

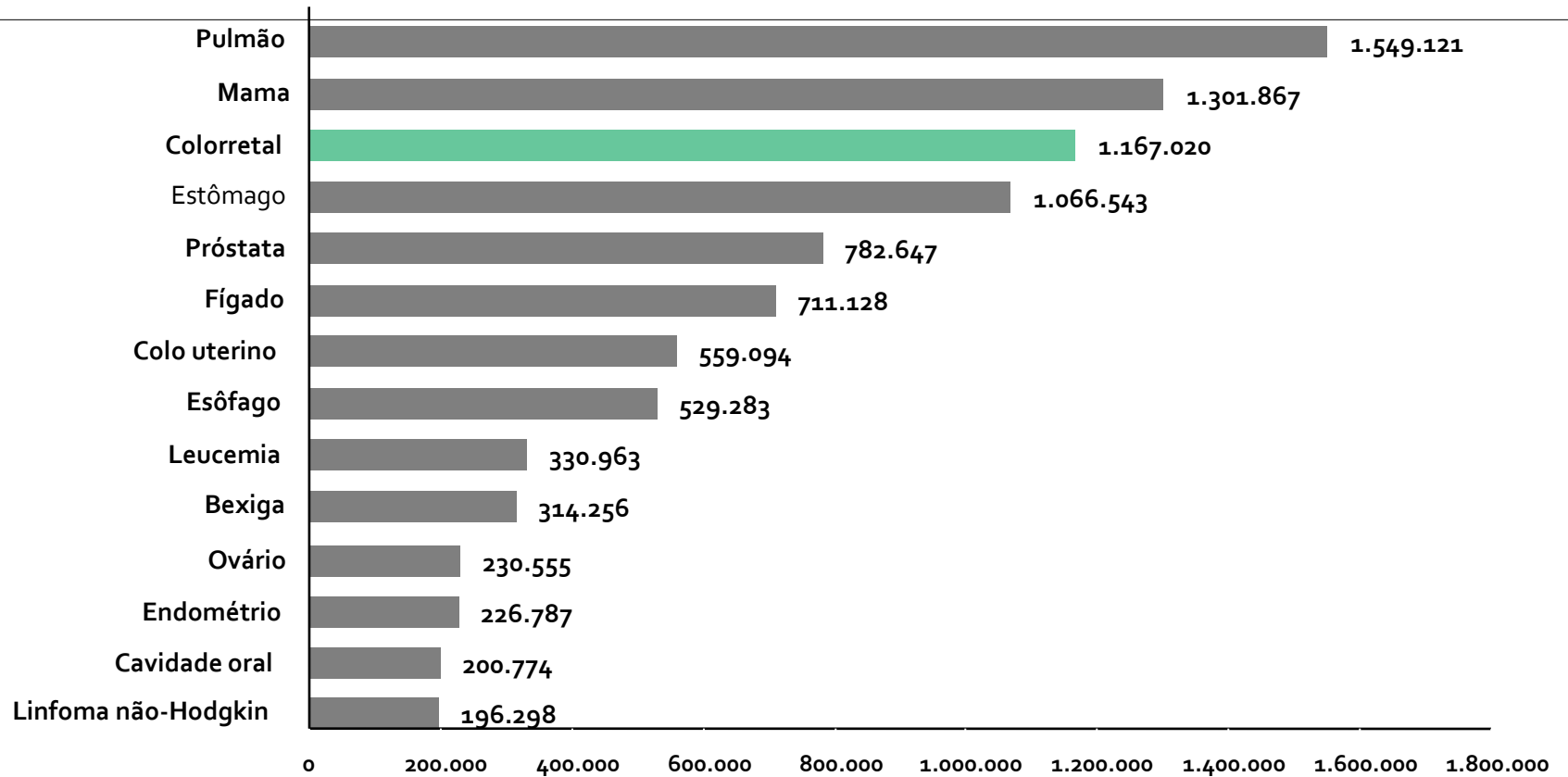
Câncer de intestino: desafios e necessidades

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A C Camargo Cancer Center
São Paulo - Brasil

Câncer Colorretal

Incidência no Mundo





1. Jemal A et al, CA Cancer J Clin 2011

2. Garcia M, et al. American Cancer Society, 2007. www.cancer.org. Accessed March 20, 2008.

3. Perz JF, et al. *J Hepatol.* 2006;45:529-538.



Câncer colorretal - EUA

Estimated New Cases

				Males	Females				
Prostate	220,800	26%				Breast	231,840	29%	
Lung & bronchus	115,610	14%				Lung & bronchus	105,590	13%	
Colon & rectum	69,090	8%				Colon & rectum	63,610	8%	
Urinary bladder	56,320	7%				Uterine corpus	54,870	7%	
Melanoma of the skin	42,670	5%				Thyroid	47,230	6%	
Non-Hodgkin lymphoma	39,850	5%				Non-Hodgkin lymphoma	32,000	4%	
Kidney & renal pelvis	38,270	5%				Melanoma of the skin	31,200	4%	
Oral cavity & pharynx	32,670	4%				Pancreas	24,120	3%	
Leukemia	30,900	4%				Leukemia	23,370	3%	
Liver & intrahepatic bile duct	25,510	3%				Kidney & renal pelvis	23,290	3%	
All Sites	848,200	100%		All Sites	810,170	100%			

Câncer colorretal - EUA

Estimated Deaths

			Males	Females			
Lung & bronchus	86,380	28%			Lung & bronchus	71,660	26%
Prostate	27,540	9%			Breast	40,290	15%
Colon & rectum	26,100	8%			Colon & rectum	23,600	9%
Pancreas	20,710	7%			Pancreas	19,850	7%
Liver & intrahepatic bile duct	17,030	5%			Ovary	14,180	5%
Leukemia	14,210	5%			Leukemia	10,240	4%
Esophagus	12,600	4%			Uterine corpus	10,170	4%
Urinary bladder	11,510	4%			Non-Hodgkin lymphoma	8,310	3%
Non-Hodgkin lymphoma	11,480	4%			Liver & intrahepatic bile duct	7,520	3%
Kidney & renal pelvis	9,070	3%			Brain & other nervous system	6,380	2%
All Sites	312,150	100%	All Sites	277,280	100%		



Incidência - INCA

Localização Primária da Neoplasia Maligna	Estimativa dos Casos Novos							
	Homens				Mulheres			
	Estados		Capitais		Estados		Capitais	
	Casos	Taxa Bruta	Casos	Taxa Bruta	Casos	Taxa Bruta	Casos	Taxa Bruta
Próstata	68.800	70,42	17.540	82,93	-	-	-	-
Mama Feminina	-	-	-	-	57.120	56,09	19.170	80,67
Colo do Útero	-	-	-	-	15.590	15,33	4.530	19,20
Traqueia, Brônquio e Pulmão	16.400	16,79	4.000	18,93	10.930	10,75	3.080	13,06
Cólon e Reto	15.070	15,44	4.860	22,91	17.530	17,24	5.650	23,82
Estômago	12.870	13,19	2.770	13,07	7.520	7,41	2.010	8,44
Cavidade Oral	11.280	11,54	2.220	10,40	4.010	3,92	1.050	4,32
Laringe	6.870	7,03	1.460	6,99	770	0,75	370	1,26
Bexiga	6.750	6,89	1.910	8,91	2.190	2,15	730	2,97
Esôfago	8.010	8,18	1.460	6,76	2.770	2,70	540	0,00
Ovário	-	-	-	-	5.680	5,58	2.270	9,62
Linfoma de Hodgkin	1.300	1,28	410	5,72	880	0,83	420	8,64
Linfoma não Hodgkin	4.940	5,04	1.490	6,87	4.850	4,77	1.680	7,06
Glândula Tireoide	1.150	1,15	470	1,76	8.050	7,91	2.160	9,08
Sistema Nervoso Central	4.960	5,07	1.240	5,81	4.130	4,05	1.370	5,81
Leucemias	5.050	5,20	1.250	5,78	4.320	4,24	1.250	5,15
Corpo do Útero	-	-	-	-	5.900	5,79	2.690	11,24
Pele Melanoma	2.960	3,03	950	4,33	2.930	2,85	1.150	4,57
Outras Localizações	37.520	38,40	9.070	42,86	35.350	34,73	8.590	36,49
Subtotal	203.930	208,77	51.100	241,30	190.520	187,13	58.710	248,46
Pele não Melanoma	98.420	100,75	19.650	92,72	83.710	82,24	22.540	95,26
Todas as Neoplasias	302.350	309,53	70.750	334,08	274.230	269,35	81.250	343,85



Incidência em homens

Localização primária	casos novos	%
Próstata	68.800	22,8%
Traqueia, Brônquio e Pulmão	16.400	5,4%
Cólon e Reto	15.070	5,0%
Estômago	12.870	4,3%
Cavidade Oral	11.280	3,7%
Esôfago	8.010	2,6%
Laringe	6.870	2,3%
Bexiga	6.750	2,2%
Leucemias	5.050	1,7%
Sistema Nervoso Central	4.960	1,6%

