A Beneficência
Portuguesa
de São Paulo

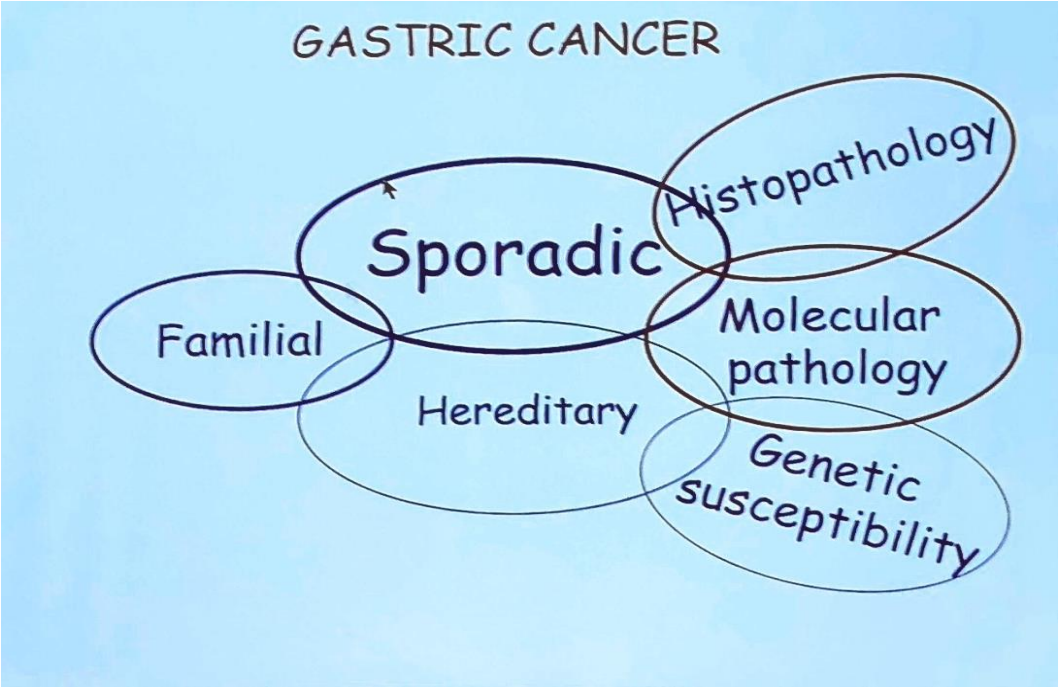
Ao infinito e além
(atualidades e futuro do câncer do estômago)

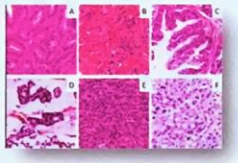
Bruno Zilberstein M.D., Ph.D., FACS

Resumo

Câncer Gástrico - Adenocarcinoma

O que há de Novo no Câncer Gástrico

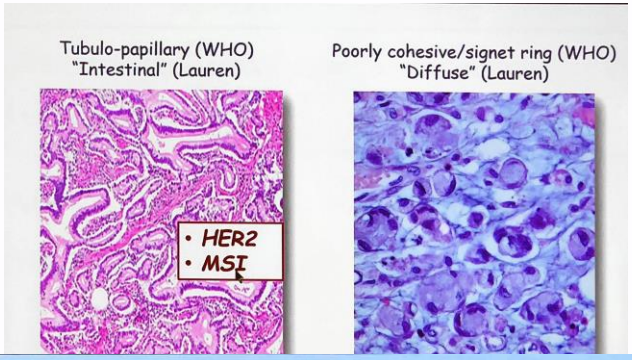


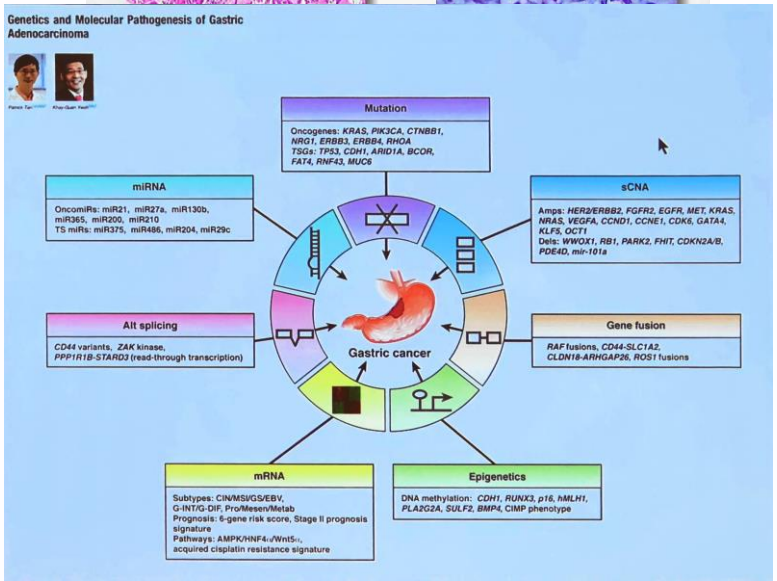


Classification of gastric cancer

Laurén (1965)	Nakamura (1968)	JGCA (2017)	WHO (2018)
Intestinal	Differentiated	Papillary: pap Tubular 1, well-differentiated: tub1 Tubular 2, moderately-differentiated: tub2	Papillary Tubular, well-differentiated Tubular, moderately-differentiated
Indeterminate	Undifferentiated	Poorly 1 (solid type): por 1	Tubular, poorly-differentiated (solid)
Diffuse	Undifferentiated	Signet ring cell carcinoma (SRC): sig Poorly 2 (non-solid type): por2	Poorly cohesive, SRC phenotype Poorly cohesive, other cell types
Intestinal/diffuse/indeterminate	Differentiated/ Undifferentiated	Mucinous	Mucinous
Mixed		Description according to the proportion (e.g. por2>sig>tub2)	Mixed
Not defined	Not defined	**Special type:** Adenosquamous carcinoma Squamous cell carcinoma Undifferentiated carcinoma Carcinoma with lymphoid stroma Hepatoid adenocarcinoma Adenocarcinoma with enteroblastic differentiation Adenocarcinoma of fundic gland type	**Histological variants:** Adenosquamous carcinoma Squamous cell carcinoma Undifferentiated carcinoma Carcinoma with lymphoid stroma Hepatoid carcinoma Adenocarcinoma with enteroblastic differentiation Adenocarcinoma of fundic gland type Micropapillary adenocarcinoma

*JGCA, Japanese Gastric Cancer Association (978-4-307-20375-3). **Table prepared in collaboration with Prof. Ryoji Kushima, Japan



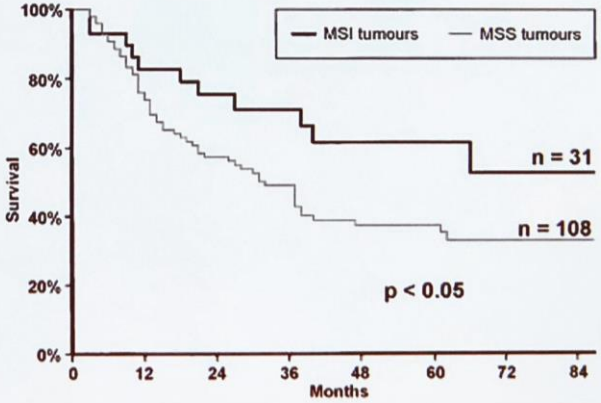


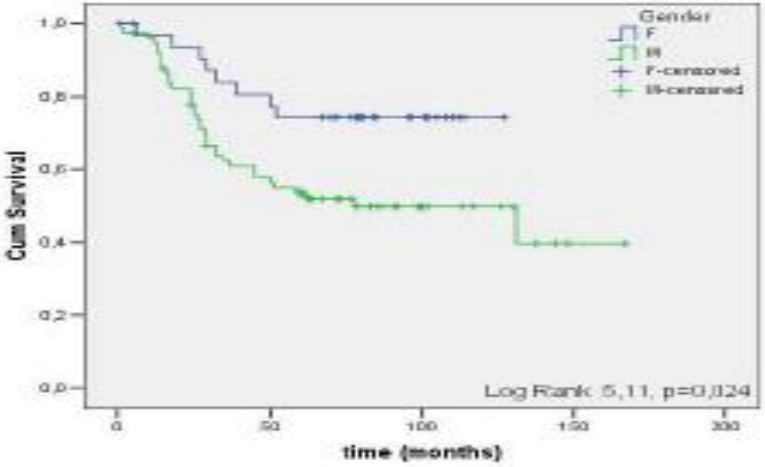
MSI in gastric carcinoma

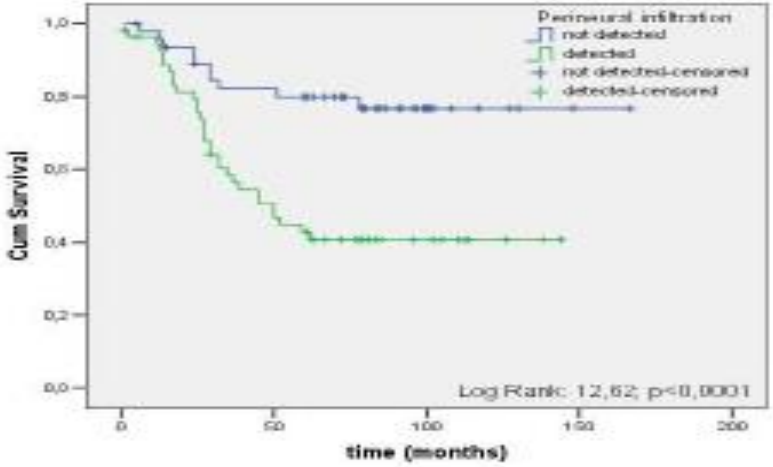
Molecular marker of good prognosis in sporadic gastric cancer

