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I Jornada ONCO-HSC de Blumenau
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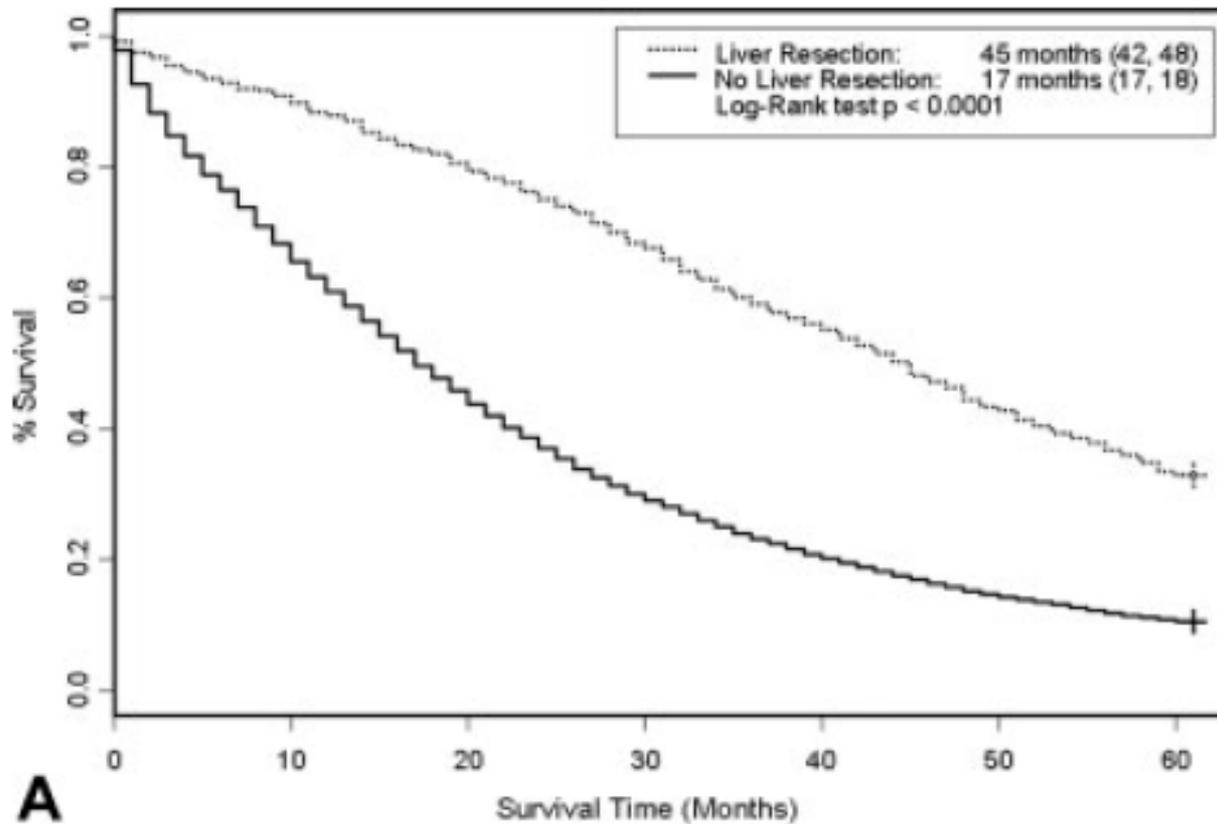


Margens menores que 1 centímetro na hepatectomia são insuficientes?

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Ressecção hepática



□ A ressecção da metástase hepática de origem colo-retal está associada com aumento na sobrevida.