Homens





Incidência em mulheres

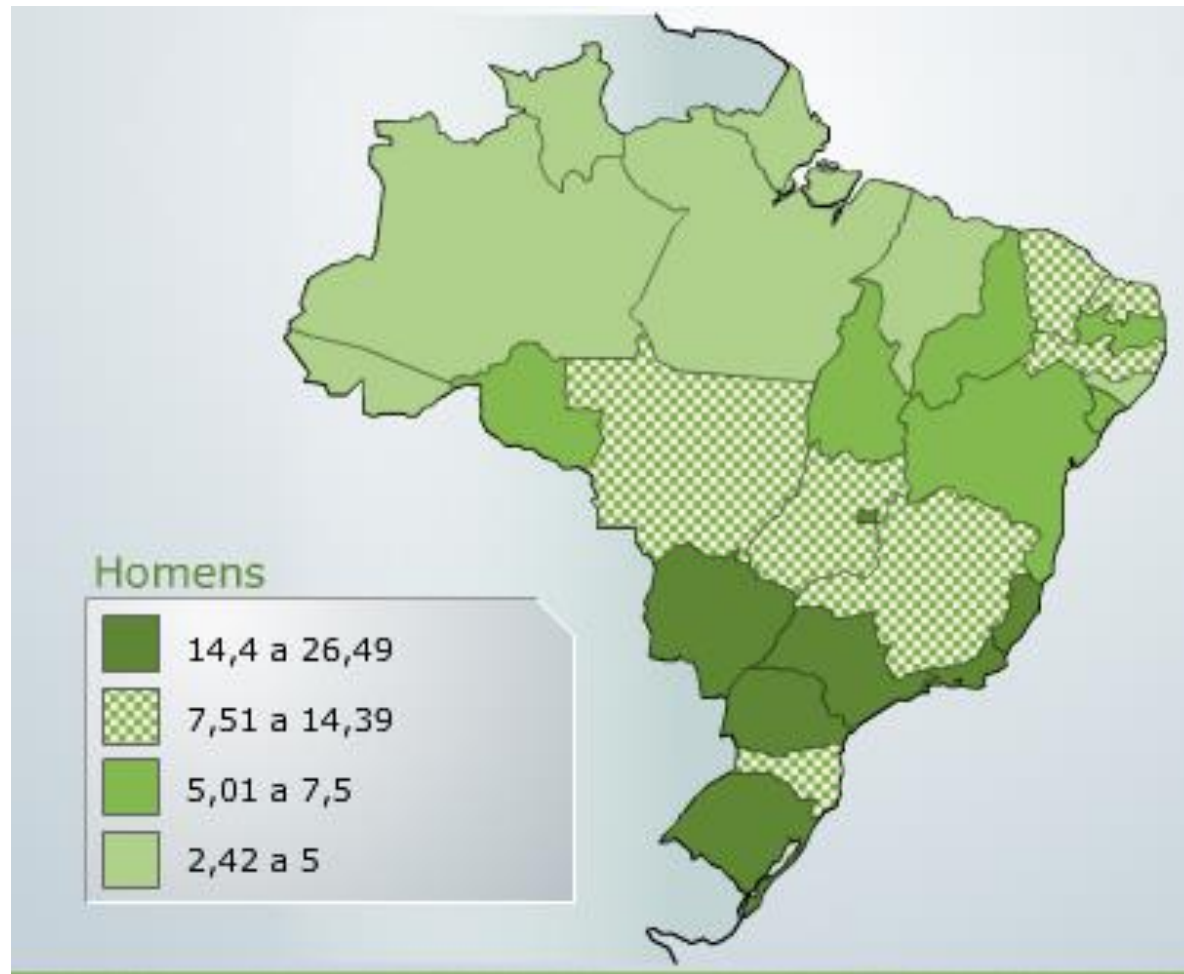
Mulheres



Localização primária	casos novos	%
Mama Feminina	57.120	20,8%
Cólon e Reto	17.530	6,4%
Colo do Útero	15.590	5,7%
Traqueia, Brônquio e Pulmão	10.930	4,0%
Glândula Tireoide	8.050	2,9%
Estômago	7.520	2,7%
Corpo do Útero	5.900	2,2%
Ovário	5.680	2,1%
Linfoma não Hodgkin	4.850	1,8%
Leucemias	4.320	1,6%