(caused by *hMLH1* promoter hypermethylation)

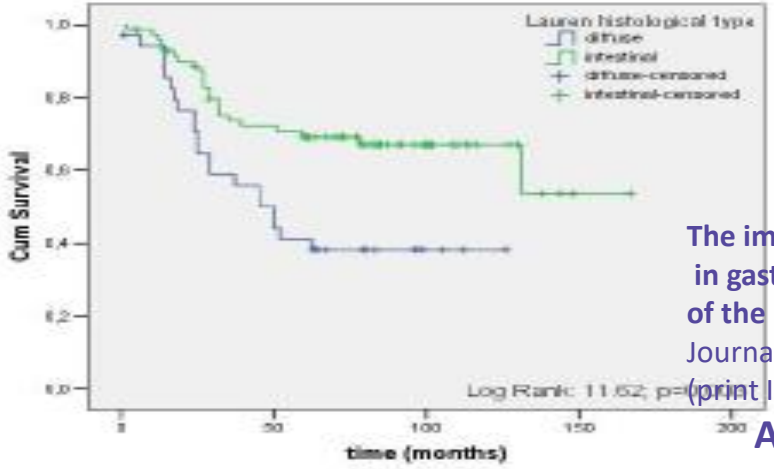
Survival of patients

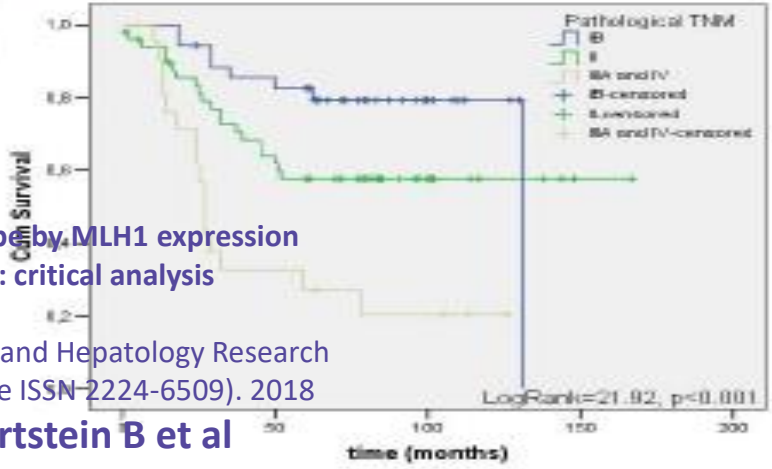






Loss of MLH1 immunoexpression was related to a beneficial impact on disease-specific survival





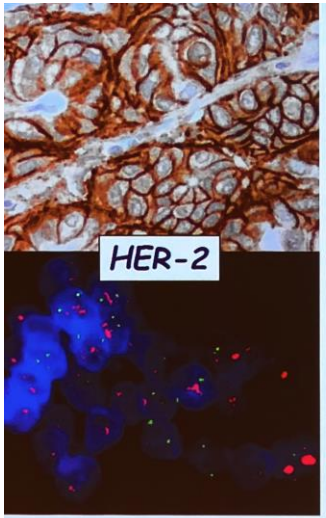
The impact of MSI phenotype by MLH1 expression in gastric adenocarcinomas: critical analysis of the Brazilian experience.

Journal of Gastroenterology and Hepatology Research (print ISSN 2224-3992, online ISSN 2224-6509). 2018

Adhemar L, Zilbertstein B et al

High-throughput Protein and mRNA Expression–based Classification of Gastric Cancers Can Identify Clinically Distinct Subtypes, Concordant With Recent Molecular Classifications

Sangjeong Ahn, MD, PhD,† So-Jeong Lee, MD,* Yonugkeum Kim, MD,* Ahrong Kim, MD,*
Nari Shin, MD,‡ Kyung Un Choi, MD, PhD,* Chang-Hun Lee, MD, PhD,*
Gi Yeong Huh, MD, PhD,§ Kyong-Mee Kim, MD, PhD,‖ Namrata Setia, MD,¶
Gregory Y. Lauwers, MD,# and Do Youn Park, MD, PhD**



HER-2
in gastric carcinoma

Prognostic factor < YES (56%) / NO (44%)

HER-2 amplification
in intestinal-type gastric carcinoma

Blood or metastases
Poor prognosis

David L *et al*; Mod Pathol 5:384, 1992
Barros-Silva J *et al*; Br J Cancer 100: 487,2009

Terapia Alvo

Gastric cancer and immune checkpoint blockade

PD-1

Predictive biomarkers

MSI-high *status*

Science

Mismatch-repair deficiency predicts response of solid tumors to PD-1 blockade

PD-L1 expression

Original Article

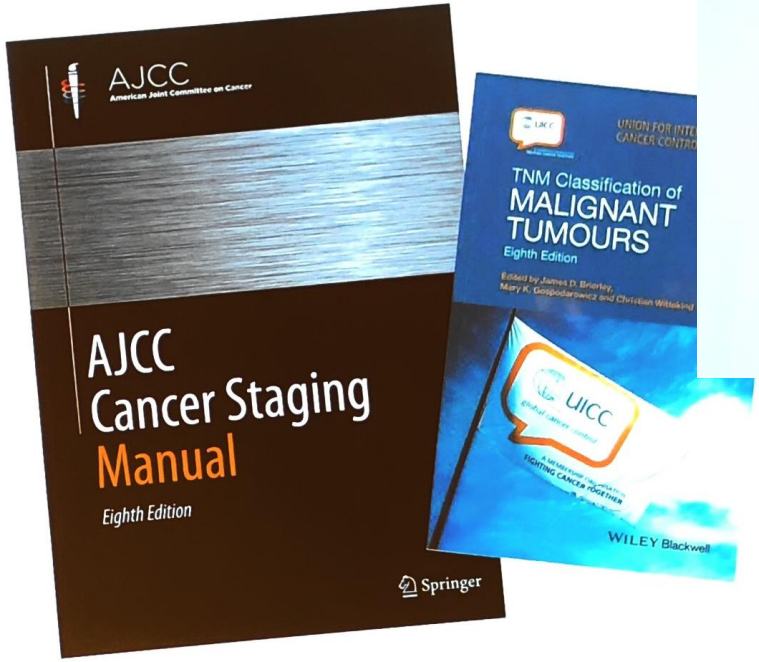
Clinical Utility of the Combined Positive Score for Programmed Death Ligand-1 Expression and the Approval of Pembrolizumab for Treatment of Gastric Cancer

EBV+ and MSI-high *status*

nature medicine — ARTICLES

https://doi.org/10.1038/s41591-018-0101-z

Comprehensive molecular characterization of clinical responses to PD-1 inhibition in metastatic gastric cancer



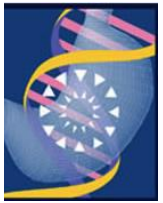
Pathological stage groups
TNM-8 & JC-15

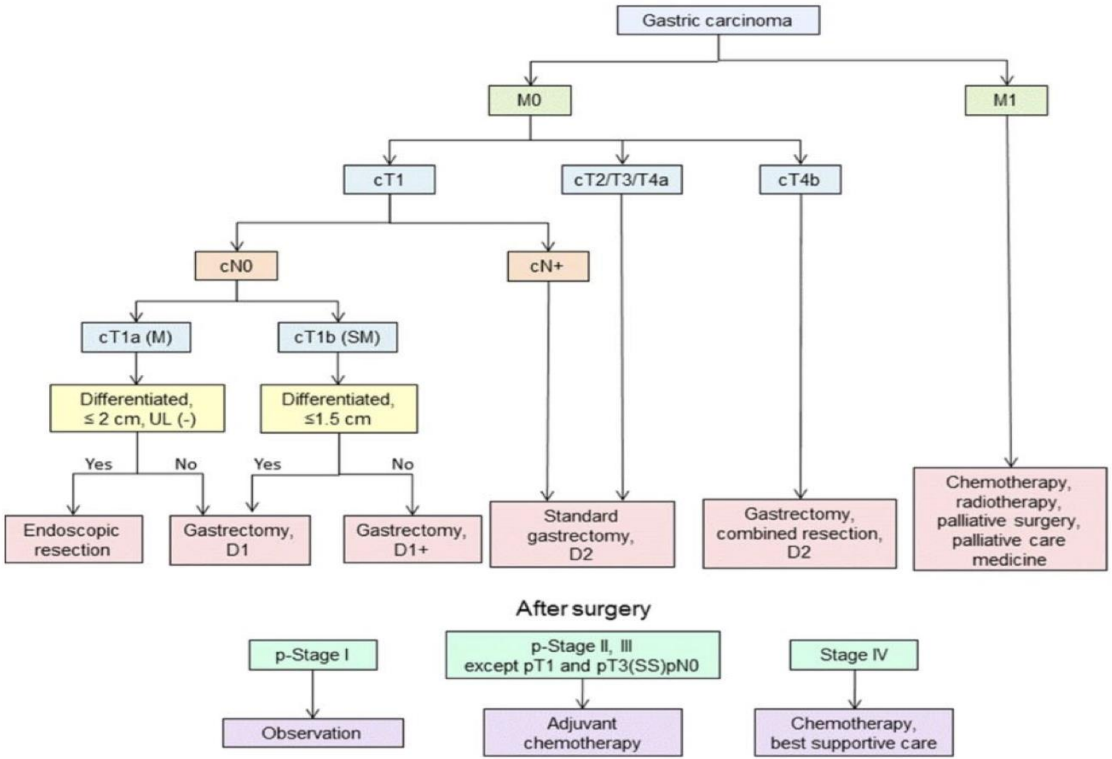
	M0					M1
	N0	N1 (1,2)	N2 (3-6)	N3a (7-15)	N3b (16-)	Any N
T1a/T1b	IA	IB	IIA	IIB	IIIB	IV
T2	IB	IIA	IIB	IIIA	IIIB	
T3	IIA	IIB	IIIA	IIIB	IIIC	
T4a	IIB	IIIA	IIIA	IIIB	IIIC	
T4b	IIIA	IIIB	IIIB	IIIC	IIIC	

