Current role of surgery and multimodal treatment in localized gastroesophageal cancer

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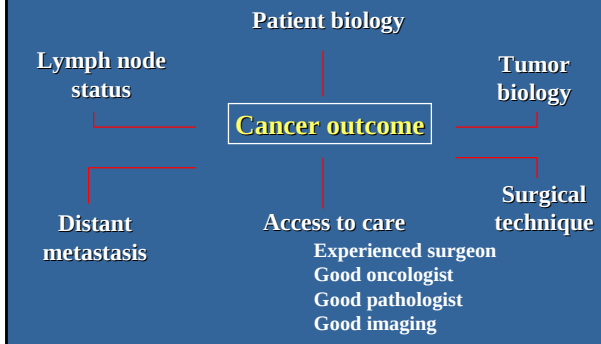
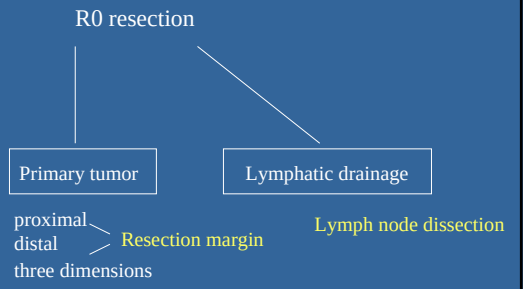


Cumulative 5-year survival in patients with resected gastric cancer

Stage	Germany (n=1564)	USA (n=10,237)	Japan n= 12,535)
I			
Ia	85.2	59	95.6
Ib	69.2	44	
II	43.7	29	70.1
III			
IIIa	28.6	13	36.3
IIIb	17.7		
IV	8.7	3	23.1

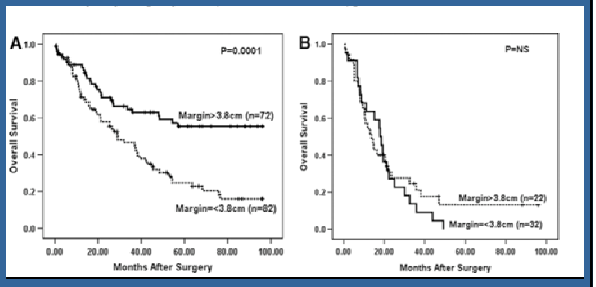
Fink U y cols. *World J Surg* 19: 509, 1995

Gastroesophageal Cancer



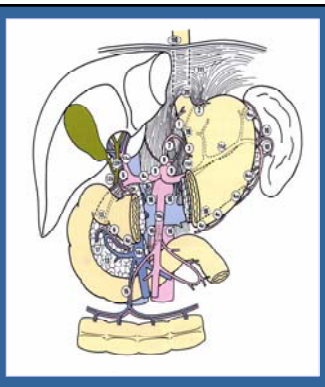
The impact of esophageal margin

Patients with ≥ T2 that underwent R0 resection with ≥ 15 nodes



≤ 6 lymph nodes + ≥ 6 lymph nodes +

Barbour AP y cols. Ann Surg 2007; 246:1-8



D1 dissection: Stations 1-6, N1 level
D2 dissection: Stations 7-11, N2 level

Goals of extended lymphadenectomy

- eliminate all visible metastatic lymph nodes
- achieve a better local control of the disease
- improve the quality of staging

D2 dissections provide more accurate surgical pathological staging

Gastric Cancer Stage Migration

D1 TNM		D2 TNM				
	Nº of	Stage (nº of patients)				
Stage	Patients	II	IIIA	IIIB	IV	% Change
II	48	30	18			38%
IIIA	49		19	21	1	61%
IIIB	24			6	18	75%

Adapted from McDonald JS. Semin Oncol 2004; 31: 566

The role of D2 lymphadenectomy in gastric cancer
Who benefits?