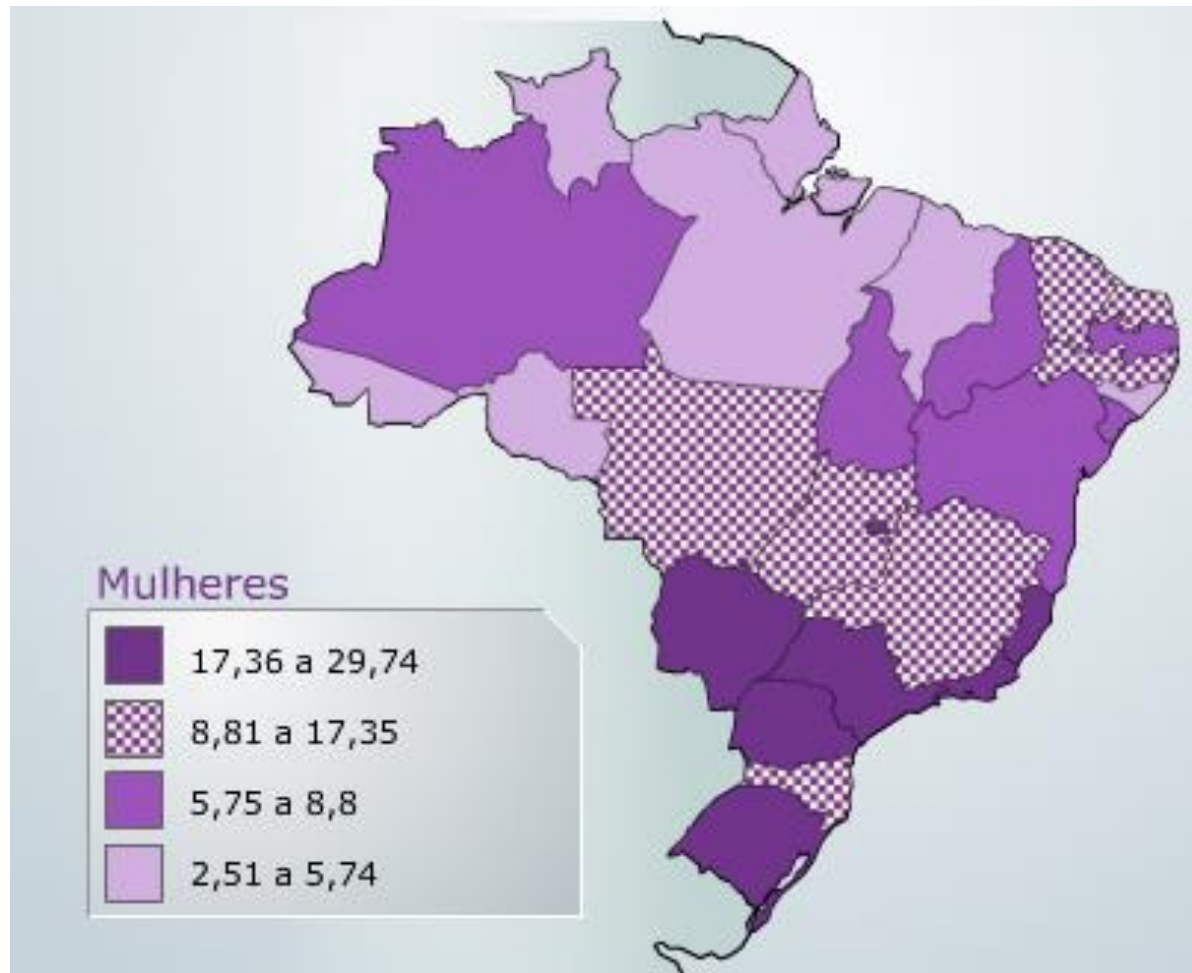


Incidência por Estado





Incidência por Estado



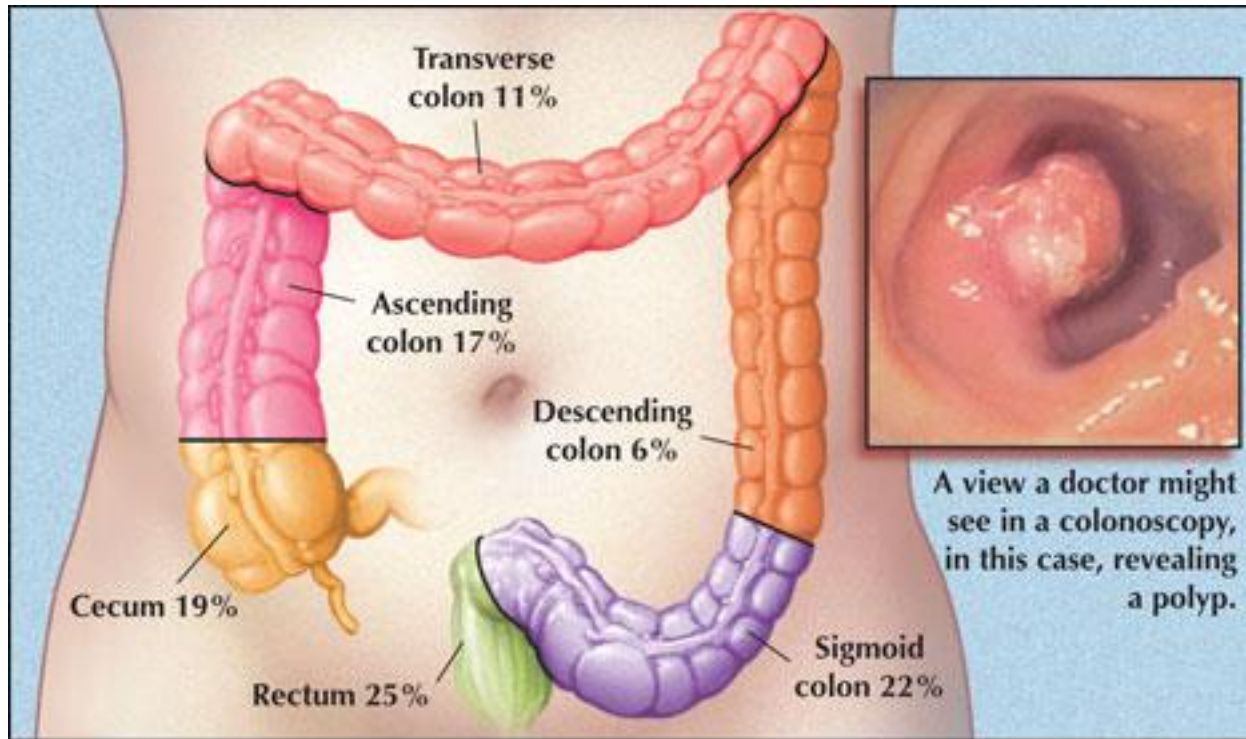
População de risco

- Idade
 - Tabagismo
 - História familiar
 - Dieta
 - Pólipos intestinais
-

Sinais e sintomas

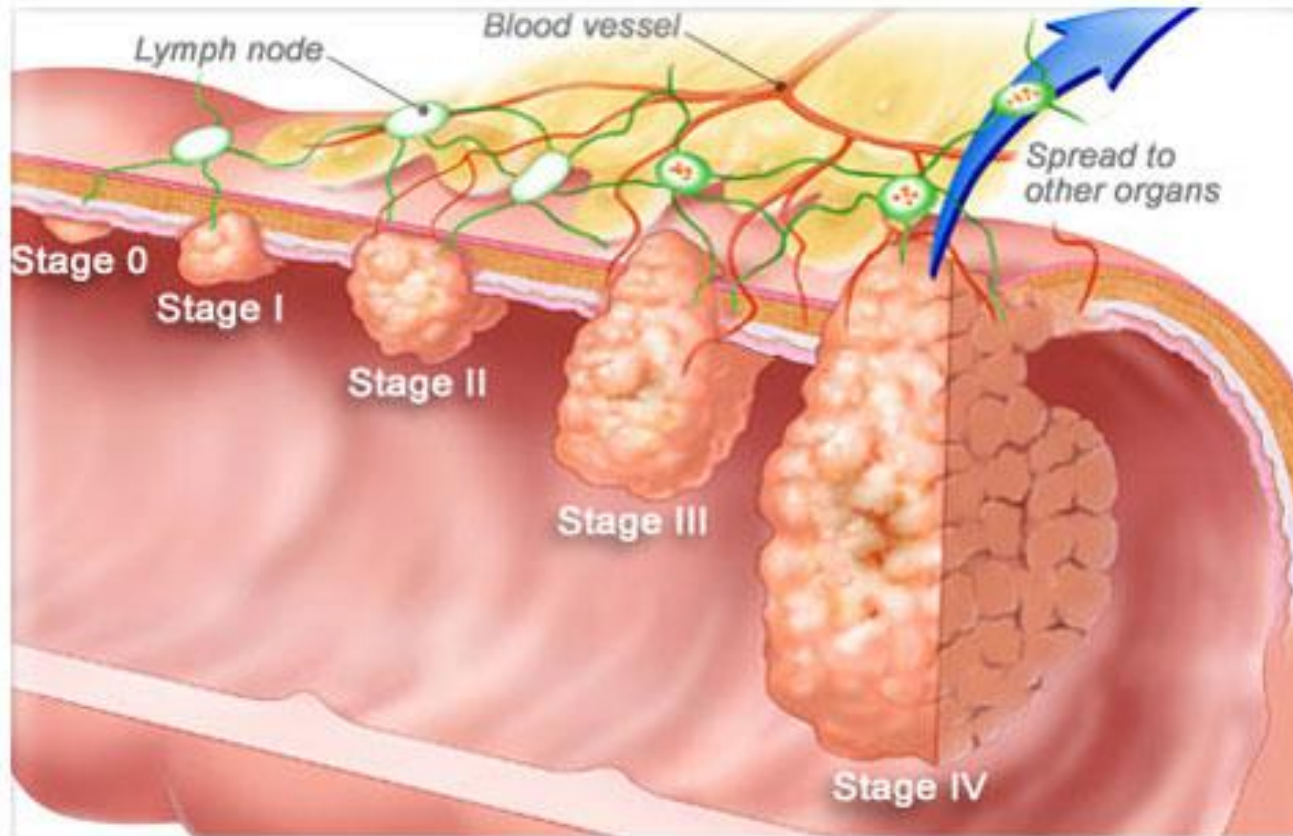
- Sangue nas fezes
 - Fraqueza / anemia
 - Fezes finas ou mal formadas
 - Dor abdominal
 - Perda de peso
 - Urgência para defecar
-

Definição anatômica

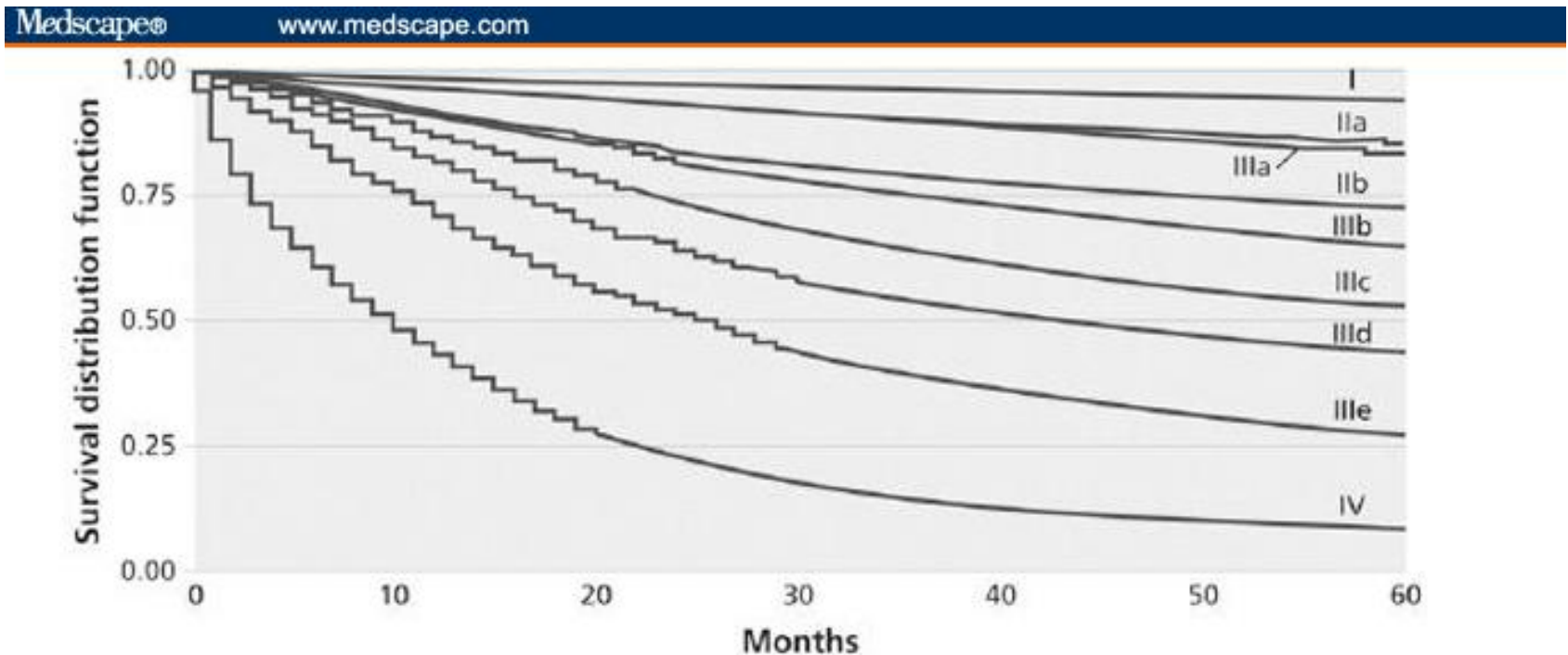


Cancer can occur anywhere in the colon, so it's important to have screening tests that examine the entire colon. Here, the percentages represent the incidence of colon cancer in the various parts of the colon.

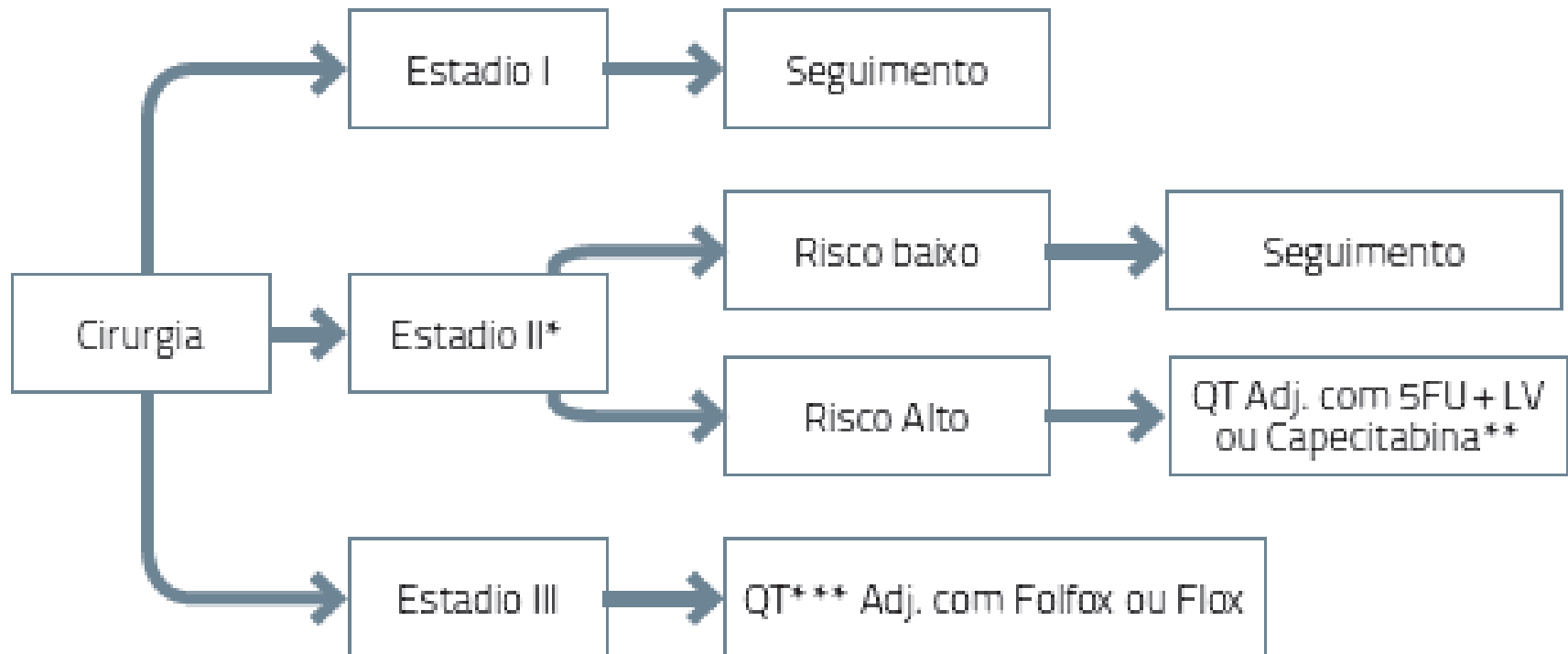
Estadiamento



Sobrevida Global



Tratamento da doença localizada



História Natural

Câncer colorretal

20% metástases ao diagnóstico
50% doença metastática durante a evolução

30-35% Metástases hepáticas
exclusivas

10-20%
Ressecção R0 up
front

Sobrevida 5 anos = 50%

80-90%
Metástases
hepáticas não
ressecáveis

65-70% Metástases extra hepática e
hepática

Irressecável
Tratamento paliativo

Sobrevida em 5 anos = 1-2%

CCR Metastático: identificando o paciente



Ressecável



Cirurgia + QT



Cura



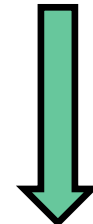
*Potencialmente
ressecável se
Downsizing*



Cura ???