Metástase hepática colo-retal

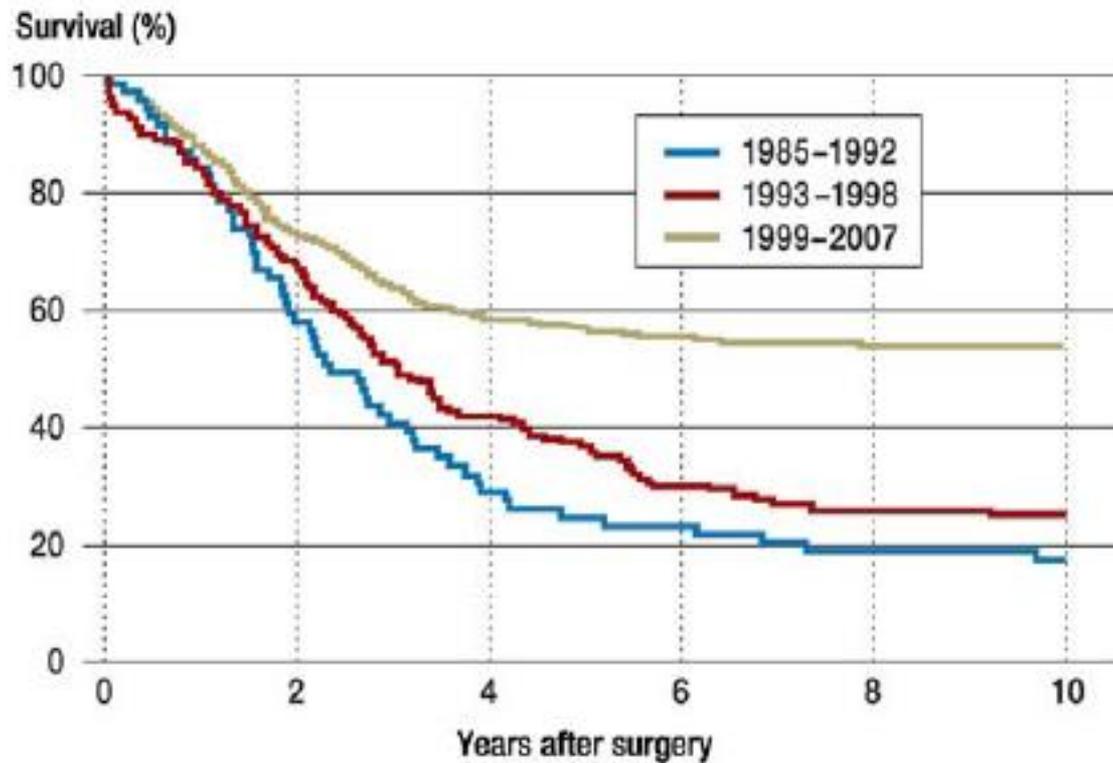
- ❑ Tratamento é a ressecção
- ❑ 58% de sobrevida em 5 anos
- ❑ 26% de sobrevida em 10 anos
- ❑ Ressecção com margem ≥ 1 cm



**A ressecção hepática proporciona a
única oportunidade de cura destes pacientes**

Resultados em meta colo-retal

FIGURE 2



Escore de risco clínico modificado

FATORES PROGNÓSTICO

Metástase nodal positiva do tumor primário

Intervalo livre de doença < 12 meses

Número de metástase hepática > 1

CEA pré-operatório acima de 100 ng por ml

Tamanho do tumor maior que 5 cm

Margem cirúrgica positiva

Doença extra-hepática

Malignidade do tumor primário

Localização no reto

Fong Y, et al. Ann Surg 230:309-321,1999

Adam et al. Surg Clin N Am 84:659-671,2004

Fatores prognósticos associados a sobrevida em 10 anos

Prognostic factor	Univariate			Multivariate		
	Hazard ratio	95% CI	P-value	Hazard ratio	95% CI	P-value
Rectal primary tumour	0.69	0.47–1.31	0.450	–	–	–
Primary LN metastasis	1.36	0.88–2.12	0.045	–	–	–
Synchronous metastasis	0.80	0.50–1.21	0.490	–	–	–
CEA >200 ng/ml	1.73	0.89–2.46	0.022	1.81	1.80–3.60	0.040
Hepatic lesion >5 cm	1.51	0.86–2.76	0.045	1.64	0.65–1.98	0.039
Number lesions >3	1.57	0.81–2.77	0.021	1.61	1.10–2.49	–
Blood loss >2000 ml	0.69	0.43–1.11	0.221	–	–	–
Positive surgical margin	1.89	1.63–3.12	0.021	1.48	1.20–3.25	0.045
≥Hemi-hepatectomy	0.79	0.49–1.48	0.455	–	–	–
Adjuvant chemotherapy	0.54	0.39–1.14	0.542			
Portal clamping	0.61	0.41–1.21	0.452			
CRS >2	3.19	1.63–4.12	<0.001	2.76	1.85–4.55	0.001

Impacto da margem positiva na sobrevida

Table 1 Clinicopathologic variables from 612 patients treated at MSKCC with 10 year follow-up and impact on overall survival

Variable	<2-Year survival (%)	2–5-Year survival (%)	5–10-Year survival (%)	>10-Year survival (%)
Synchronous disease	13	11	5	7
Node-positive primary tumor	63	56	52	50
Preoperative CEA >200 ng/mL	16	11	8	7
Disease-free interval <12 months	51	46	36	36
Number of hepatic metastases >1	59	51	32	39
Size of hepatic metastases >5 cm	53	41	41	35
Positive resection margin (liver)	20	10	9	0
Resection > or = lobectomy	63	63	62	68
> or = 4 hepatic metastases	23	16	11	5



O fator isolado mais importante que afeta negativamente o prognóstico após a ressecção é o envolvimento da margem de ressecção pelo tumor.