Bonenkamp (1999) Cuschieri (1996)	D2 dissection did not improve overall survival and was associated with a higher operative morbidity and mortality
Siewert (1998)	Improved 5-year survival rates were confined to the subset of patients with stage II and IIIA There was no increase in mortality
Harrison (1998)	Better survival in patients with T3N0 stage

Impact of Total Lymph Node Count on Staging and Survival After Gastrectomy for Gastric Cancer: Data From a Large US-Population Database

David D. Smith, Rebecca R. Schwarz, and Roderich E. Schwarz

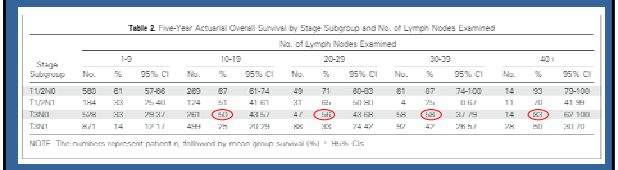


Table 2. Five-Year Actuarial Overall Survival by Stage Subgroup and No. of Lymph Nodes Examined

Stage Subgroup	No. of Lymph Nodes Examined														
	1-9			10-19			20-29			30-39			40+		
	No.	%	95% CI	No.	%	95% CI	No.	%	95% CI	No.	%	95% CI	No.	%	95% CI
T1/2N0	580	61	57-66	289	67	61-74	49	71	60-83	61	87	74-100	14	93	79-100
T1/2N1	744	53	49-58	124	53	43-63	31	62	48-76	4	75	30-95	11	70	43-89
T3N0	598	53	49-57	261	54	48-59	47	64	53-75	58	68	57-79	14	90	69-100
T3N1	1,473	34	32-37	484	35	30-39	106	48	39-57	60	47	38-57	28	60	46-74

NOTE: The numbers represent patients, followed by mean group survival (%). CI, 95% CIs.

Smith DD et al. J Clin Oncol 2005; 23:7114-7124

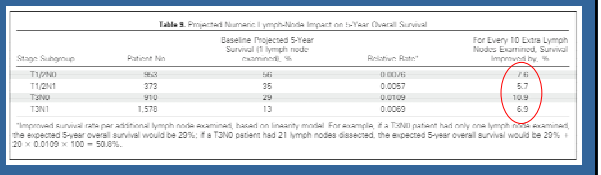


Table 3. Projected Numeric Lymph-Node Impact on 5-Year Overall Survival

Stage Subgroup	Patient No.	Baseline Projected 5-Year Survival (0 lymph nodes examined), %	Relative Rate*	For Every 10 Extra Lymph Nodes Examined, Survival Improved by, %
T1/2N0	1,963	66	0.00243	7.6
T1/2N1	973	35	0.0057	5.7
T3N0	910	29	0.0109	10.9
T3N1	1,578	13	0.0069	6.9

*Improved survival rate per additional lymph node examined, based on linearity model. For example, if a T3N0 patient had only one lymph node examined, the expected 5-year overall survival would be 29%. If a T3N0 patient had 21 lymph nodes dissected, the expected 5-year overall survival would be 29% + 20 × 0.0109 × 100 = 50.8%.

Smith DD et al. J Clin Oncol 2005; 23:7114-7124

Our experience (n = 206)
1989-1998

R0 resections 164 (79,6%)
R1 resections 23
R2 resections 19
→ (20,4%)

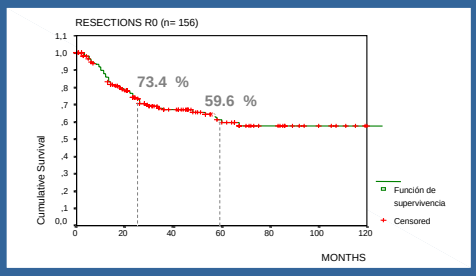
60-days mortality
8 (4,9%)

156

D1 lymphadenectomy: 50 (32.1 %) D2: 106 (67.9 %)

Fondevila C et al. Br J Cancer 2004; 248:549-556

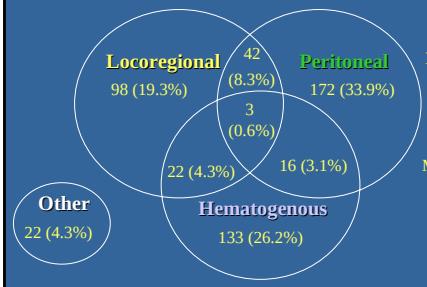
Our experience (1987 - 1998)



Mean follow-up: 43 months (CI 95%= 37-49, range= 2-191).