Irressecável



Tratamento
paliativo

Nosso arsenal terapêutico

- Quimioterapia: Fluoropirimidinas, oxaliplatina e irinotecano;

- Anti-EGFR: Cetuximab e Panitumumab

- Anti- Angiogênicos:

Anti- VEGF: Bevacizumab e Aflibercept* (VEGF Trap)

Anti-VEGFR 2: Ramicirumab*

ITK multi-alvo: Regorafenib*; (Anti-VEGR_{1, 2 3})

*Não disponíveis no Brasil

Oxaliplatina e Irinotecano + 5FU

Oxaliplatina

Estudo	N	Esquema	Taxa R	SLP (m)	SG (m)	2a linha
De Gramont A, et al. Fase III	420	FOLFOX ₄ LV5FU ₂	50,0%	9,0	16,2	58,1%
			21,9%	6,2	14,7	60,5% (28%)
			p = 0,0001	p = 0,0001	p = 0,13	
Giacchetti S, et al. Fase III	200	5-FU/LV + I-OHP 5-FU/LV	53%	8,7	19,4	-
			16%	6,1	19,9	-
			p < 0,0001	p = 0,048	p = NS	
Hospers GAP, et al. Fase III	302	5-FU/LV + I-OHP 5-FU/LV	45,7%	6,7	13,8	60,3% (20%)
			35,8%	5,6	13,3	64,2%
			p = 0,045	p = 0,016	p = NS	

Irinotecano

Estudo	N	Esquema	Taxa R	SLP (m)	SG (m)	2a linha
Saltz LB, et al. Fase III	683	CPT-11 + 5-FU/LV 5-FU/LV CPT-11	50%	7,0	14,8	52%
			28%	4,3	12,6	70%
			29%	4,2	12,0	79%
			p < 0,001	p = 0,004	p = 0,042	
Douillard JY, et al. Fase III	387	CPT-11 + 5-FU/LV 5-FU/LV	49%	6,7	17,4	49%
			31%	4,4	14,1	65%
			p < 0,001	p < 0,001	P = 0,032	

Saltz LB, et al. N Engl J Med 2000;343:905-14

De Gramont A, et al. J Clin Oncol 2000; 18:2938-47

Hospers GAP, et a. Ann Oncol 2006;17:443-449

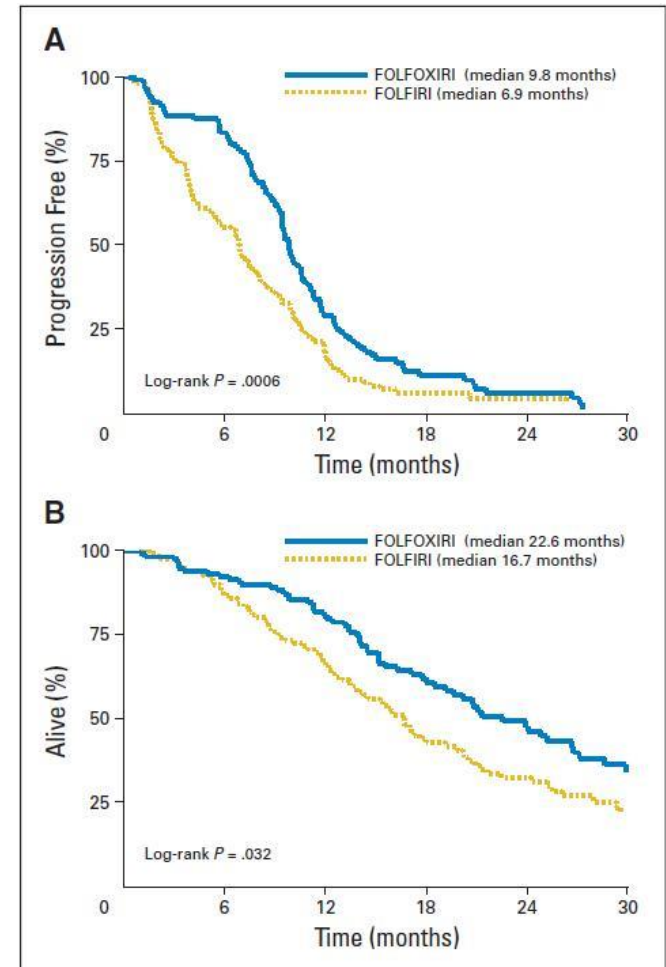
Giacchetti S, et al. J Clin Oncol 2000;18:136-147

Douillard JY, et al. Lancet 2000;355:1041-47

Três Drogas Quimioterápicas

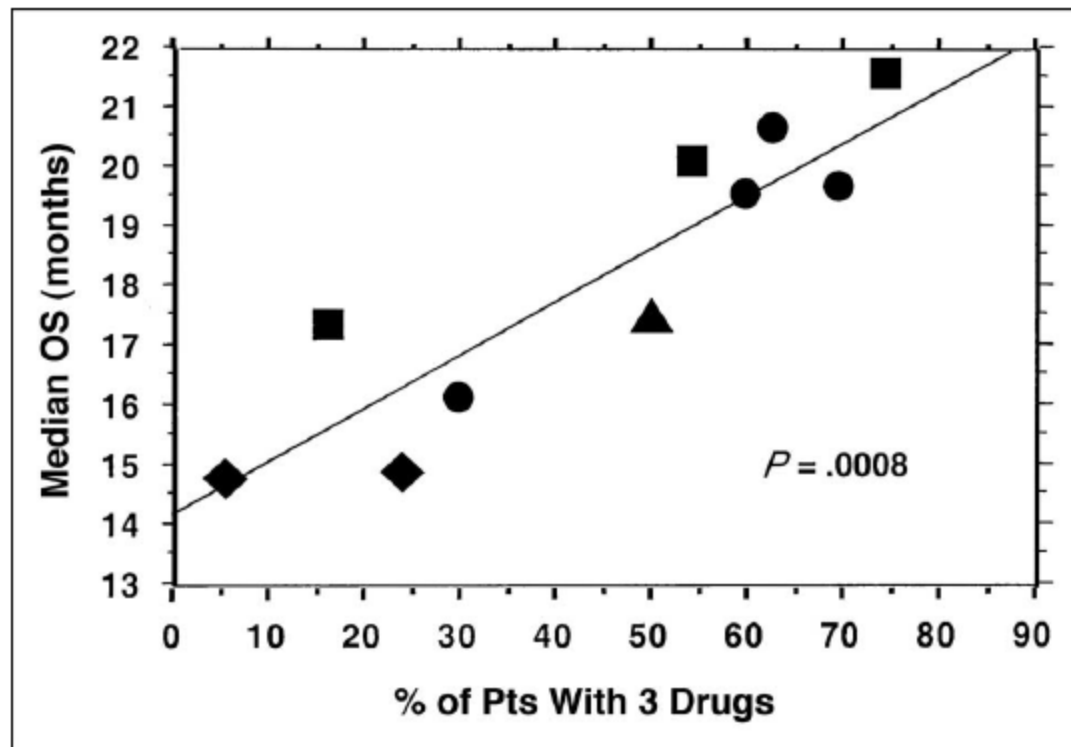
FOLFOXIRI vs FOLFIRI

	FOLFIRI n=122	FOLFOXIRI n=122
RR	34%	60%
SLP	6,9m	9,8m
SG	16,7m	22,6m
R0 Resection	6% (7 pts)	15% (18 pts)
Liver Only Metastases	n=42	n=39
R0 Resection	12%	36%



Survival of Patients With Advanced Colorectal Cancer Improves With the Availability of Fluorouracil-Leucovorin, Irinotecan, and Oxaliplatin in the Course of Treatment

Axel Grothey, Daniel Sargent, Richard M. Goldberg, and Hans-Joachim Schmoll



QT c/ Anti-Angiogênicos vs QT, 1a linha: Overview

Todos estudos em 1a Linha com Bevacizumab

Questões: Papel em esquemas mais ativos? TR? SG?

Estudo	Fase	Agentes	N (wt)	TR	SLP (m)	SG(m)
Hurwitz et Al.	III	IFL c/ ou s/ Bevacizumab	813	45%vs 35% (p:0,001)	10,6 vs 6,2 (p:<0,001)	20,3 vs 15,6 (p<0,001)
AVEX (idosos>70a)	III	Xeloda c/ ou s/ Beva	280	19% vs 10% (p:0,042)	9,1 vs 5,1 (p<0,001)	20,7 vs 16,8 (p<0,182)
No 16966	III (2 x2)	FOLFOX/XELOX c/ ou /s Bevacizumab	1.401	47% vs 49% (p: NS)	9,4 vs 8,0 (p:0,0023)	21,3 vs 20 (p:NS)
Stathopoulos	III	FOLFIRI c/ ou s/ Bevacizumab	222	37% vs 35% (p: NS)	- (p:NS)	25 vs 22 (p:0,13)
BICC-C	IV 2 períodos	FOLFIRI, IFL, CAPIRI c/ ou s/ Beva	117	58% vs 47% FOLFIRI c/ Beva vs IFL c/ Beva	-	28 vs 19 FOLFIRI c/ Beva vs IFL c/ Beva (p:0,037)
TREE-2	(vs TREE-1)	FOLFOX/CAPOX e 2a coorte c/ Beva	223	Aumento numérico	Aumento numérico	Aumento numérico

Wang M, 2014; Metanálise Bevacizumabe 1a linha (6 RCT, 3.066 pts)

ORR: +4,5% SLP: 0,60 SG: 0,83, p<0,001

QT c/ Anti-Angiogênicos vs QT, 2a linha: Overview

No estudo VELOUR 30% dos pacientes usaram Beva na primeira linha

No Estudo RAISE: 100% dos pacientes usaram Beva na primeira linha

Estudo	Fase	1a Linha	Agentes	N	TR	SLP	SG
E3200	III	5FU ou Irinotecano	FOLFOX+Beva	829	23%	7,3m	12,9 m
			FOLFOX		8,6%	4,7m	10,8m
			Bevacizumabe		3,3% (p<0,001)	2,7m (p<0,001)	10m (p:0,011)
VELOUR	III	FOLFOX (30% + Beva)	FOLFIRI c/ ou s/ Aflibercept	1226	20% vs 11% (p:0,001)	6,9m vs 4,7m (p:<0,001)	13,5m vs 12,1m (p:0,0032)
RAISE	III	Oxaliplatina+ Fluoro + Beva	FOLFIRI+ Ramircirumab/Plac ebo	1072	13,4% vs 12% (p:0,6)	5,7mvs 4,5m (<0,005)	13,3m vs 11,7m (p:0,02)

QT c/ Anti-EGFR vs QT, 1a linha, KRAS éxon 2 selvagem: Overview

População Geral (Não selecionada para ressecção)

KRAS exon 2 selvagem

Questões em aberto: interação com Oxaliplatina e tipo/administração da Fluoropirimidina

Estudo	Fase	Agentes	N	TR	SLP	SG
CRYSTAL	III	FOLFIRI c/ou/ cetuximab	1198	57,3% vs 40% (p:<0,0001)	9,9m vs 8,4m (p:0,0012)	23,5m vs 20m (p:0,009)
OPUS	II	FOLFOX c/ ou /s cetuximab	337	61% vs 37% (p:0,01)	7,7m vs 7,2m (p:0,016)	22,8m vs 18,5m (p:0,39)
PRIME	III	FOLFOX c/ ou /s Panitumumab	1183	55% vs 48% (p:0,06)	9,6m vs 8,0m (p:0,02)	23,9m vs 19,7m (p:0,072/0,03)
MRC Coin	III	FOLFOX/CAPOX c/ ou s/ Cetuximab	729	64% vs 57% (p:0,049)	8,6m vs 8,6m (p:0,6)	17,9m vs 17m (p:0,68)
NORDIC VII	III	FLOX c/ ou /s cetuximab	348	46% vs 47% (p:0,87)	7,9m vs 8,7m (p:0,66)	20m vs 22m (p:0,66)

