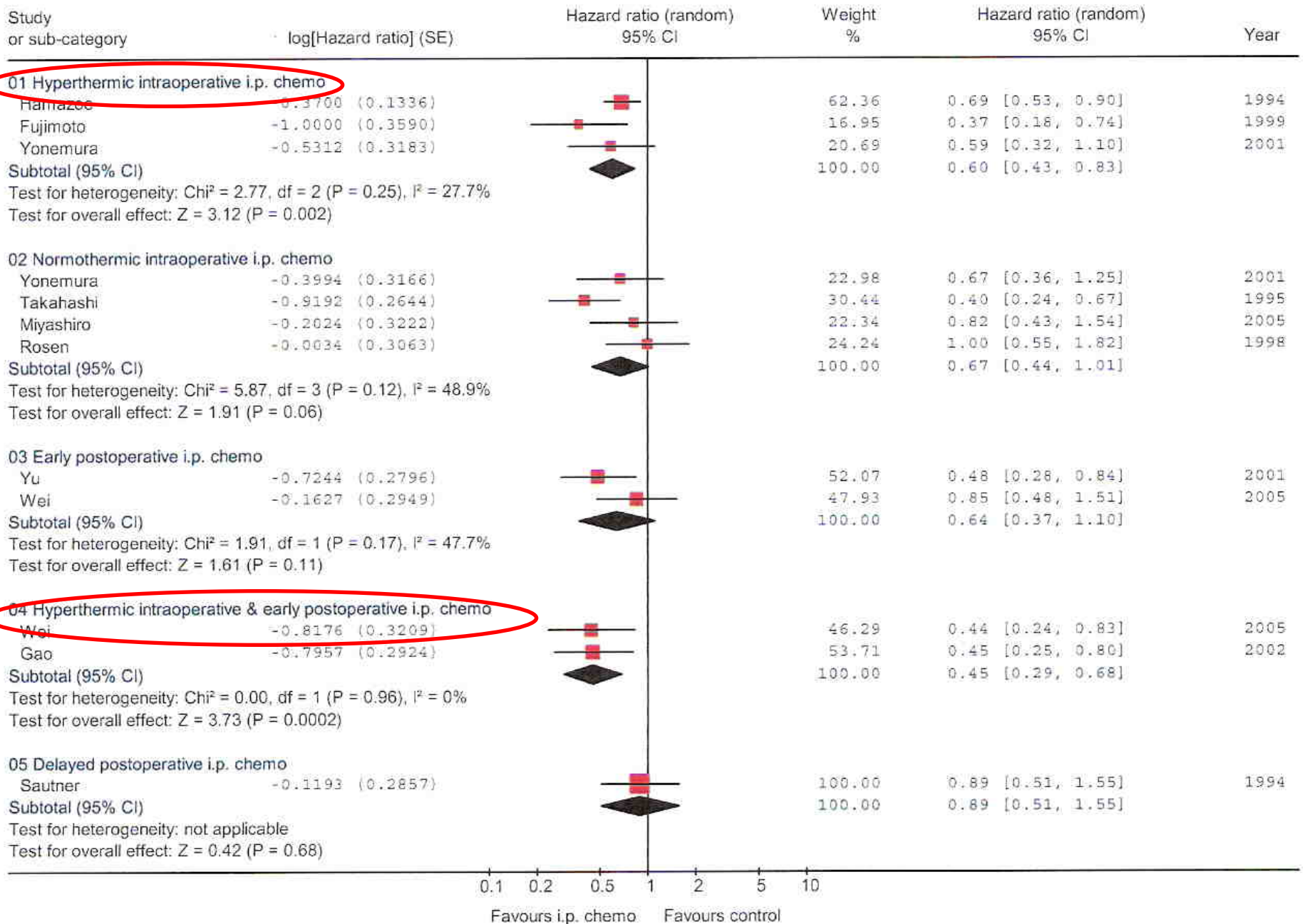


	THIPC (n=15)	Surgery alone (n=39)
Gender(M/F)	12/3	12/27
Age	57.1±9.2	66.6±9.6
T	T1	1
	T2	2
	T3	11
	T4	1
N	N0	4
	N1	3
	N2	8
	N3	1

	peritoneal recurrence	
	+	-
THIPEC	7 (46.7%)	8
Surgery alone	25(64.1%)	14

Yonemura et al- Hepatogastroenterology 2001; 48:1776-82.
 Intraoperative chemohyperthermic peritoneal perfusion as an adjuvant to gastric cancer: final results of a randomized controlled study

Review: Ajuvant Intraoperative Chemotherapy for Advanced Gastric Cancer
 Comparison: 01 Adjuvant intraperitoneal chemotherapy vs. control
 Outcome: 03 Overall survival





Phase III Randomized Trial:

D2+HIPEC Trial

Radical Resection (D2) plus Intraoperative Hyperthermic Chemoperfusion (HIPEC) in Gastric Cancer with High Risk of Peritoneal Recurrence