New **clinical** stage groups
TNM-8 & JC-15

	M0		M1
	N0	N(+)	Any N
T1/T2	I	IIA	IVB
T3/T4a	IIB	III	
T4b	IVA		

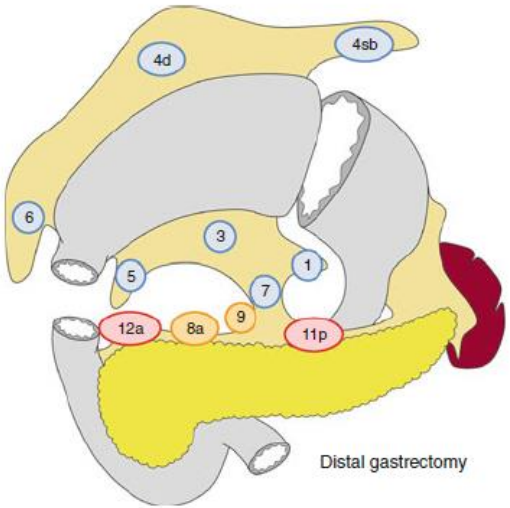
ALGORITMO DE TRATAMENTO DO CÂNCER GÁSTRICO



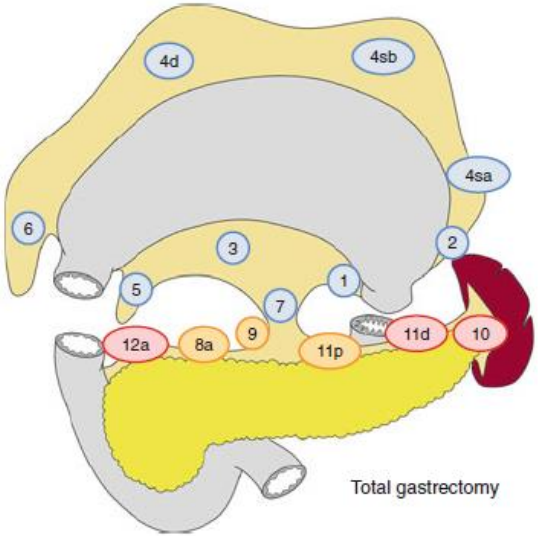


Japanese Gastric Cancer Association. Gastric Cancer 2017.

Linfadenectomia de acordo com o Tipo de Gastrectomia

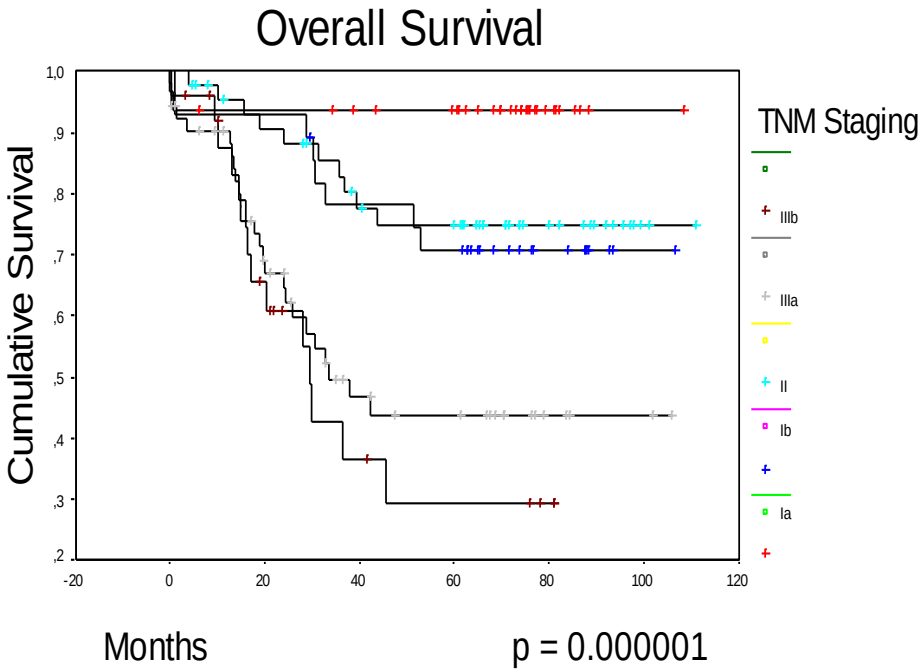


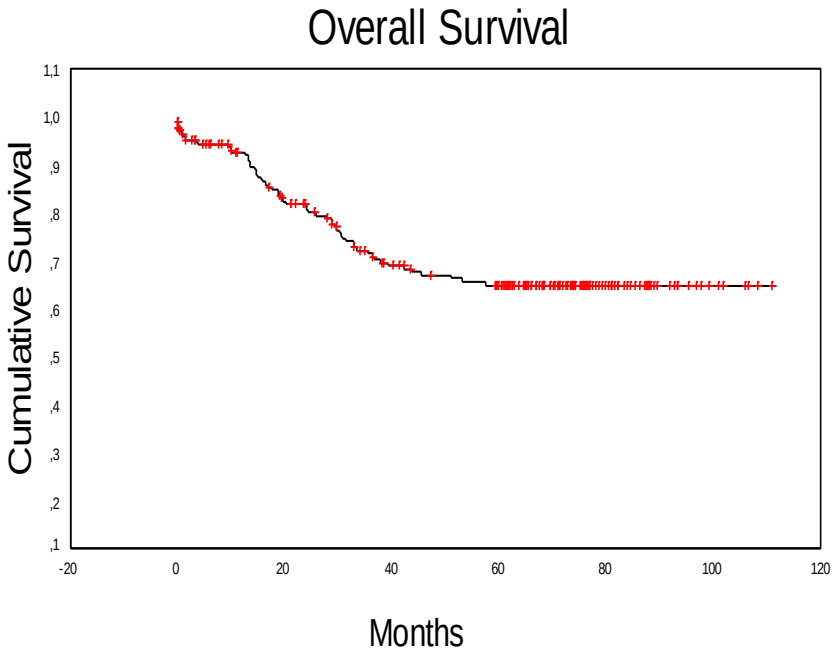
D0: Lymphadenectomy less than D1
D1: Nos. 1, 3, 4sb, 4d, 5, 6, 7
D1+: D1 + Nos. 8a, 9
D2: D1 + Nos. 8a, 9, 11p, 12a.



D0: Lymphadenectomy less than D1
D1: Nos. 1–7
D1+: D1 + Nos. 8a, 9, 11p
D2: D1 + Nos. 8a, 9, 10, 11p, 11d, 12a.

Sobrevida a longo prazo do Tratamento Cirúrgico Radical do Câncer Gástrico
1467 pacientes HC-ICESP-FMUSP