A margem de ressecção cirúrgica é o único fator que pode ser diretamente influenciado pelas mãos do cirurgião.



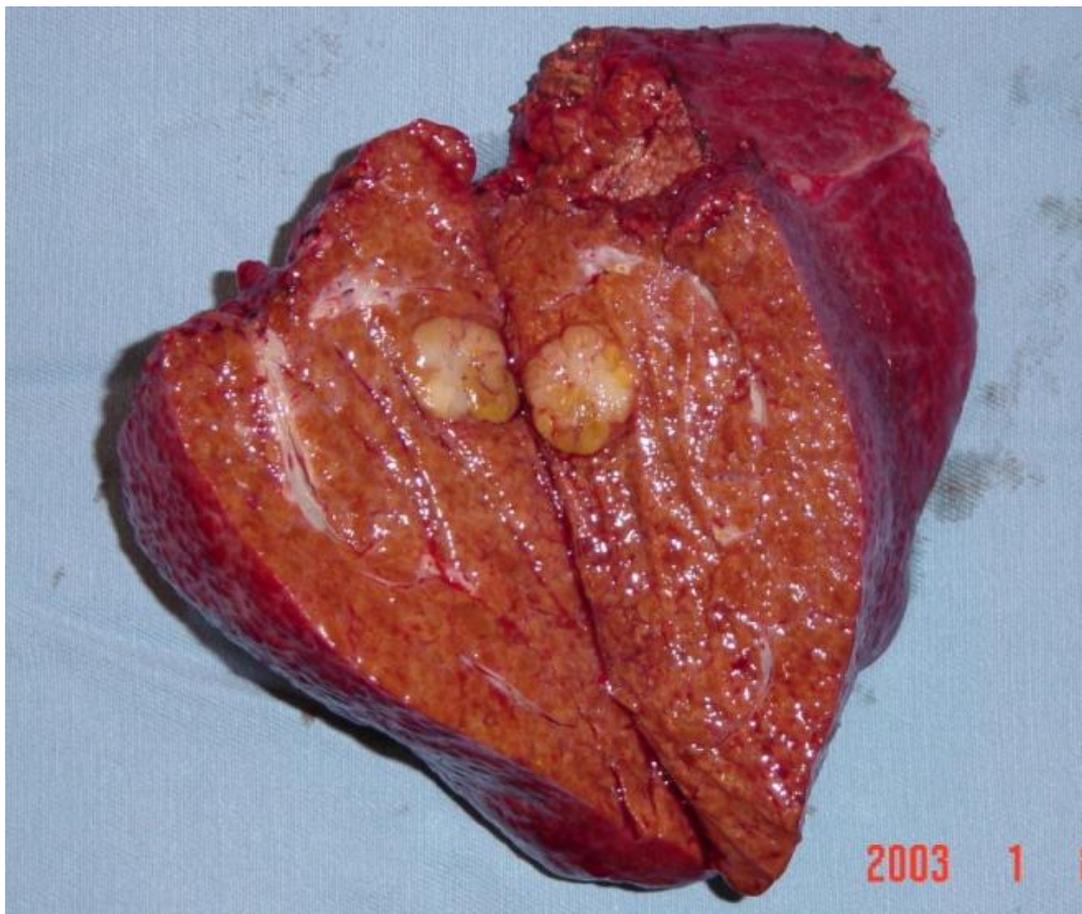
A regra de 1 cm ainda é válida?

Situações em que a ressecção com 1 cm de margem pode não ser possível

- Localização profunda no fígado
- Proximidade a vasos
- Tamanho da lesão
- Múltiplas lesões
- Ressecções sucessivas