Quimioterapia e Taxa de Resposta

Estudos fase III

População não-selecionada para ressecção

Esquema	Taxa de Resposta
FOLFOX/FOLFIRI	54-55%
FOLFOXIRI	60%
FOLFOXIRI+BEVACIZUMABE	65%
FOLFIRI+ CETUXIMABE (ALL RAS)	66,5%

CCR Metastático

Identificando o Paciente



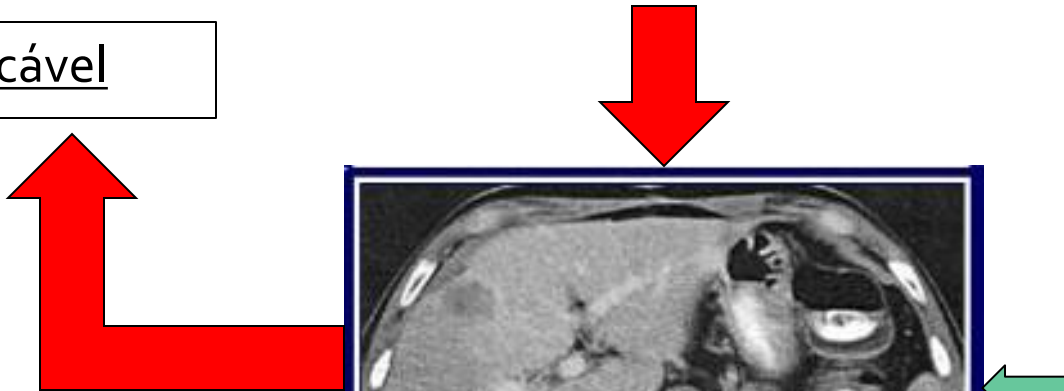
Ressecável



Irressecável

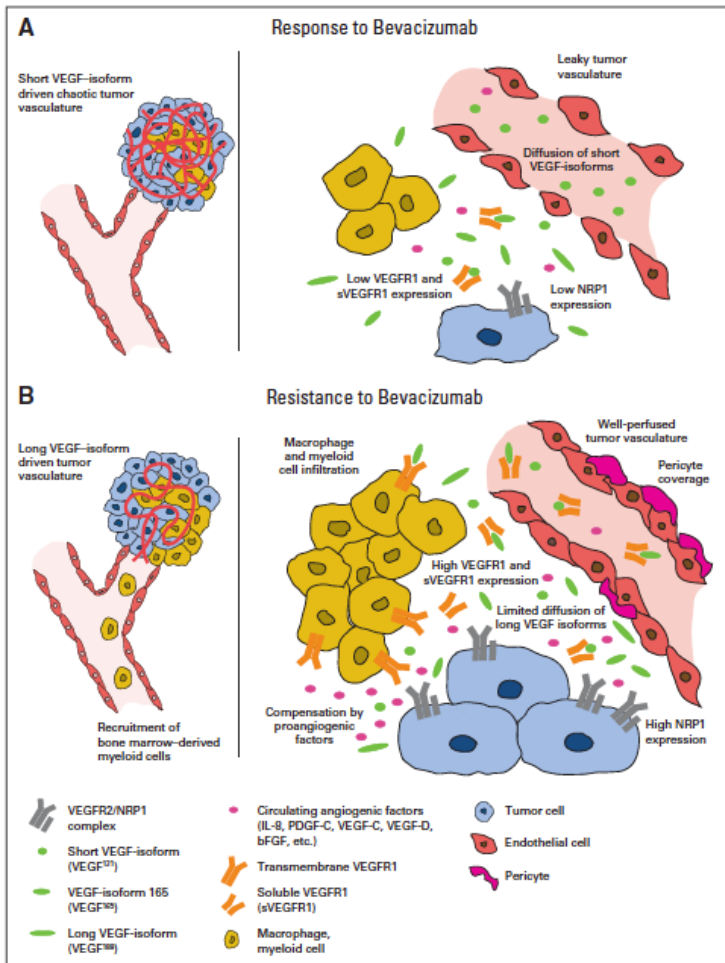


Terapia sistêmica
+/- tratamento local



Otimizando a seleção de
pacientes: biomarcadores

Biomarkers for Anti-angiogenetic treatment

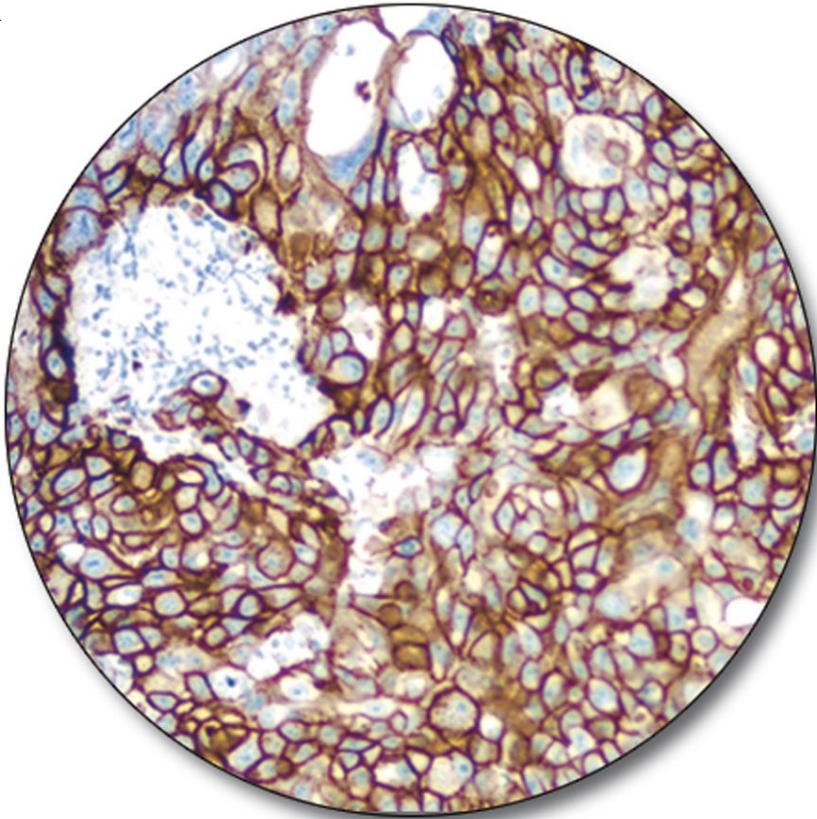


Bevacizumab and Aflibercept are both targeting VEGF-A

Both do not target tumor cells!

Multiple efforts have been made to identify biomarkers

EGFR in Colorectal Cancer



EGFR IHC – Colorectal Carcinoma

- Expresso em 25 a 82% dos adenocarcinomas colorretais
- Hiperexpresso (2 a 3+) em 35-49%

J. P. Spano. *Annals of Oncology*, vol. 16, no. 2, pp. 189–194, 2005

N. S. Goldstein. *Cancer*, vol. 92, pp. 1331–1346, 2001.

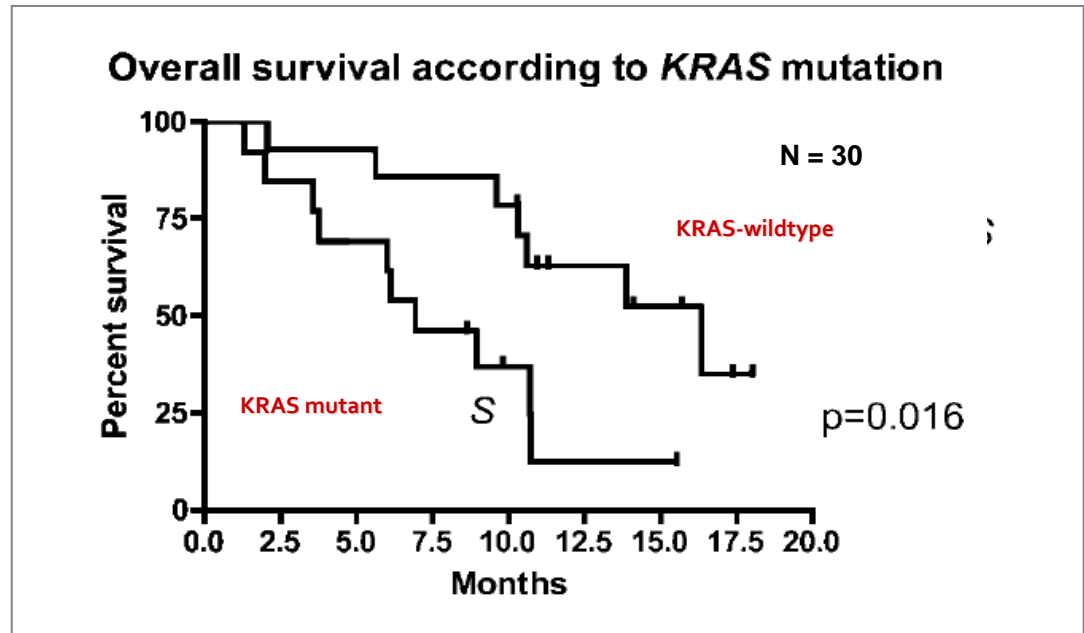
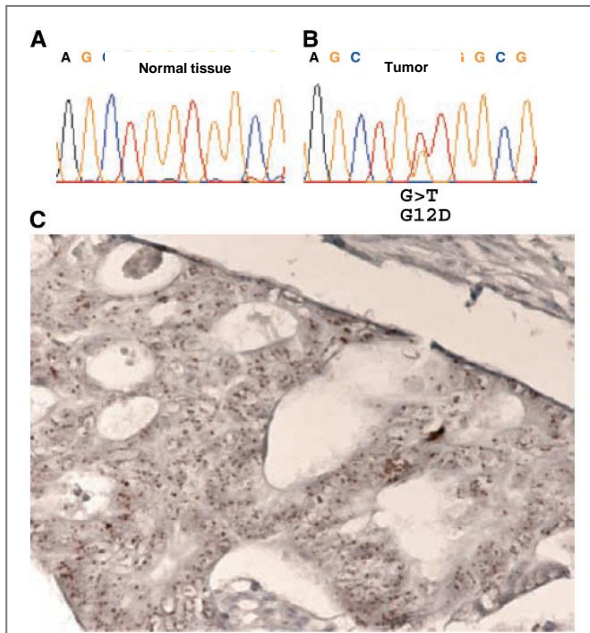
J. A. McKay. *Cancer*, vol. 38, no. 17, pp. 2258–2264, 2002.