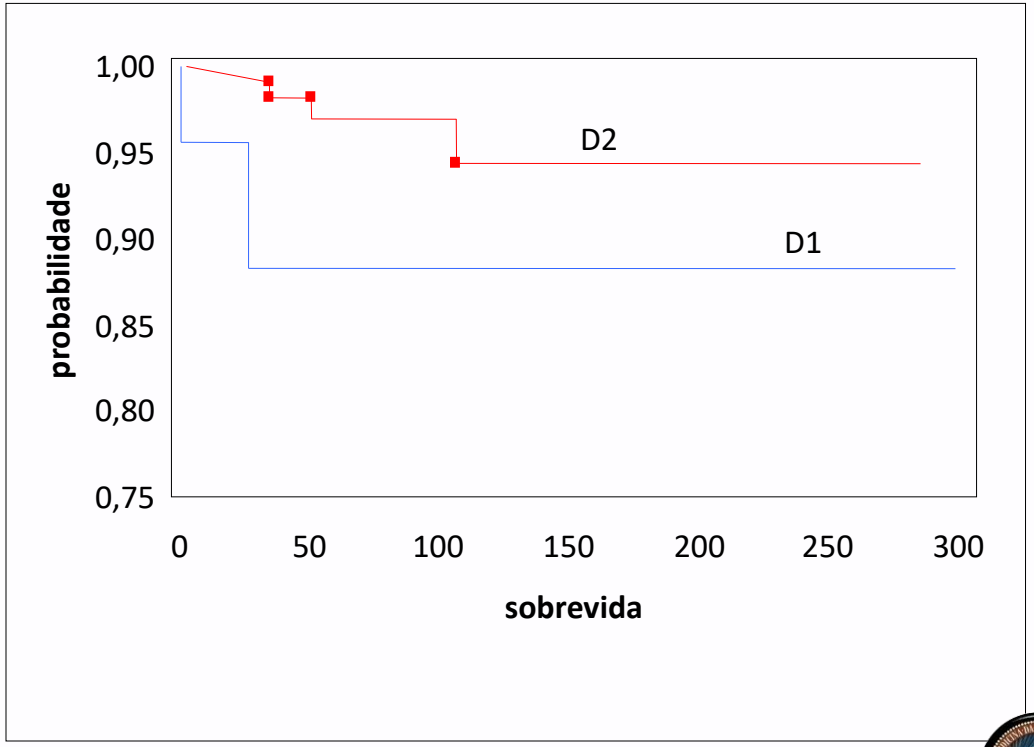


A Beneficência Portuguesa de São Paulo

Serviço de Cirurgia do Estômago e Intestino Delgado HC-FMUSP

Bruno Zilberstein

Câncer Gástrico Precoce



5 Y: 97 %

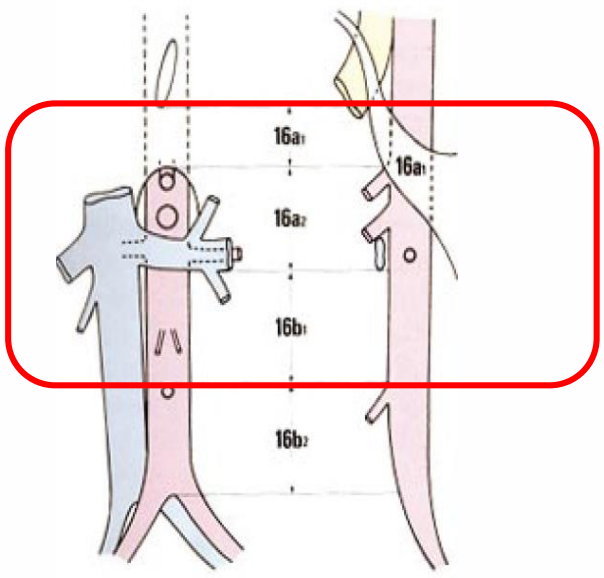
10 Y: 94,4%

Jacob, CE, 2010

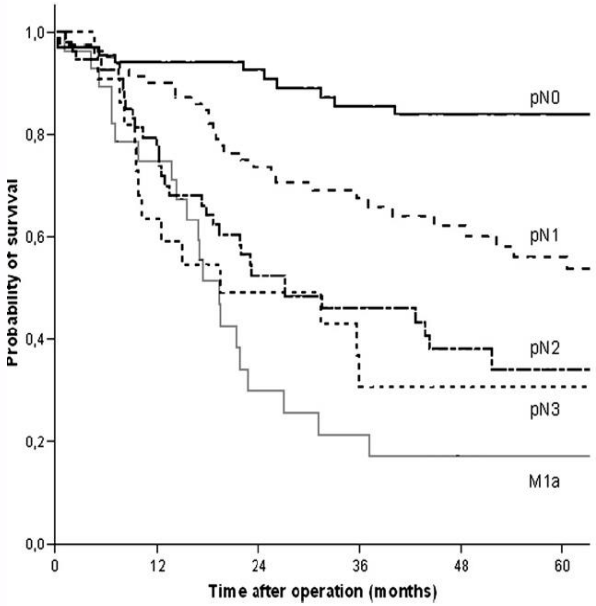
Dissecção Linfonodal Para–Aortica PAND

Super-extended (D3) lymphadenectomy in advanced gastric cancer

F. Roviello [a], C. Pedrazzani [a,*], D. Marrelli [a], A. Di Leo [b], S. Caruso [a], S. Giacopuzzi [b], G. Corso [a], G. de Manzoni [b]



- 254 patients – D3
- 37 patients had para-aortic N+
  - 29% of patients with GEJ tumors; 7% of all the others (P<0,001)

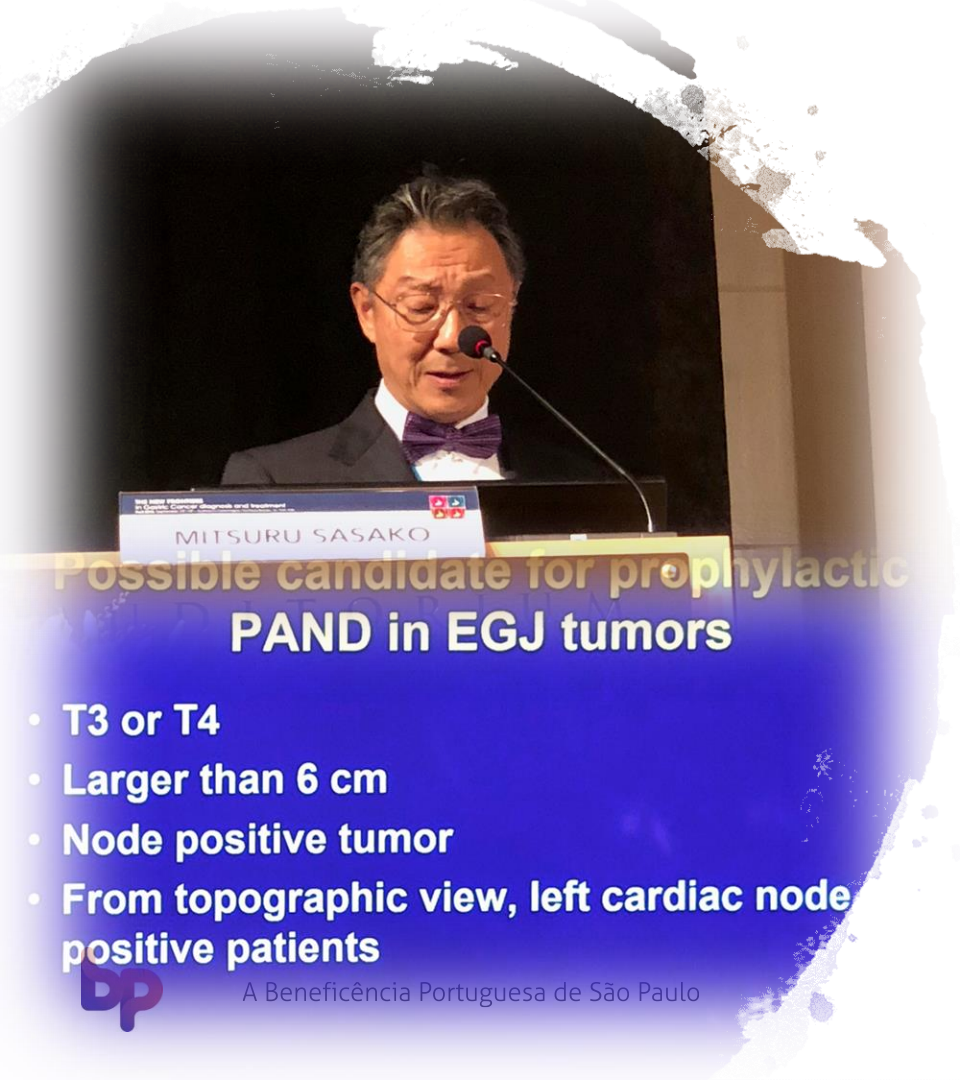


Pacientes com Alto Risco de Metastatses Linfonodais Para-aorticas

1. Cancer estadio T3/T4
2. Histologia Mista/Difusa
3. Terço Superior / Siewert III

Risco de invasão do linfonodo das estaçoes 16 a e b cerca de 50%

Roviello, de Manzoni et al, 2014



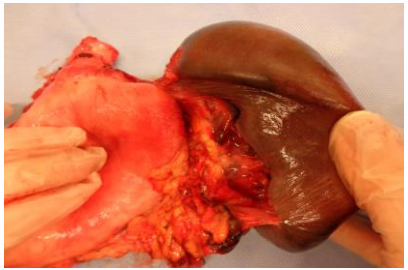
Nova indicação da PAND no Japan

Sasako, 2018

Classificação Japonesa do Câncer Gástrico: 3a Edição

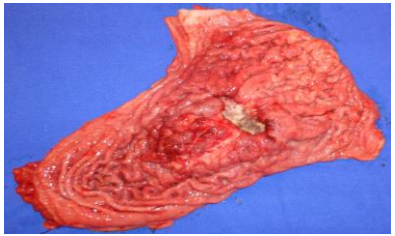
Gastric Cancer (2011) 14:101–112

T3- T4a

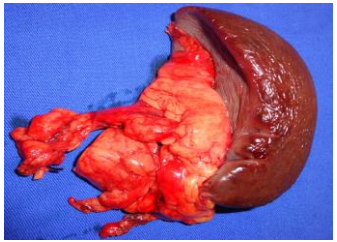


T1 Tumor confined to the mucosa (M) or submucosa (SM)
T1a Tumor confined to the mucosa (M)
T1b Tumor confined to the submucosa (SM)1
T2 Tumor invades the muscularis propria (MP)
T3 Tumor invades the subserosa (SS)

T4 Tumor invasion is contiguous to or exposed beyond the serosa (SE) or tumor invades adjacent structures (SI)
T4a Tumor invasion is contiguous to the serosa or penetrates the serosa and is exposed to the peritoneal cavity (SE)
T4b Tumor invade estruturas adjascentes(SI).



T4b



Invasão da serosa com **envolvimento do pequeno e/ou grande omentum é classificado como T4a**, not T4b.

Invasão do mesocolon transverso não é T4b a menos que invada os vasos colicos ou penetre na face posterior do mesocolon.