Fondevila C et al. Br J Cancer 2004; 248:549-556

Patterns of recurrence after curative resection



1987-1995 (N = 2328)

Recurrence:

652 (28.0%)

Mean time to recurrence: 21.8 meses

Yoo CH y cols. Br J Surg 87: 236, 2000

Current options to decrease recurrence

Postoperative

Chemotherapy

Chemo-radiotherapy

→ **Early attack againts**:
Micrometastasis
Circulating cells
Exfoliated cells
Reduce recurrences

Preoperative

Chemotherapy

Chemo-radiotherapy

→ Increase R0 resections
Reduce recurrences

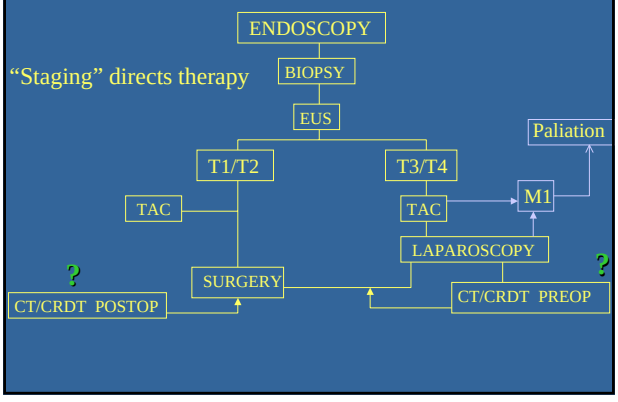
Preoperative tumor staging

Multidetector computed tomography (CT)

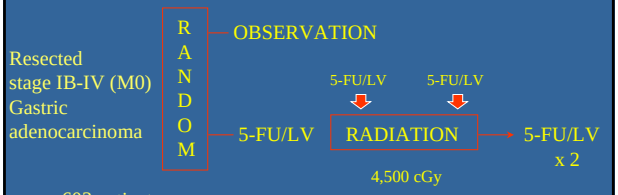
Endoscopic ultrasonography ± fine-needle aspiration

Staging laparoscopy

Positron emission tomography (PET)



Adjuvant chemoradiation: SWOG 9008/INT 0116



n = 603 patients
Median follow-up 3.3 yrs

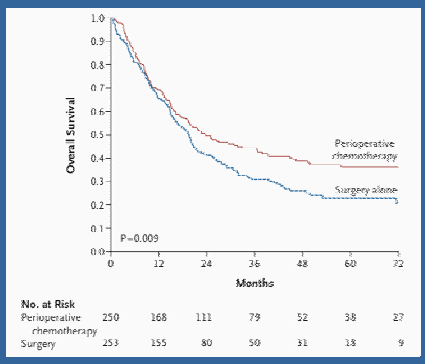
	Observation	Treatment	p value
DFS	32%	49%	0.001
OS	41%	52%	0.03

Perioperative Chemotherapy versus Surgery for resectable Gastroesophageal Cancer. MAGIC TRIAL

Grupo A: 3 preoperative and 3 postoperative cycles of intravenous epirubicin and cisplatin on day 1, plus continuous fluorouracil

Grupo B: Surgery alone

	Chemotherapy	Surgery alone	Benefit (95% CI)
survival 2 years	50% (44%-56%)	41% (35%-48%)	9% (3%-18%)
survival 5 years	36% (30%-43%)	23% (17%-29%)	13% (4%-22%)
Median survival	24 months	20 months	4 months (2-13 months)



Cunningham D et al. N Engl J Med 2006; 355:11-20

FNCLCC 94012 - FFCD 9703 Trial

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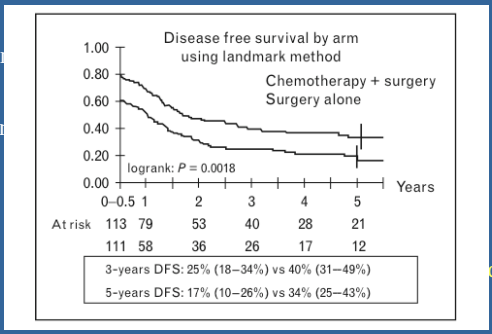