M. B. Resnick. *Clinical Cancer Research*, vol. 10, no. 9, pp. 3069–3075, 2004

***KRAS* Mutation Status Is Predictive of Response to Cetuximab Therapy in Colorectal Cancer**

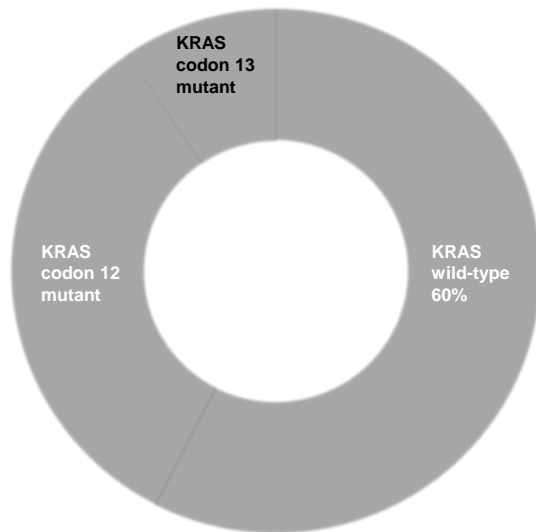
Astrid Lièvre,^{1,3} Jean-Baptiste Bachet,³ Delphine Le Corre,¹ Valérie Boige,⁴ Bruno Landi,² Jean-François Emile,³ Jean-François Côté,^{1,2} Gorana Tomasic,⁴ Christophe Penna,³ Michel Ducreux,⁴ Philippe Rougier,³ Frédérique Penault-Llorca,⁵ and Pierre Laurent-Puig^{1,2}

¹Université Paris-Descartes, Institut National de la Santé et de la Recherche Médicale UMR-775; ²Assistance Publique-Hôpitaux de Paris, Hôpital Européen Georges Pompidou, Paris, France; ³Assistance Publique-Hôpitaux de Paris, Hôpital Ambroise Paré, Boulogne Billancourt, France, Université de Versailles Saint-Quentin-en-Yvelines, Versailles, France; ⁴Institut Gustave Roussy, Villejuif, France; and ⁵Centre Jean Perrin, Clermont-Ferrand, France, Université Auvergne, Clermont-Ferrand, France

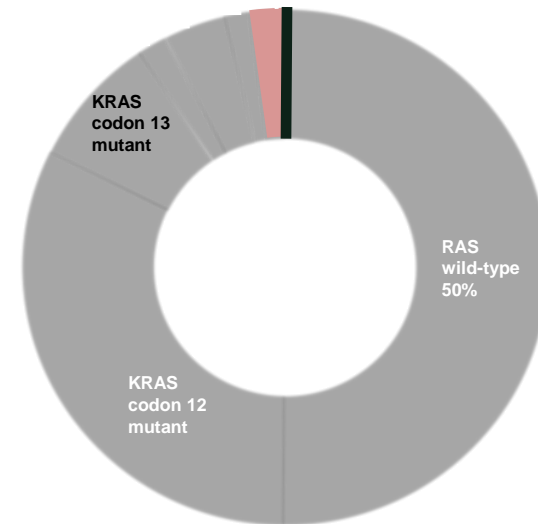


Extended RAS analysis

KRAS exon 2 wild-type



Extended RAS wild-type

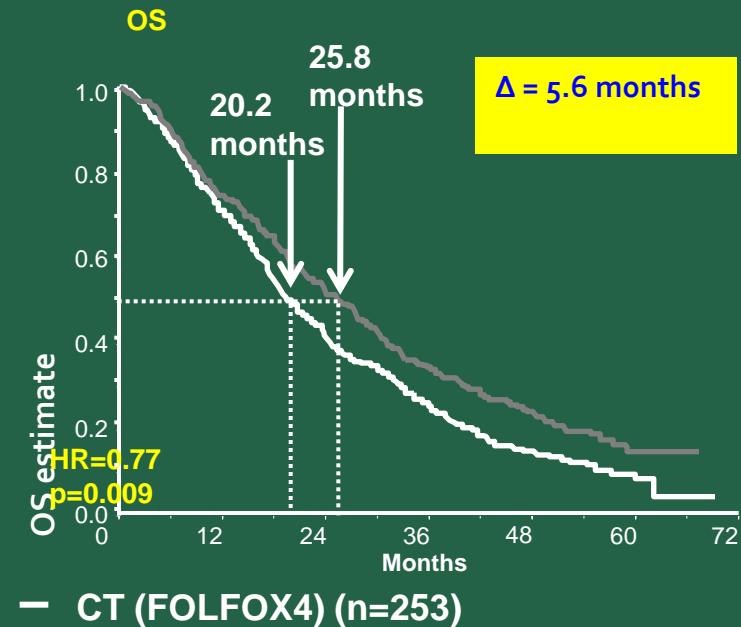
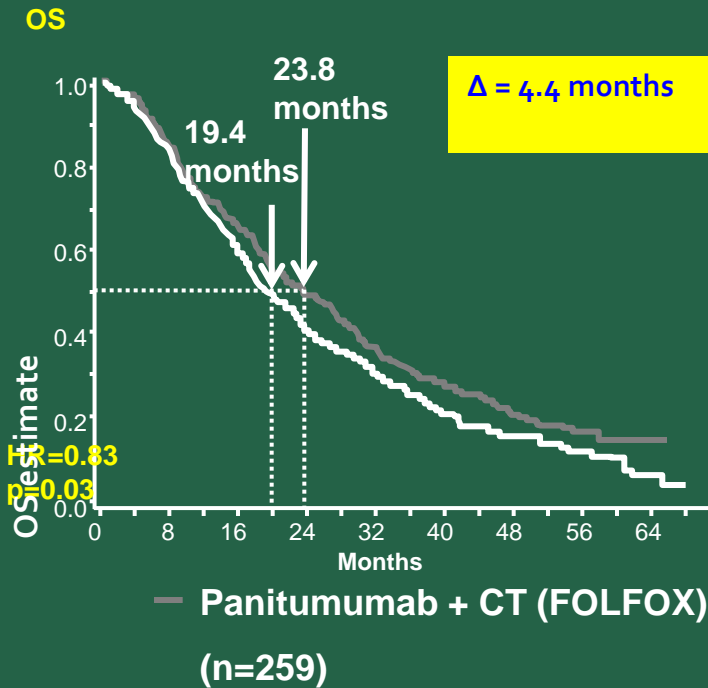


Extended RAS analysis PRIME - study

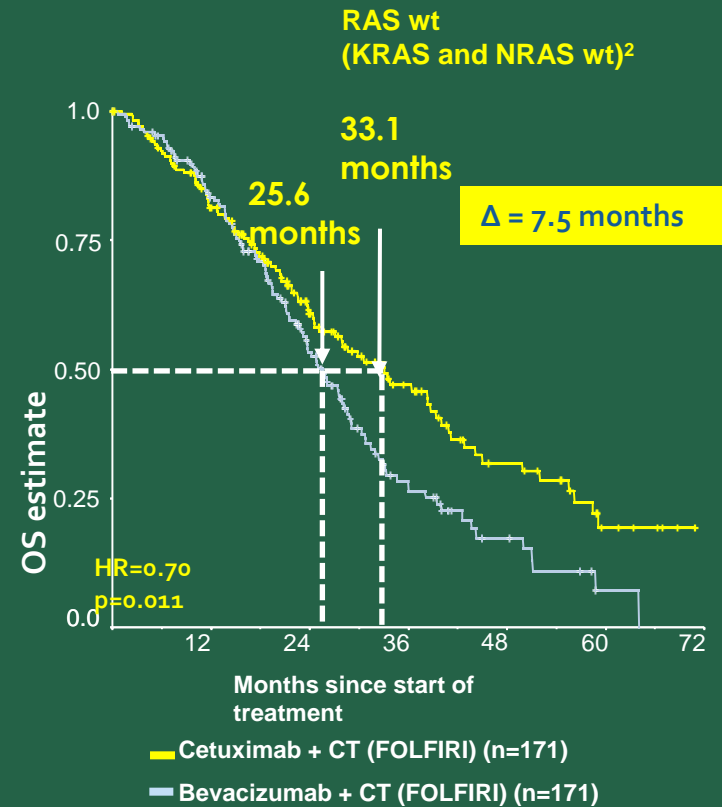
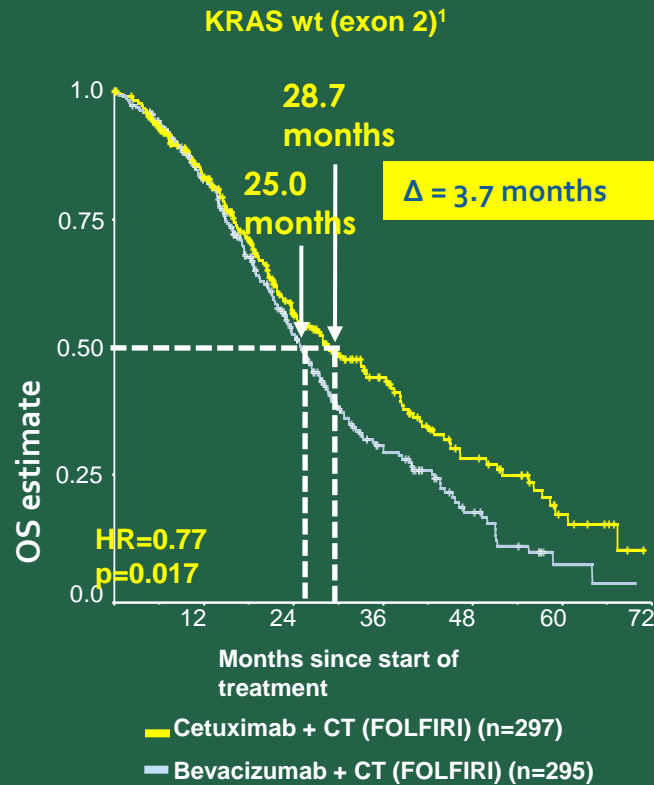


PRIME: KRAS wt (exon 2)

PRIME: RAS wt
(KRAS and NRAS wt)



Extended RAS analysis FIRE-3 - study

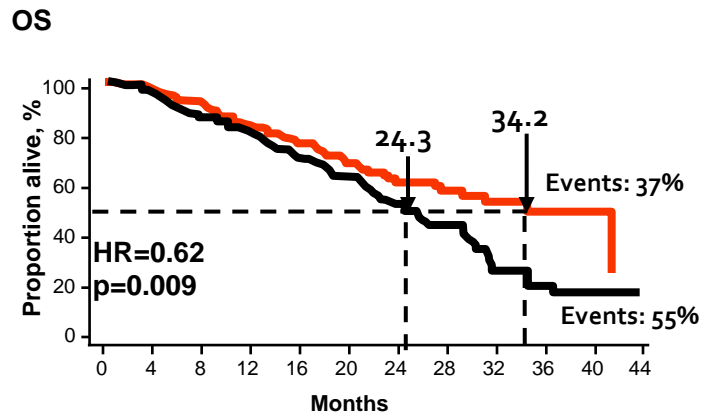


1. Heinemann V, et al. ASCO 2013 (Abstract No. LBA3506);
2. Stintzing S, et al. ECC 2013 (Abstract No. LBA17)

Extended RAS analysis PEAK - study

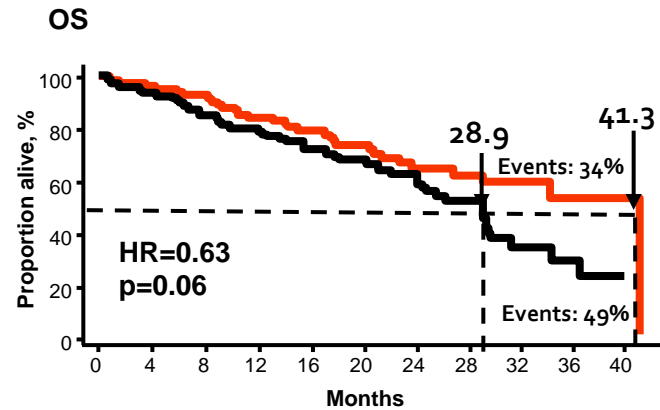


PEAK: KRAS wt (exon 2)