RESULTADOS

Penetração na parede (n=208)	%
mucosa	
submucosa	
muscular propria	
subserosa	
serosa	
invasion de estruturas adjascentes	

Autor	N	Morbid Total(%)	Morbid com esplene (%)	Morbid com pancreate e esplene (%)
Bonenkamp et al, 1995	711	44	41	55
Cuschieri et al, 1996	400	37	54	56
Bozzetti et al, 1999	624	13	19	37
Onate-Ocana, 2000	208	20	42	47
Kasakura et al ,2000	1938	22	40	75
Martin et al, 2001	1283	31	29	37
Mafune et al, 2005	272	39	22	48
Serv Cir Est HC, 2006	842	24	40	48

Zilberstein, B; Gastric Cancer, 2006

Ressecção Multivisceral

No pac 1043

RMV 237 22,7%

Idade > 60 a

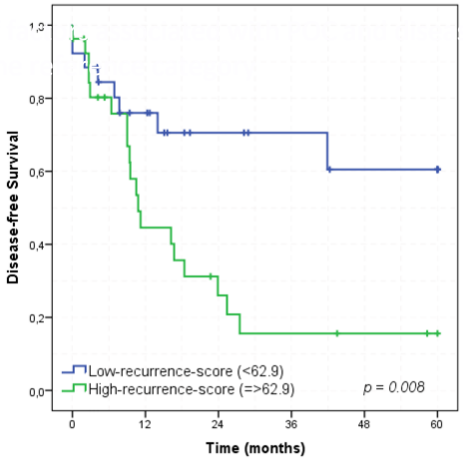
Sexo Masc

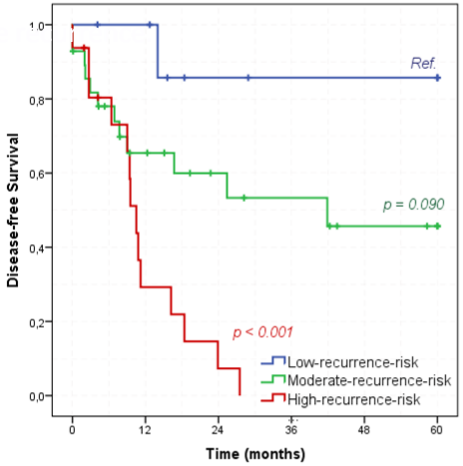
N+

+ 2 org ressec

D1/D2

R0





Extended Local Resection for Advanced Gastric Cancer

Increased Survival Versus Increased Morbidity

Robert C. G. Martin, II, MD, David P. Jaques, MD, Murray F. Brennan, MD, and Martin Karpeh, MD

From the Gastric and Mixed Tumor Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, New York

- Single institution (MSKCC), 1985-2000
- 1,133 R0 resection, 268 MVR (24%)
- pT4b: 14%
- High morbidity, slightly better survival

Câncer Gastrico Avançado T4b

A ressecção multivisceral do CaG T4b não é um procedimento habitual

A **ressecção R0** é fundamental para a sobrevida

O **comprometimento linfonodal** é fator prognóstico

A **Laparoscopia** é muito útil para decidir a factibilidade cirúrgica

Terapia de conversão - Definição

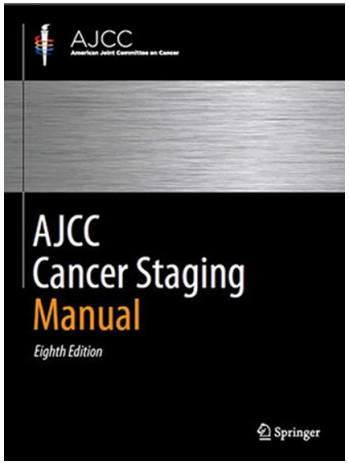
- **Tratamento cirúrgico após quimioterapia** de um tumor que foi previamente classificado como tecnicamente/oncologicamente **irressecável** ou marginalmente ressecável

- Tumores EC IV

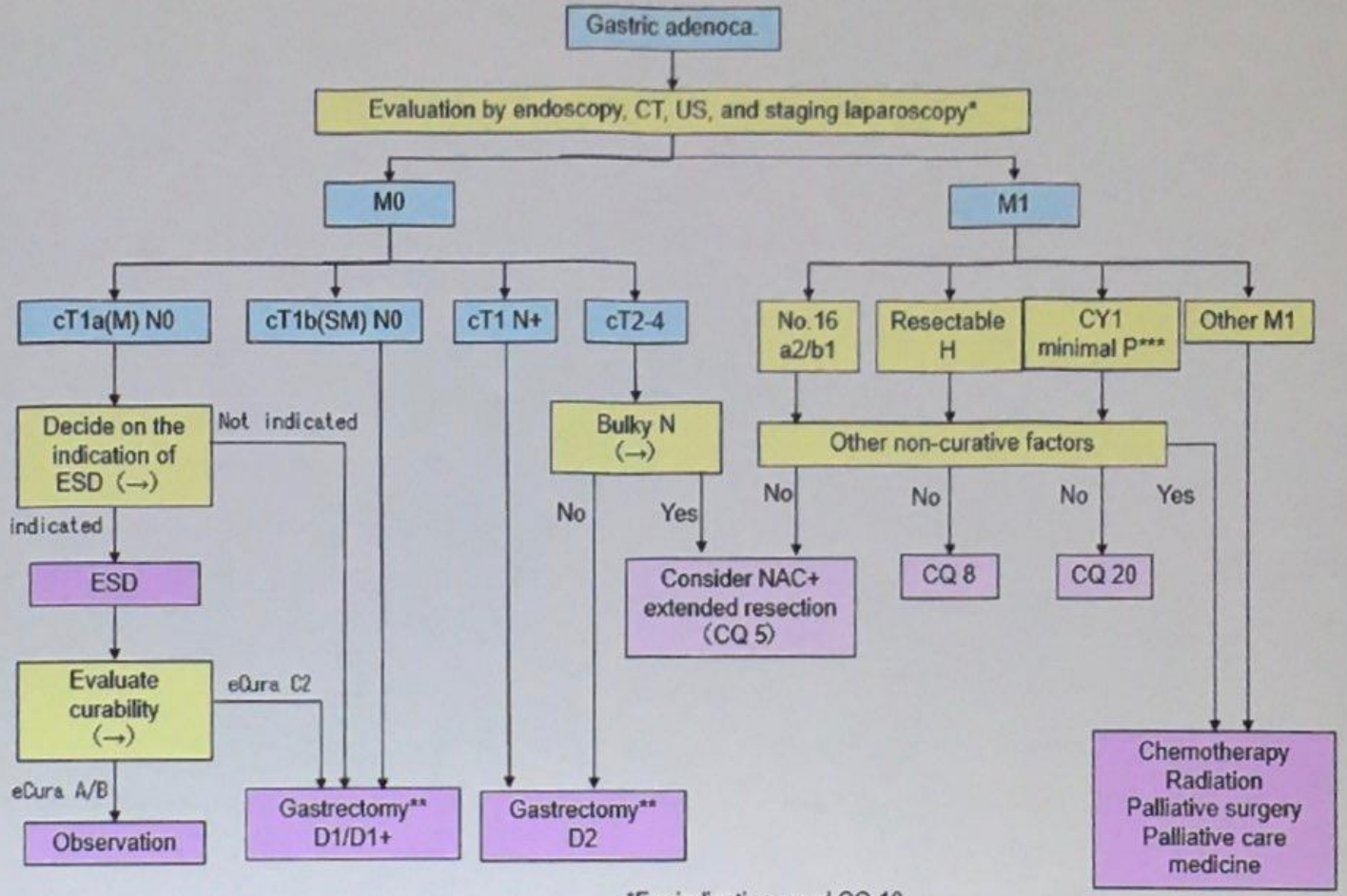
- " Qt indução" + "cirurgia adjuvante"