Alfredo Garofalo, MD

National Cancer Center Regina Elena

Rome

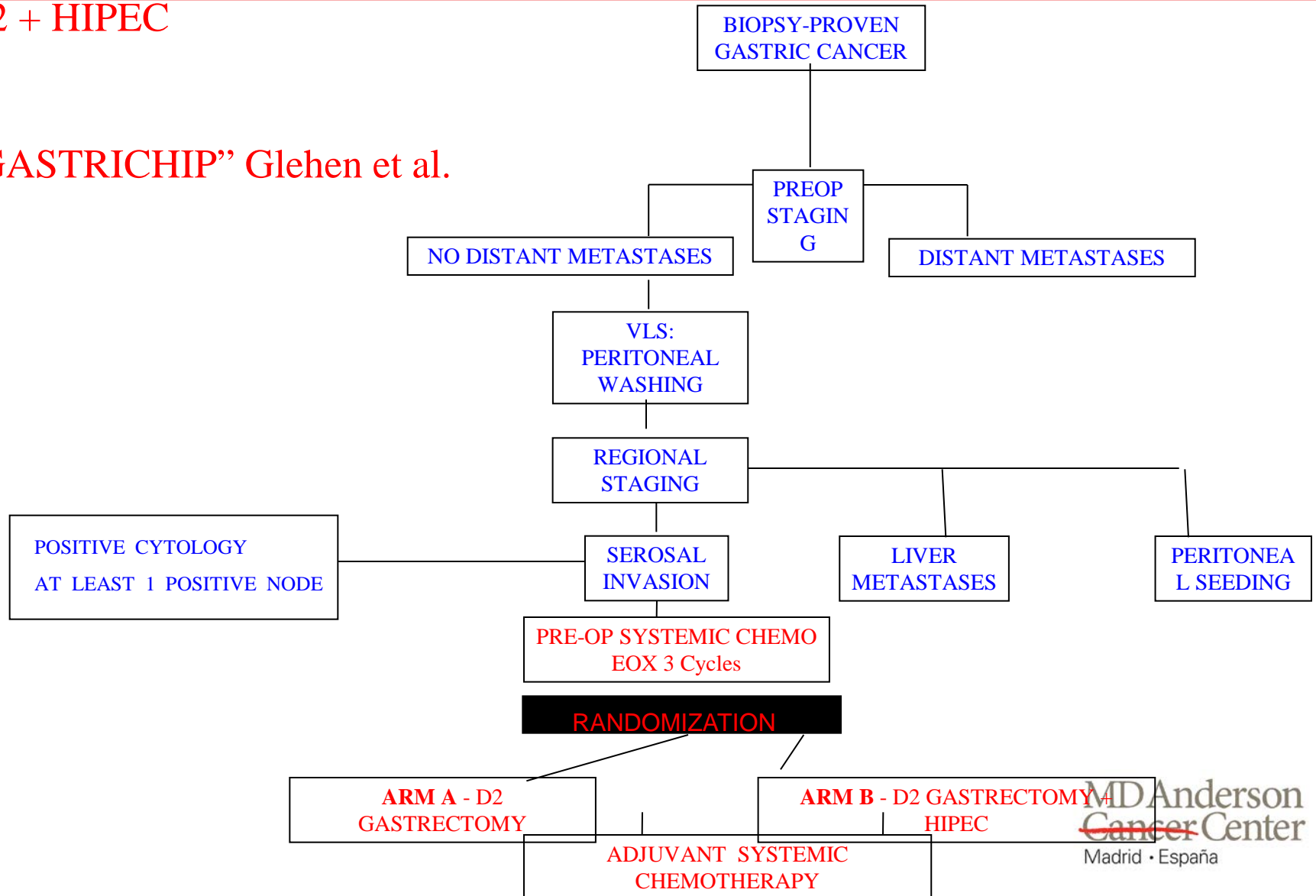
garofalo@ifo.it

STUDY PROPOSAL

Phase III Randomised Trial

D2 + HIPEC

“GASTRICHIP” Glehen et al.



Neo Adjuvant Systemic Chemotherapy

Randomization

D2 Gastrectomy

D2 Gastrectomy

HIPEC (41.5-42.5°C on peritoneum for 30')

Oxaliplatin (Oxaliplatin 300mg/m² with
2.5 Lt of perfusate/m² for 30')

Adjuvant Systemic Chemotherapy

Conclusiones y Mensajes Clave

1. La mejora en los resultados terapéuticos en cáncer gástrico pasan por diseñar tratamientos eficaces dirigidos contra el componente peritoneal de la enfermedad
2. La presencia de células tumorales libres en cavidad peritoneal por si sola supone un pronóstico sombrío (estadio IV)
3. La estadificación del cáncer gástrico localmente avanzado no está completa si no incluye una laparoscopia exploradora con citología del lavado peritoneal (TNM 7) para detectar diseminación peritoneal macro o microscópica

Conclusiones y Mensajes Clave

4. Existe evidencia científica de que la quimioterapia intraperitoneal perioperatoria es eficaz para el control locorregional de la enfermedad tras resección curativa, evitando la recidiva peritoneal y prolongando la supervivencia global
5. En los casos de citología peritoneal positiva la quimioterapia intraperitoneal es un tratamiento probablemente más eficaz que la quimioterapia sistémica por si sola.

Conclusiones y Mensajes Clave

6. Las guías de práctica clínica actuales indican una actitud paliativa ante un tumor gástrico resecable con citología peritoneal positiva.
Debemos fomentar estudios que exploren un abordaje multimodal con intención curativa en estos casos, que incluyan el uso de la quimioterapia ip. , e incluir a estos pacientes en los mismos.



MD Anderson
~~Cancer Center~~
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¡Muchas Gracias !

sgonzalez@mdanderson.es

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