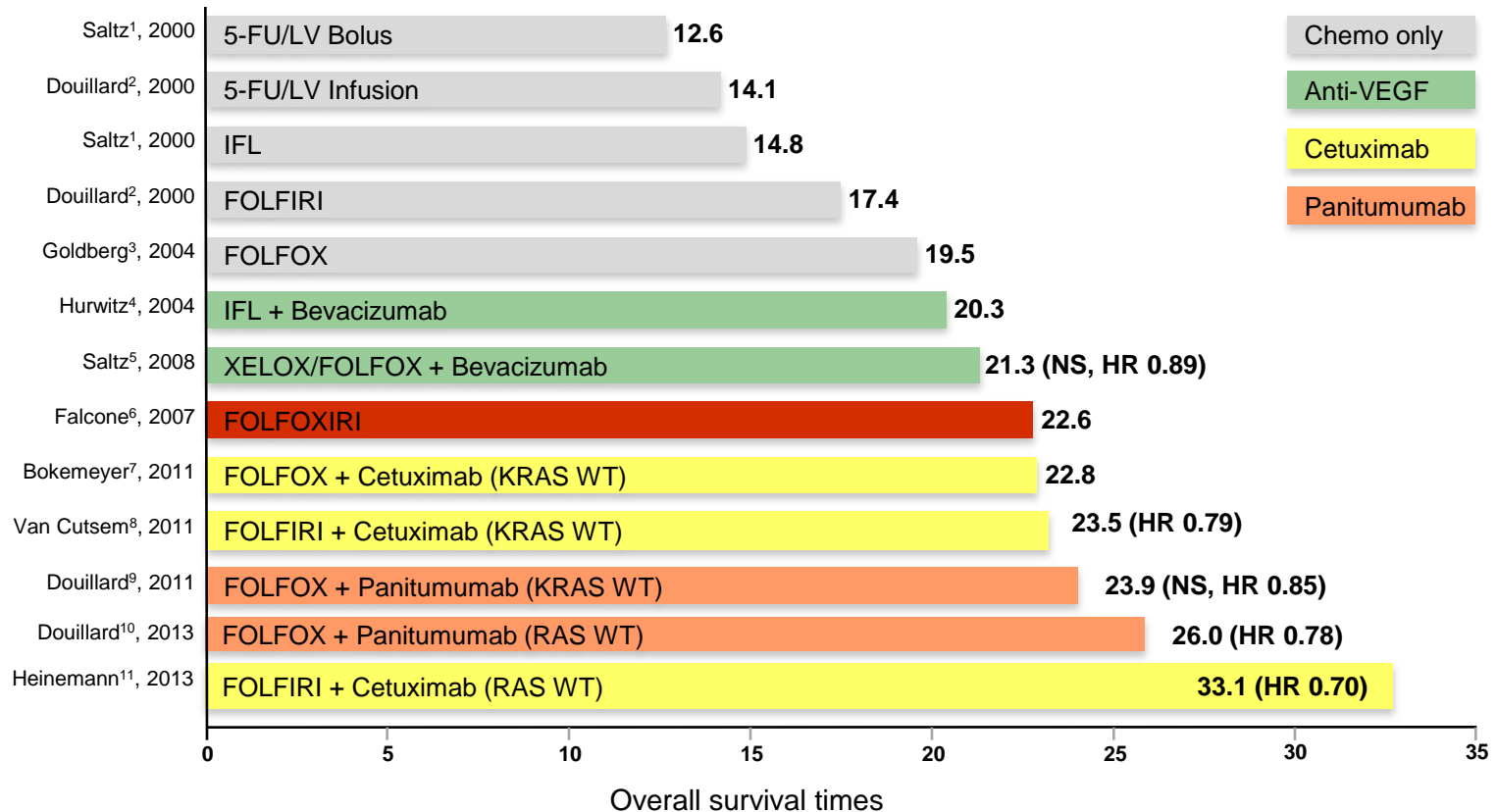
- Bevacizumab + mFOLFOX6 (n=143)
- Panitumumab + mFOLFOX6 (n=142)

PEAK: RAS wt



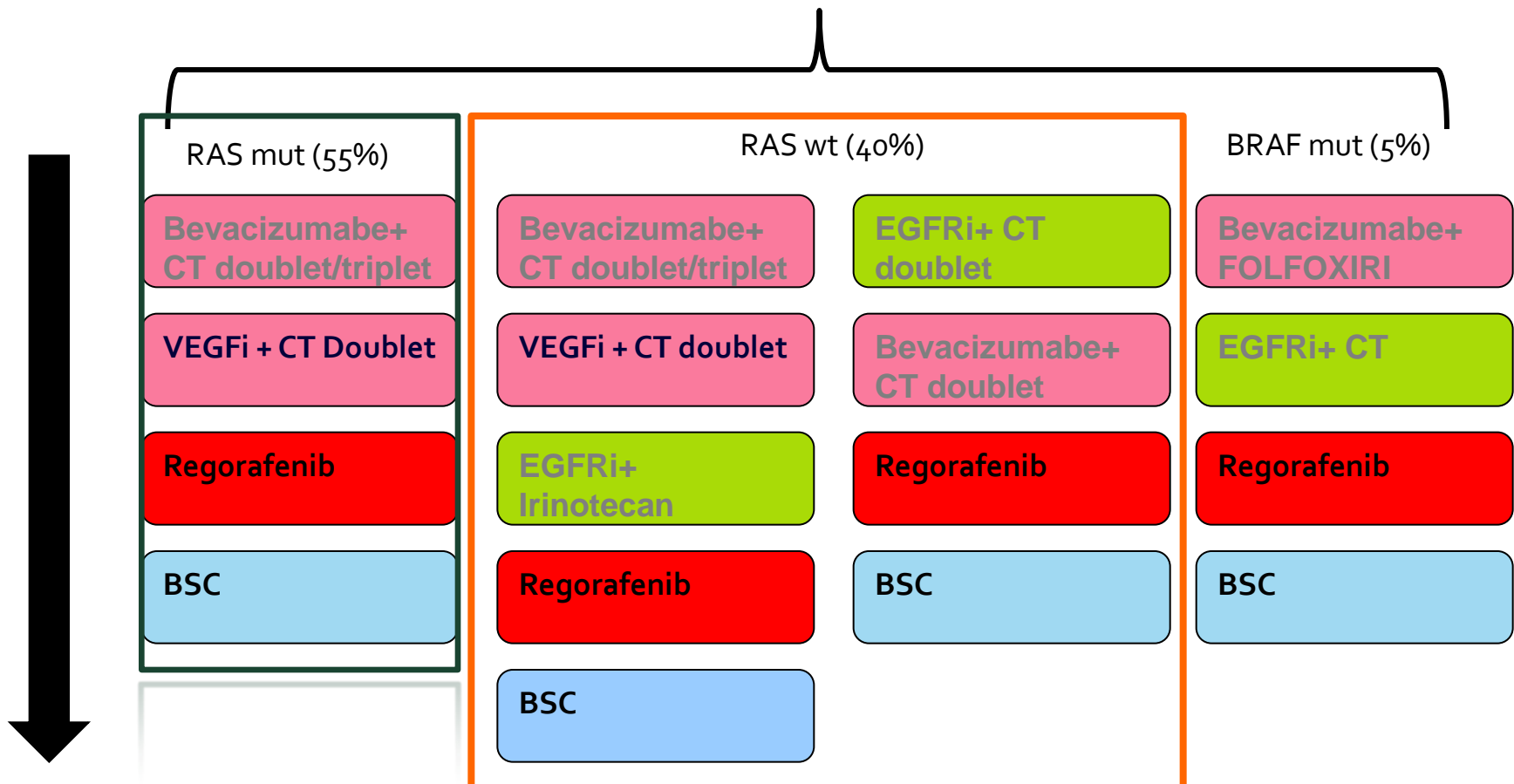
- Bevacizumab + mFOLFOX6 (n=82)
- Panitumumab + mFOLFOX6 (n=88)