- **Objetivo é ressecção R0 e cura**

- 8ª Edição cTNM
  - IVa – T4b N1-2-3 M0
  - IVb – Tx Nx M1



K.Yoshida et al. Gastric Cancer 2016; 19:329-338

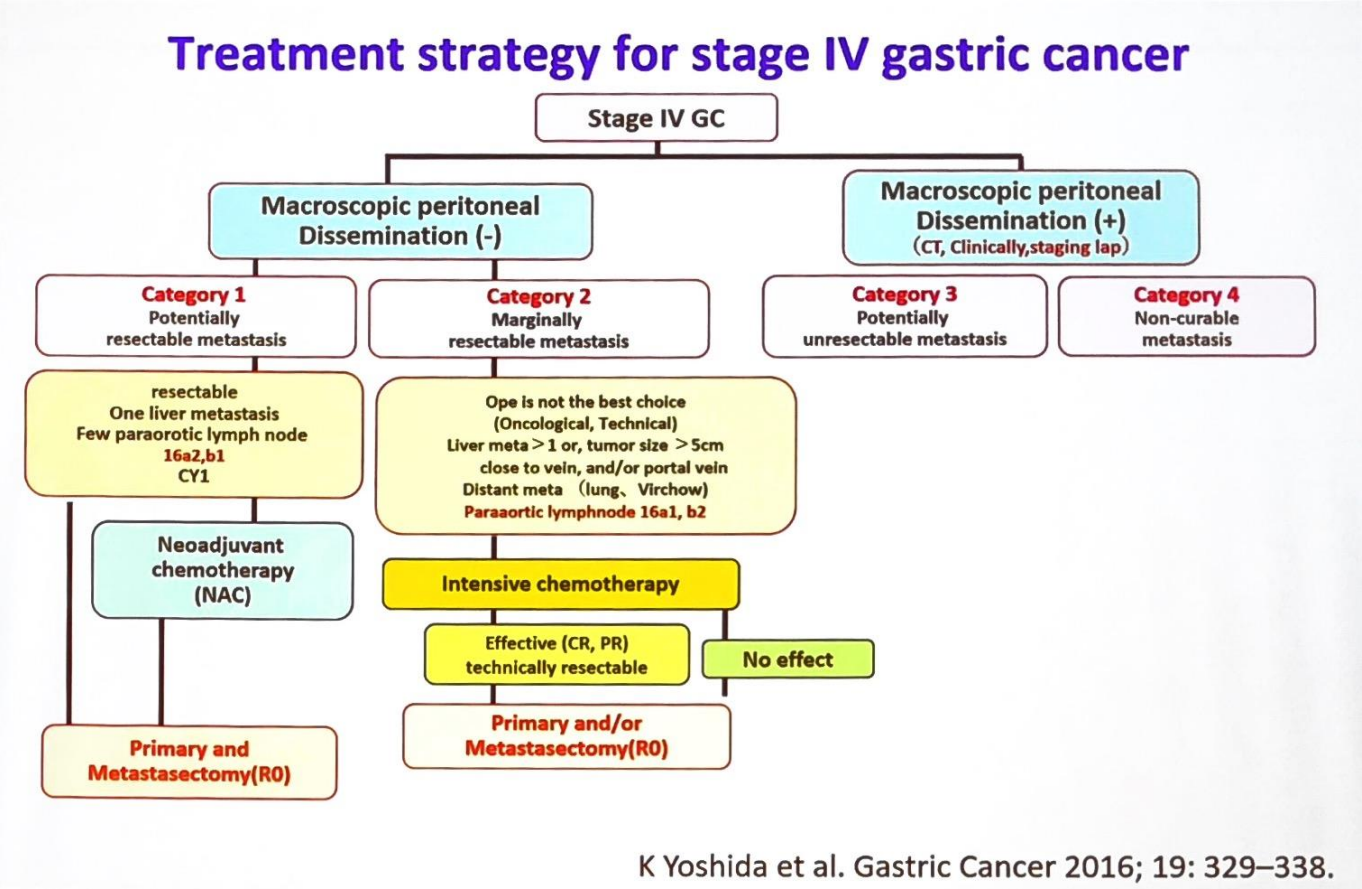


*For indication, read CQ 10

** For indication of laparoscopic approach, read page 17

***Small amount of deposits adjacent to the stomach and on the omentum that can be co-resected easily.

Terapia de Conversão

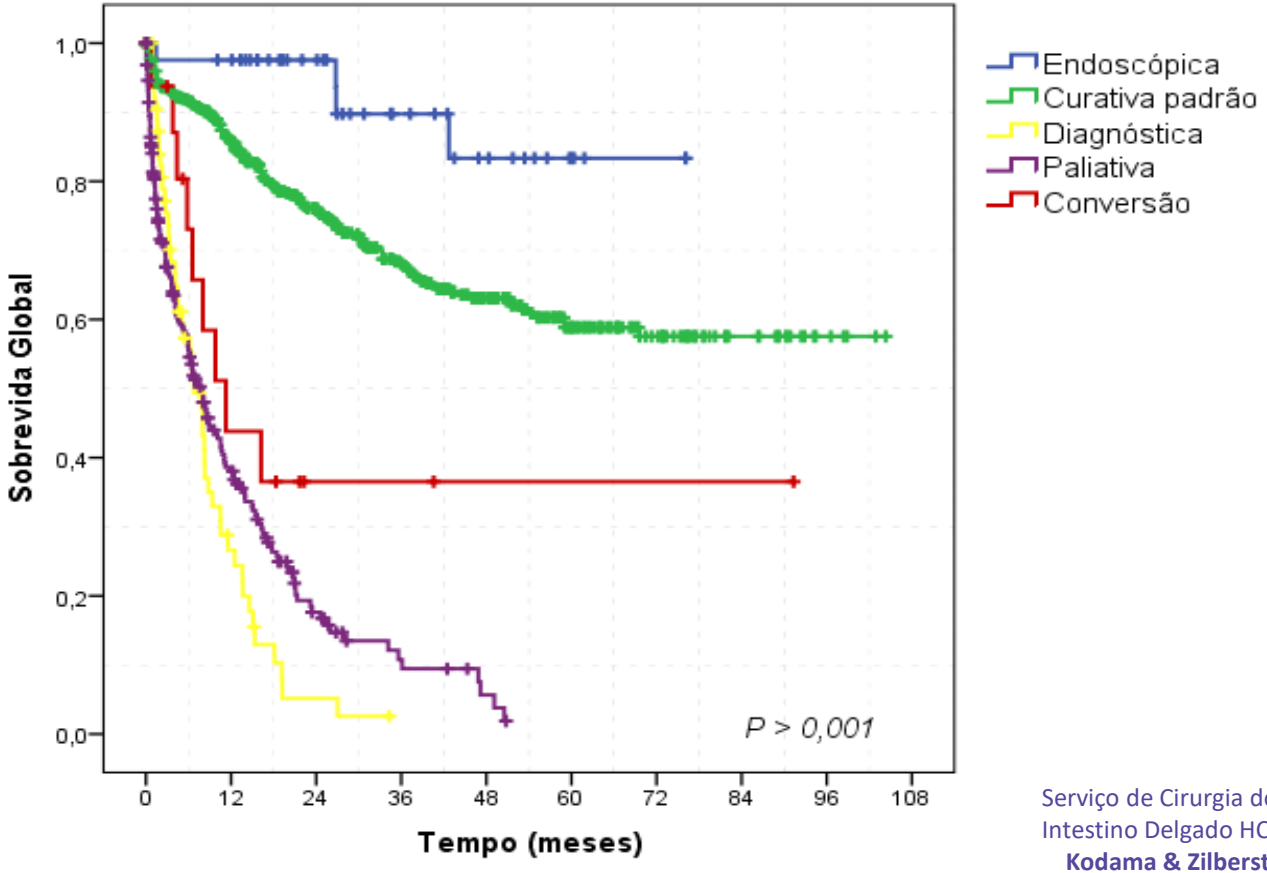


K Yoshida et al. Gastric Cancer 2016; 19: 329–338.

Terapia de conversão – Curva de sobrevida

N total 1003

Conv. 19 1,6%



Serviço de Cirurgia do Estômago e Intestino Delgado HC-FMUSP

Kodama & Zilberstein et al, 2019

Terapia de conversão – Perpectivas

- Definição objetiva de irressecabilidade

- Terapia peritoneal pode auxiliar
  - HIPEC X Qt intraperitoneal
  - Protocolo de pesquisa HC-FMUSP em implantação

- Definição do objetivo da quimioterapia no início do tratamento
  - Viés de classificação nas análises retrospectivas
  - % de casos que iniciam a conversão e chegam na cirurgia

- Identificar os respondedores é um desafio
  - Novas drogas podem melhorar ainda mais

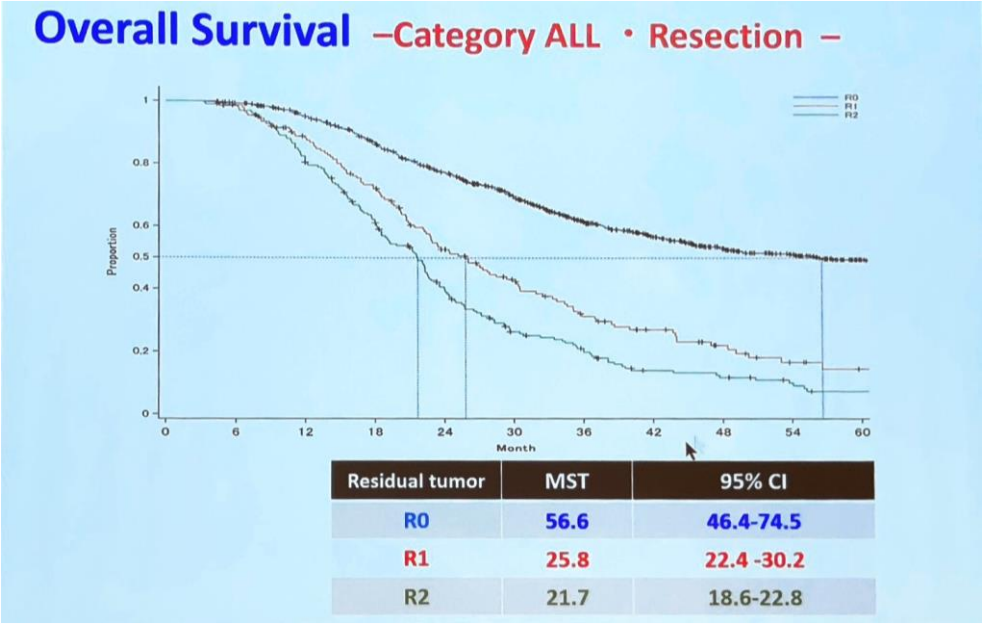
Cuidado ao fechar o prognóstico cirúrgico

TRATAMENTO INDIVIDUALIZADO

“TAYLOR MADE PROCEDURE”

Serviço de Cirurgia do Estômago e Intestino Delgado HC-FMUSP
Kodama & Zilberstein et al

Terapia de Conversão



Residual tumor	MST	95% CI
R0	56.6	46.4-74.5
R1	25.8	22.4 -30.2
R2	21.7	18.6-22.8

Conclusão

A Terapia de Conversão para o estádio IV do CaG é segura e pode ser uma nova estratégia para melhorar a sobrevida, principalmente se a ressecção for R0 incluindo a doença peritoneal

K.Yoshida et al. Gastric Cancer 2016; 19:329-338

Ressecção de Metastases Hepáticas

Influence of Surgical Resection of Hepatic Metastases From Gastric Adenocarcinoma on Long-term Survival: Systematic Review and Pooled Analysis

Sheraz R. Markar, MRCS, MSc, MA, Sameh Mikhail, FRCS,*† George Malietzis, MRCS,* Thanos Athanasiou, PhD, FRCS,* Christophe Mariette, PhD, MD,‡ Mitsuru Sasako, PhD, MD,§ and George B. Hanna, PhD, FRCS**

(Ann Surg 2016;263:1092–1101)

39 artigos 606 pacientes

Effect of candidate prognostic factors upon survival

Ann Surg Oncol (2015) 22:589–596
DOI 10.1245/s10434-014-4018-6

Annals of SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

Prognostic variables	n	Median survival	95 % CI	Univariate p value	Multivariate p value	Odds ratio	95 % CI
T							
T1–T2	26	9.9	5.7–14.1	0.014	0.036	2.0	1.2–3.3
T3	10	3.4	0.1–8.2				
T4	137	6.2	5.2–7.2				
x	22	3.1	2.4–3.7				
Hepatic metastases							
H1	65	7.4	5.2–9.6	<0.001	0.003	2.0	1.3–2.9
H2	22	5.6	4.2–7.0				
H3	62	3.6	2.2–5.0				
	46	6.7	5.3–7.1				