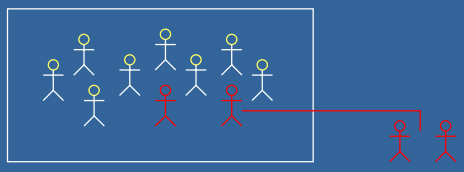
cles

Ychou M et al. Proc Am Soc Clin Oncol 2006

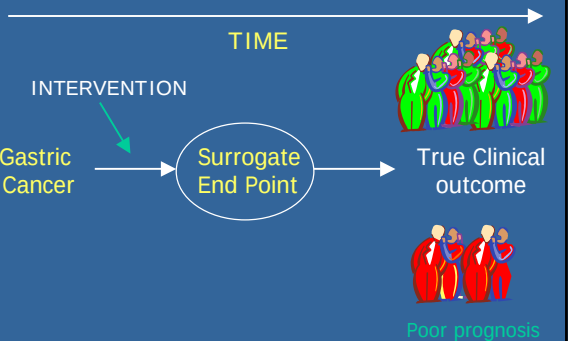
Fundamental question after an R0 resection

Who should receive chemotherapy?

Which regimen?



Some of them will recur



Fleming TR. Ann Intern Med 1996; 125: 605-613

Positive VEGF Immunostaining Independently Predicts Poor Prognosis in Curatively Resected Gastric Cancer Patients: Results of a Study Assessing a Panel of Angiogenic Markers

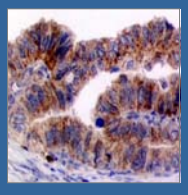
Óscar Vidal · Antonio Soriano-Izquierdo · Manuel Pera · José I. Elizalde · Antonio Palacín · Antoni Castells · Josep M. Piqué · Alain Volant · Jean P. Metges

J Gastrointest Surg; 12:1005-1014,2008

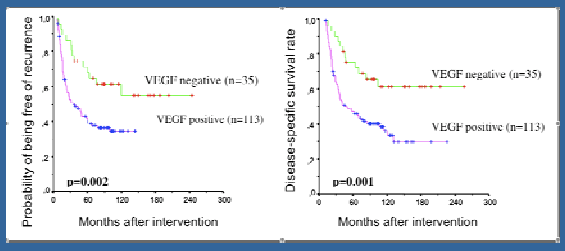
148 R0 resections

Stages:

I	56 (38%)
II	39 (26%)
III	42 (28%)
IV	11 (8%)



Mean follow-up: 63 ± 4 months



Vidal O et al. J Gastrointest Surg; 12:1005-1014,2008

Circulating angiogenic factors in gastrointestinal cancer

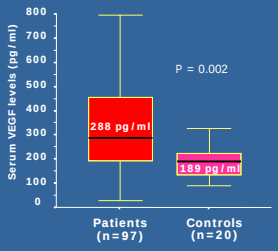
Potential advantages as biomarkers

1. Can be performed without the need of surgical specimen
2. It may allow preoperative evaluation of angiogenic activity before surgical removal of a tumor
3. It is noninvasive and can be repeated serially
4. Quantitative immunoassay is more precise compared with semiquantitative techniques such as immunostaining

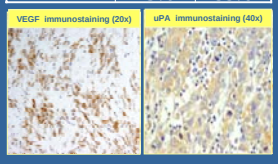
Poon RT et al. J Clin Oncol; 19:1207-1225,2001

Circulating preoperative VEGF levels in gastric cancer patients

Serum VEGF and uPA levels were quantitatively measured by ELISA



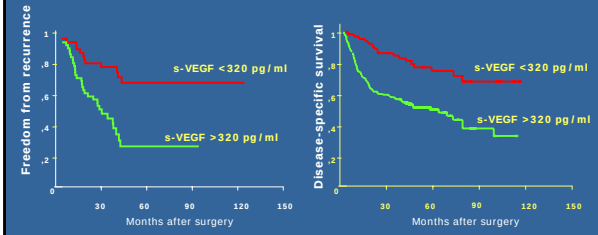
	VEGF	uPA
Positive	51%	12%
Negative	49%	88%