1st-line treatment decisions in mCRC



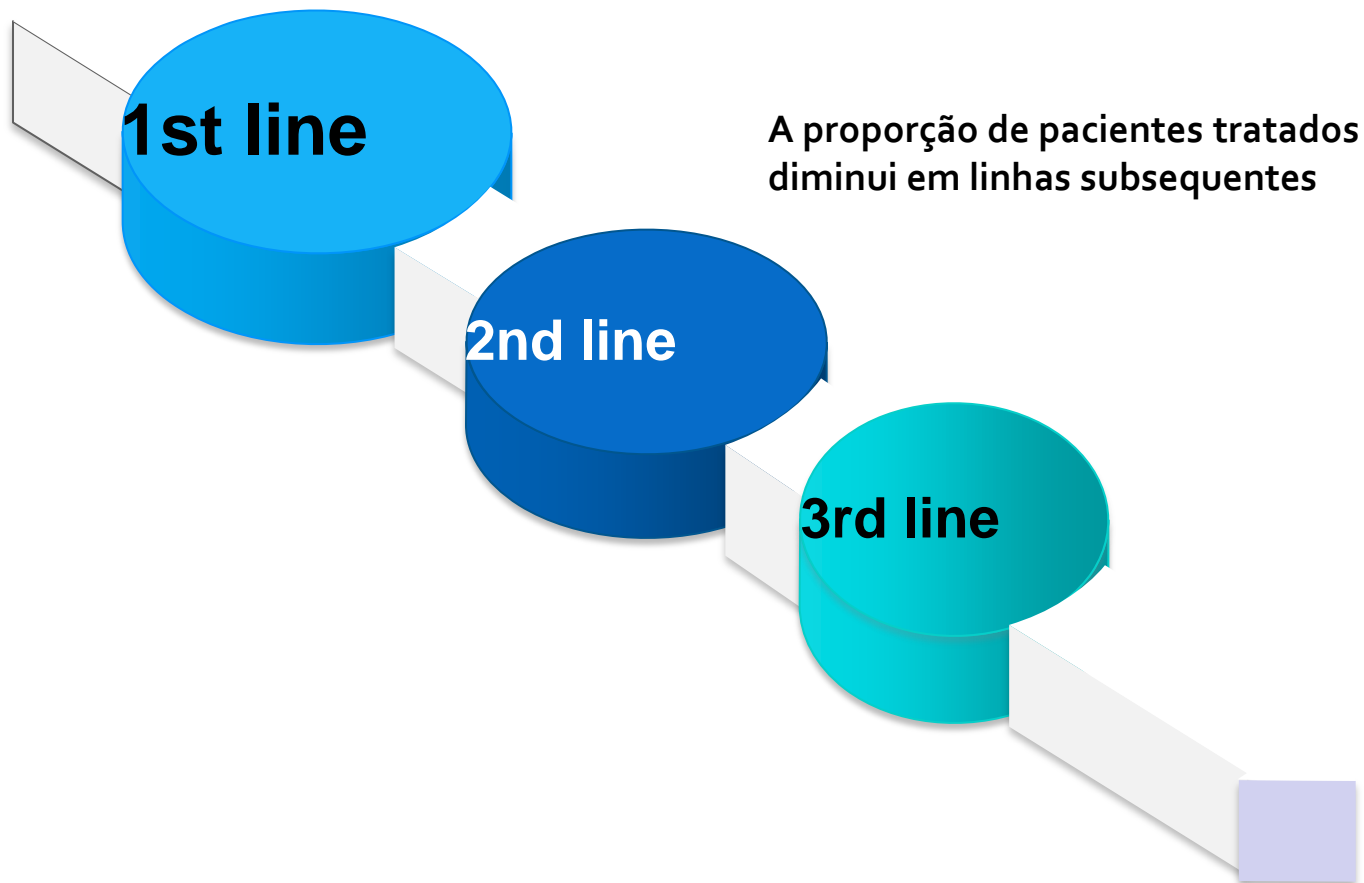
1. N Engl J Med 2000; 343: 905–914. 2. Lancet 2000; 355: 1041–1047. 3. J Clin Oncol 2004; 22: 23–30. 4. N Engl J Med 2004; 350: 2335–2342. 5. J Clin Oncol 2008; 26: 2013–2019. 6. J Clin Oncol 2007; 25: 1670–1676. 7. Ann Oncol 2011; 22: 1535–1546. 8. J Clin Oncol 2011; 29: 2011–2019. 9. J Clin Oncol 2011; 29 (Suppl): 3510. 10. N Engl J Med 2013; 369: 1023–1034. 11. ESMO 2013

Fluxo de tratamento da doença metastática - ESMO

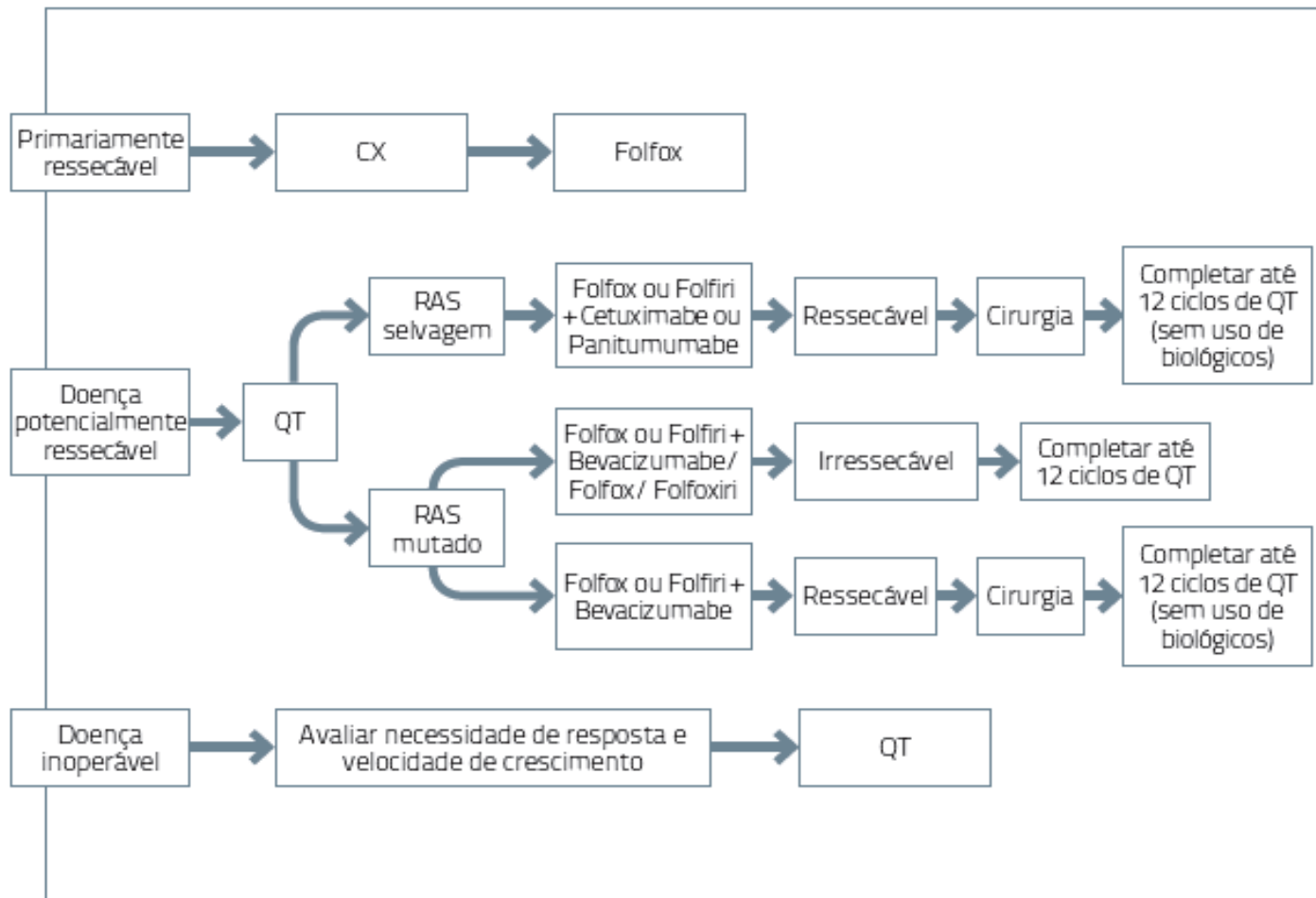


Adapted from Sridharan et al. Oncology 2014

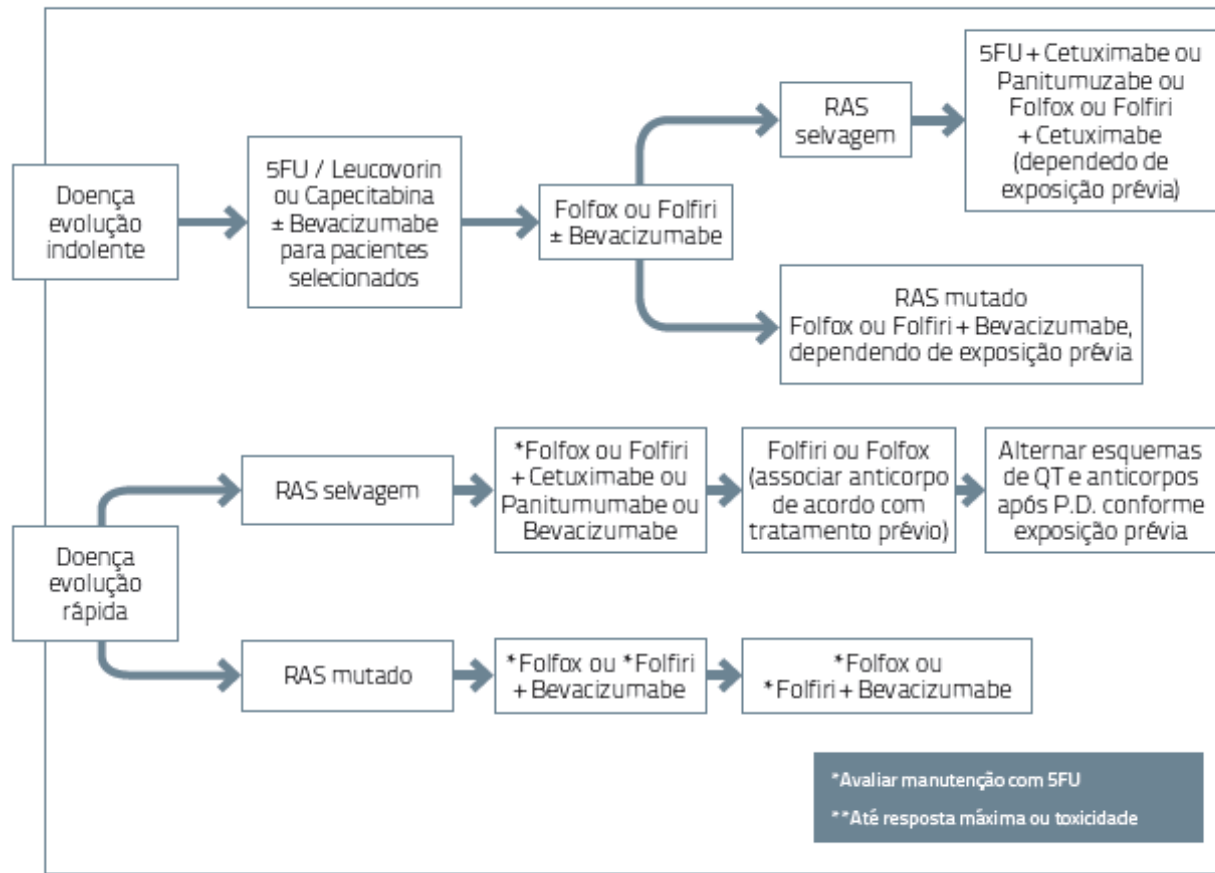
Importância do tratamento em 1ª linha



Rotina A C Camargo



Rotina A C Camargo



Nossos desafios (I)

DIAGNÓSTICO PRECOCE

- Identificar população de risco (\$)
- Pesquisa de sangue nas fezes (\$)
- Colonoscopia (\$\$)

TRATAMENTO CURATIVO

- Cirurgia (\$\$)
 - QT adjuvante (\$\$)
-

Nossos desafios (II)

DOENÇA METASTÁTICA: \$\$\$\$\$\$\$\$\$\$.....\$\$

Identificar corretamente a intenção do tratamento

- Avaliação e discussão multidisciplinar
 - Uso imprescindível de biomarcadores: All RAS
 - Fazer uso do melhor de cada estratégia para um paciente individual
 - Evitar esquemas possivelmente deletérios
 - Levar em consideração: qualidade de vida, toxicidade e custo benefício
-

Muito obrigado



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