Risk Factors:
T > 2
H 3

ELSEVIER
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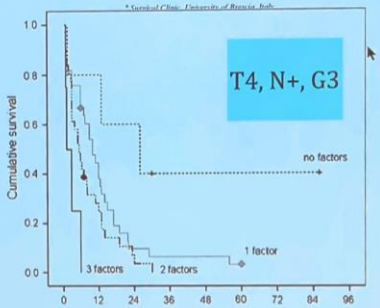
Metachronous hepatic metastases from gastric carcinoma: A multicentric survey

G.A.M. Tiberio [a,*], A. Coniglio [a], A. Marchet [b], D. Marrelli [c], S. Giacopuzzi [d], L. Baiocchi [a], F. Roviello [c], G. de Manzoni [d], D. Nitti [b], S.M. Giulini [a,1]

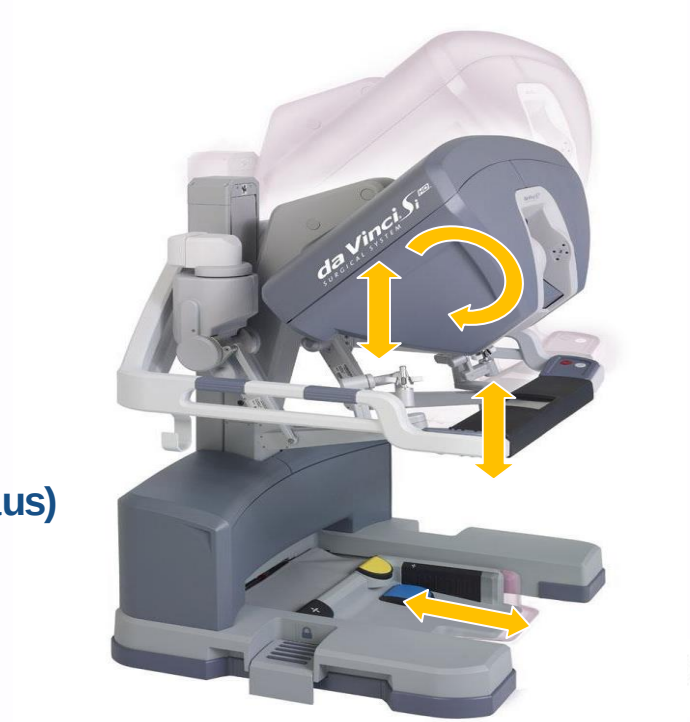
[a] Surgical Clinic, University of Brescia, Italy



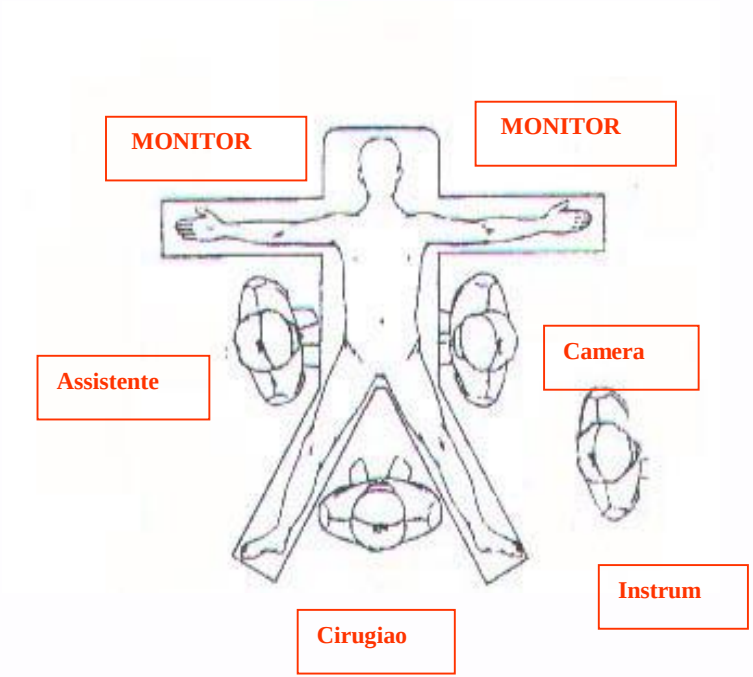
O caminho para o Conforto, Ergonomia e Segurança

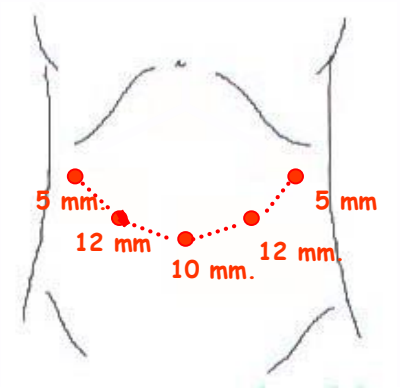
- 4 ajustes ergonomicos

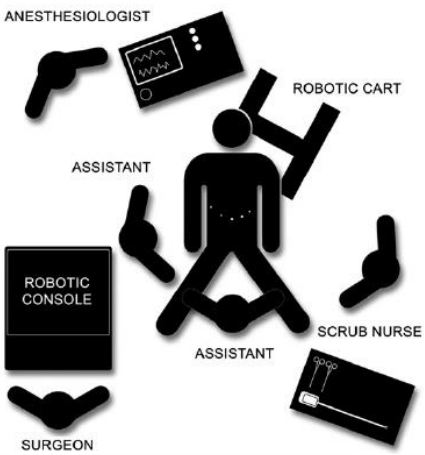
Magnificação
Alta definição
Imagem 3D
Liberdade de movimento(7 graus)