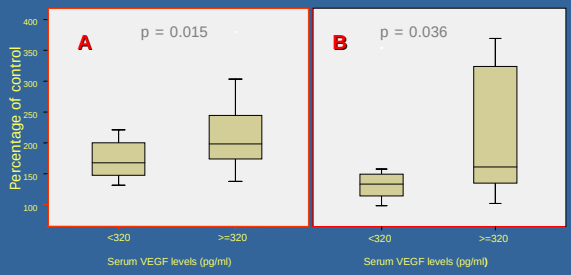
Disease-specific survival (Multivariate analysis)

		HR	95% CI	p value
s-VEGF	< 320 pg/mL			
	> 320 pg/mL	4	1.1-8.4	p=0.004
Lymphadenectomy	D2			
	D1	9	1.8-16	p=0.001
pT stage	T1			
	T2	2.6	1-11	p=0.010
	T3	5.9	1.1-26	p=0.018
pN stage	N0			
	N1	2.9	1.1-7.3	p=0.022
	N2	5.6	1.8-16	p=0.002
	N3	8.2	2.9-23	p=0.029

Preoperative serum VEGF levels in gastric cancer patients
Prognostic significance



Cell Proliferation Assay | Endothelial Cell Tube Formation Assay



Molecular factors representing a possible target for novel therapeutic agents in gastric cancer

Molecular factor	Therapeutic agent
c-erb B-2	Trastuzumab
Matrix metalloproteinase	Marimastat
EGFR	Cetuximab (colon)
	Tarceva (lung)
VEGFR	Sunitinib, Sorafenib
VEGF	Bevacizumab

- Shah MA et al. J Clin Oncol 24:5201-5206, 2006
- MAGIC B ST03 Trial (ECF + bevacizumab)

Conclusions

Advanced gastric cancer has a high risk of recurrence.

Irrespective of the surgical procedure used for treatment of gastric cancer, the effectiveness of surgical resection is poor.

Adjuvant chemoradiation appears to be a reasonable treatment option after inadequete surgery or high risk of relapse.

Perioperative systemic approach looks promising for the treatment of locally advanced gastroesophageal cancer.

Preoperative biomarkers of survival and recurrence would be invaluable in individualising patient treatment.

The Number of Lymph Nodes Removed Predicts Survival in Esophageal Cancer: An International Study on the Impact of Extent of Surgical Resection

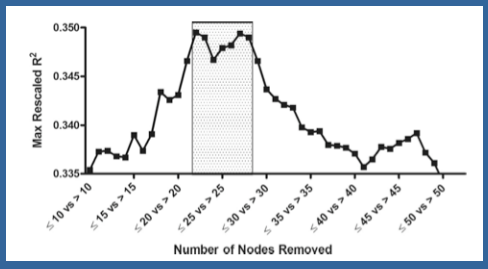
Christian G. Peyre, MD, Jeffrey A. Hagen, MD,* Steven R. DeMeester, MD,* Nasser K. Altorki, MD,† Ernuamo Ancona, MD,‡ S. Michael Griffin, MD,¶ Arnulf Hölscher, MD,§ Toni Lerut, MD, PhD,** Simon Law, MD,¶¶ Thomas W. Rice, MD,‖ Alberto Rusch, MD,‡ Jan J. B. van Lanschot, MD,‡ John Wong, MD, PhD,¶¶ and Tom R. DeMeester, MD**

TABLE 6. Independent Predictors of Survival at 5 Years By Logistic Regression in 2166 Patients With Complete 5-Year Follow-up

Rank	Factor	χ^2	*P* Value
1	Tumor depth (T)	364	<0.0001
2	Presence of nodal metastasis (N)	124	<0.0001
3	No. nodes removed*	48	<0.0001
4	No. involved nodes*	47	<0.0001
5	Cell type	21	<0.0001

*Modeled as a continuous variable.

Peyre CG et al. Ann Surg 2008; 248:549-556



Peyre CG et al. Ann Surg 2008; 248:549-556