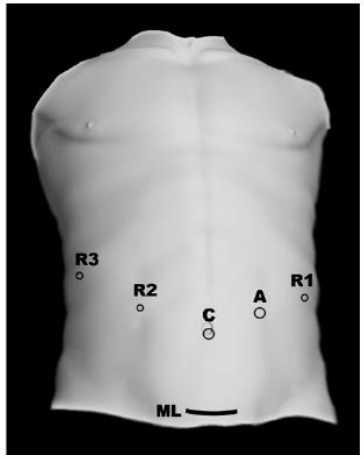


Gastrectomia Minimamente Invasiva

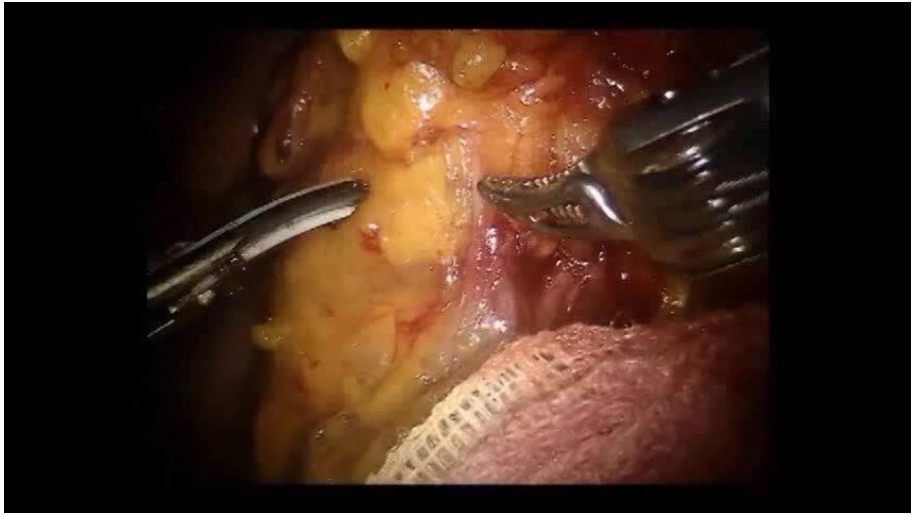




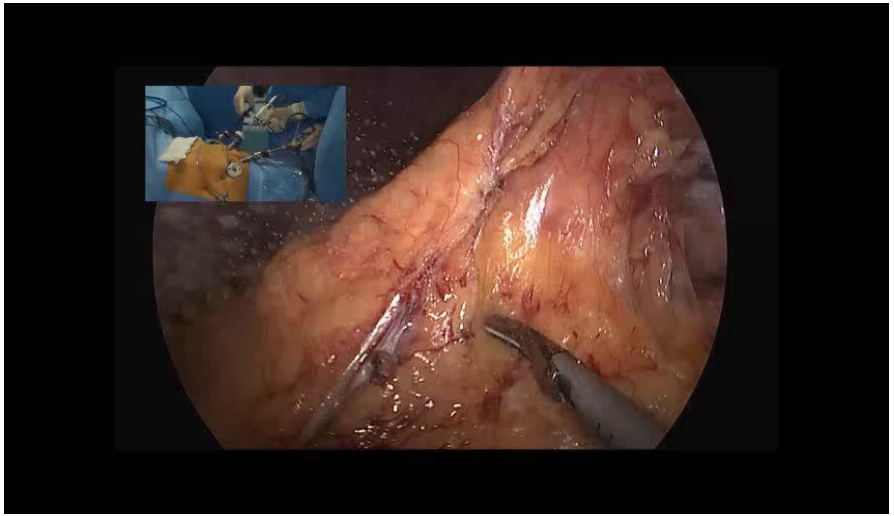




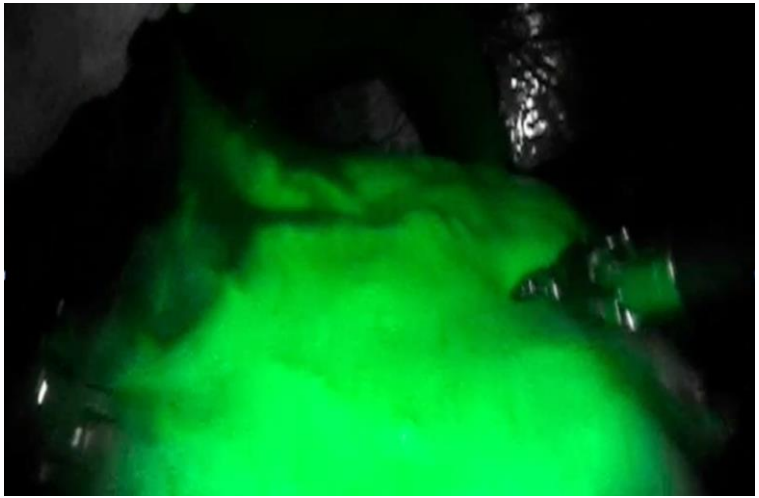
Minimally Invasive Robotic Gastrectomy



LAPAROSCOPIC

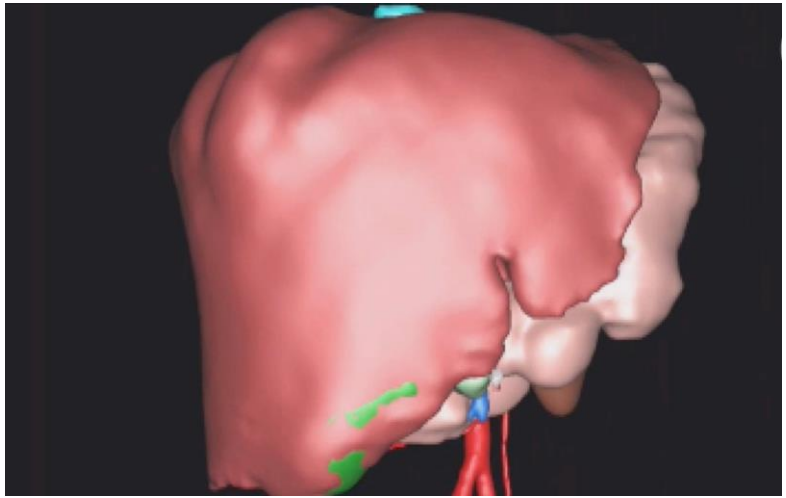


Realidade Aumentada



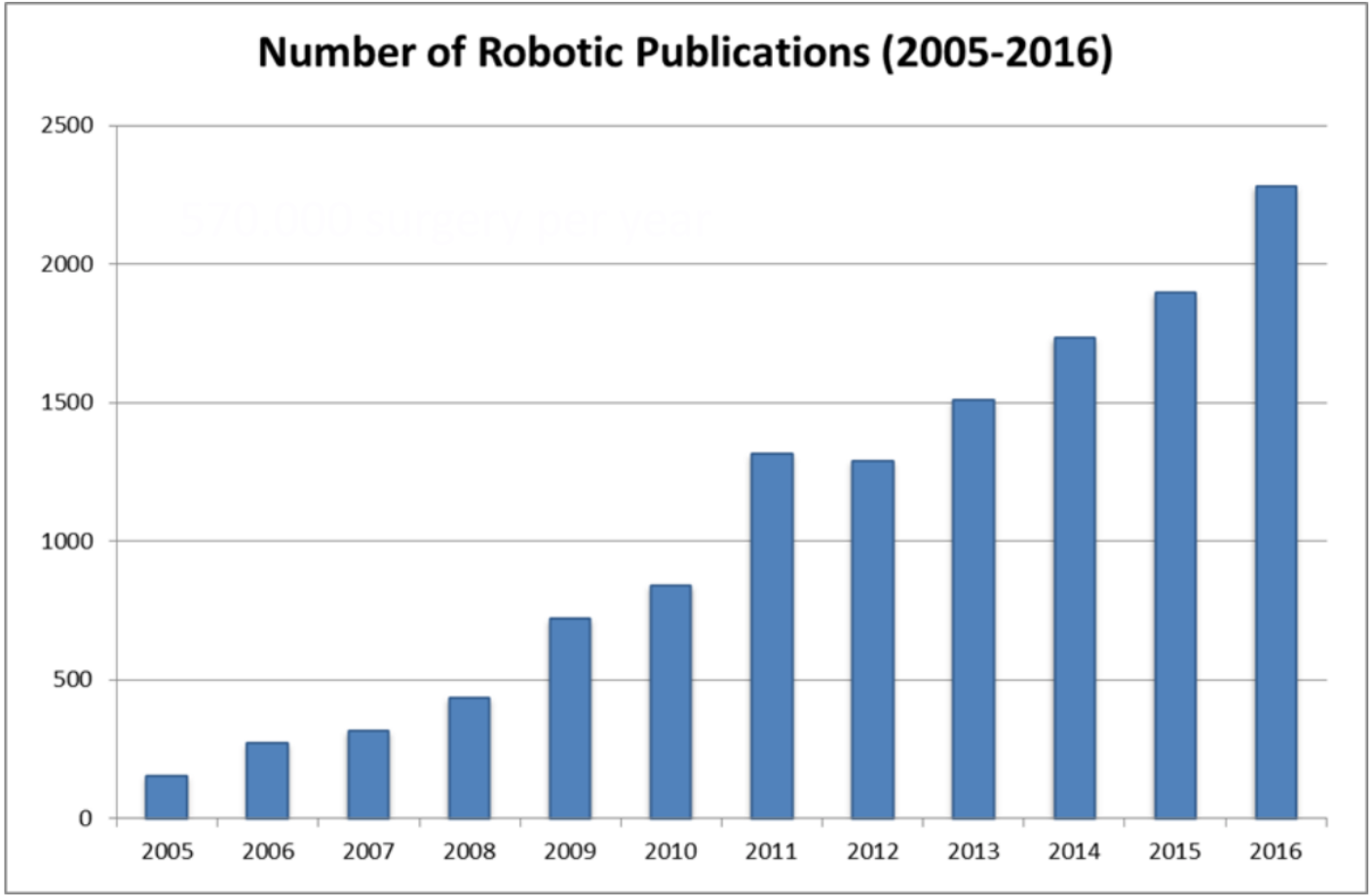
Linfografia por fluorescência

Diferenciação e Identificação Anatômica



Cirurgia guiada por imagem

Planejamento cirúrgico, rehearsal e integração


Number of Robotic Publications (2005-2016)
2500
2000
1500
1000
500
0
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016

J Gastric Cancer. 2018 Mar;18(1):90-98
https://doi.org/10.5230/jgc.2018.18.e10
pISSN 2093-582X·eISSN 2093-5641

jgc Journal of Gastric Cancer

Original Article

Check for updates

Successful Robotic Gastrectomy Does Not Require Extensive Laparoscopic Experience

Ji Yeong An [1,*], Su Mi Kim [1,*], Soohyun Ahn [2,3], Min-Gew Choi [1], Jun-Ho Lee [1], Tae Sung Sohn [1], Jae-Moon Bae [1], Sung Kim [1]

25 casos

Curva de aprendizado é menor do que na gastrectomia laparoscópica

Cirurgia Robótica no Câncer Gástrico

Terashima et al. Gastric Cancer. 2015

Table 2 Meta-analysis of robotic gastrectomy

ROBÓTICA X LAPAROSCÓPICA

ROBÓTICA X CONVENCIONAL

Reporter	Year	Country	Facility	Comparison	Analyzed reports	Results
Liao	2013	China	Southern Medical University	RG[a] vs. OG[b]	20, 22, 29, 31	Surgery time (OG < RG), bleeding (OG > RG), days in hospital (OG > RG)
Xiong	2012	China	Chongqing Medical University	RG vs. LG[c]	20, 21, 27	Surgery time (LG < RG), bleeding (LG > RG)
Xiong	2013	China	Sichuan University	RG vs. LG	20, 21, 29, 30, 31, 32, 34, 37, 38	Surgery time (LG < RG), bleeding (LG > RG), days in hospital (LG > RG), distal margins (LG < RG)
Liao	2013	China	Southern Medical University	RG vs. LG	21, 29, 30, 31, 37, 38, one report in Chinese	Surgery time (LG < RG), bleeding (LG > RG)
Shen	2014	China	Chinese PLA General Hospital	RG vs. LG	21, 27, 29, 30, 31, 34, 37, 38	Surgery time (LG < RG), bleeding (LG > RG), distal margins (LG < RG)
Hyun	2013	South Korea	Korea University	RG vs. LG vs. OG	20, 21, 22, 28, 29, 31, 37, 38, one report unknown	Surgery time (LG < RG) (OG < RG), bleeding (OG > RG), days in hospital (OG > RG)
Marano	2013	South Korea	Yonsei University	RG vs. LG vs. OG	20, 21, 22, 27, 28, 29, 37	Surgery time (LG < RG) (OG < RG), bleeding (LG > RG), days in hospital (OG > RG)
Zong	2014	Japan	The University of Tokyo	RG vs. LG vs. OG	17, 20, 21, 22, 27, 28, 29, 30, 31, 32, 37, 38	Surgery time (OG < RG) (LG < RG), bleeding (OG > RG), (LG > RG)

TEMPO OPERATÓRIO MAIOR

NÚMERO DE LINFONODOS E COMPLICAÇÕES PÓS OPERATÓRIAS SEMELHANTES

MENOS SANGRAMENTO

MENOR TEMPO DE INTERNAÇÃO

MARGENS DISTAIS MAIORES

[a] Open gastrectomy

Conclusões

- ✓ **O Tratamento multimodal** melhora o prognóstico bem como a sobrevida
- ✓ **Novos medicamentos biológicos** tem futuro promissor
- ✓ **CMI** e o auxilio do Robô na sua execução é uma realidade e representam técnicas cirúrgicas promissoras

Obrigado pela atençã
brunozilb@gmail.com