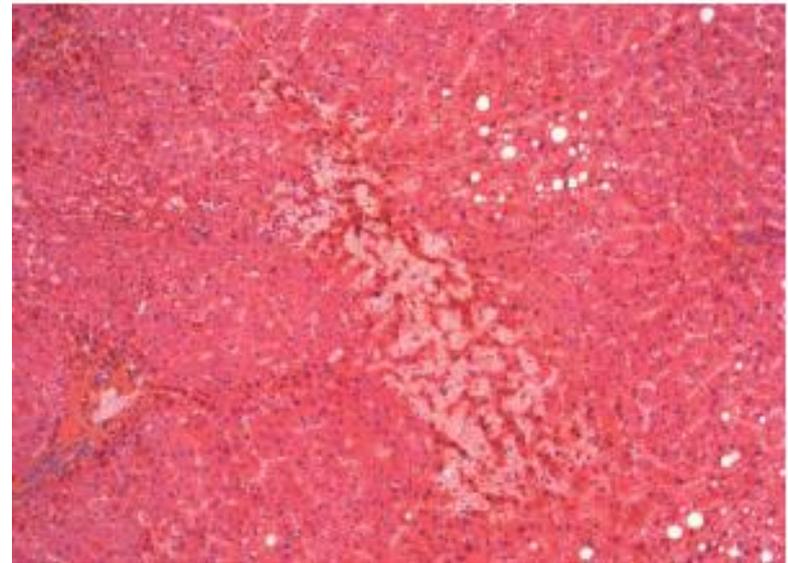






Margem excessiva

Metástase hepática



Clavien PA, 2010

Medida da margem de ressecção

Table 1. Median shrinkage of liver parenchyma after fixation for 24 h in formalin

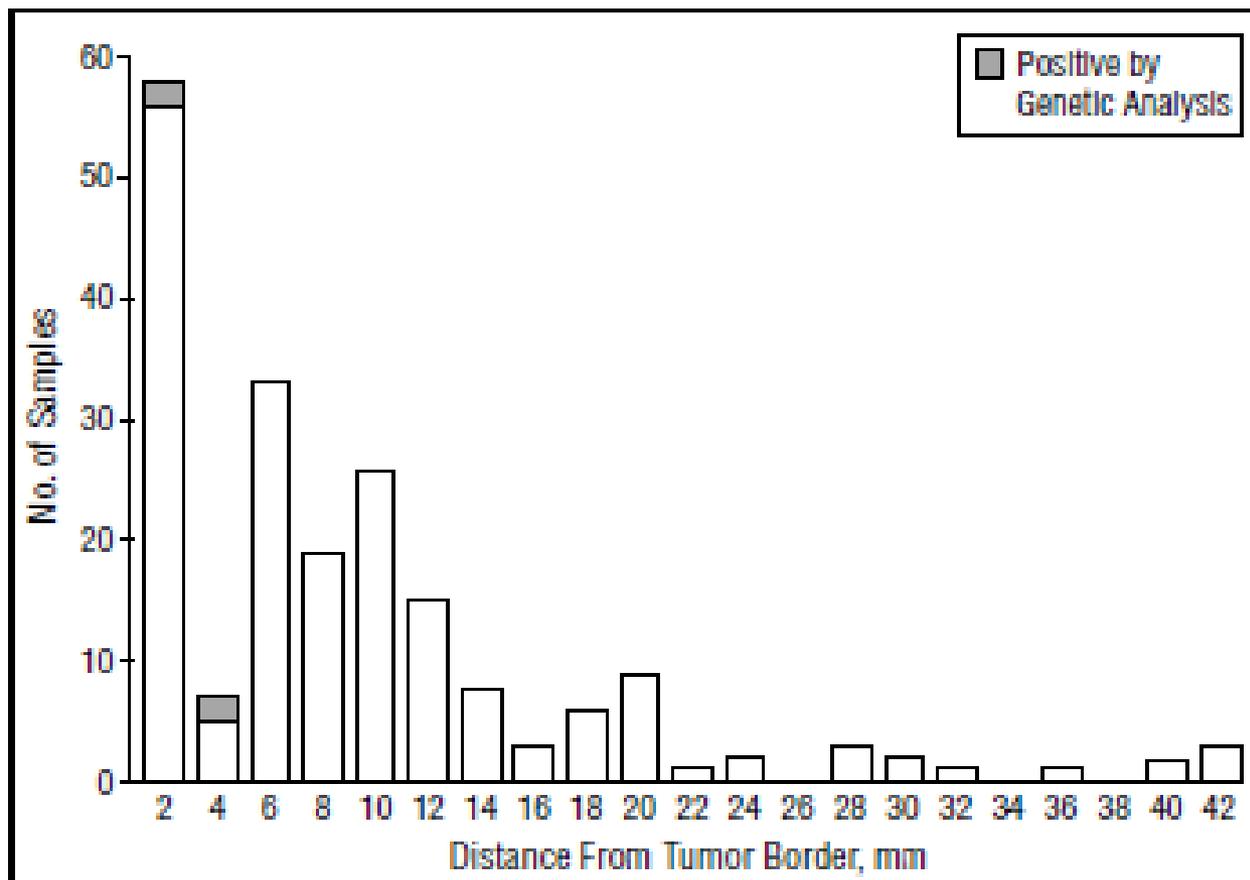
Distance between sutures (mm)	Median shrinkage (and range) (mm)	Significance*
10 (n = 17)	0 (0-3)	t = 2.89 p < 0.05
30 (n = 18)	2 (0-5)	t = 5.79 p < 0.05
50 (n = 18)	4 (0-7)	t = 6.28 p < 0.05

* Student's t test

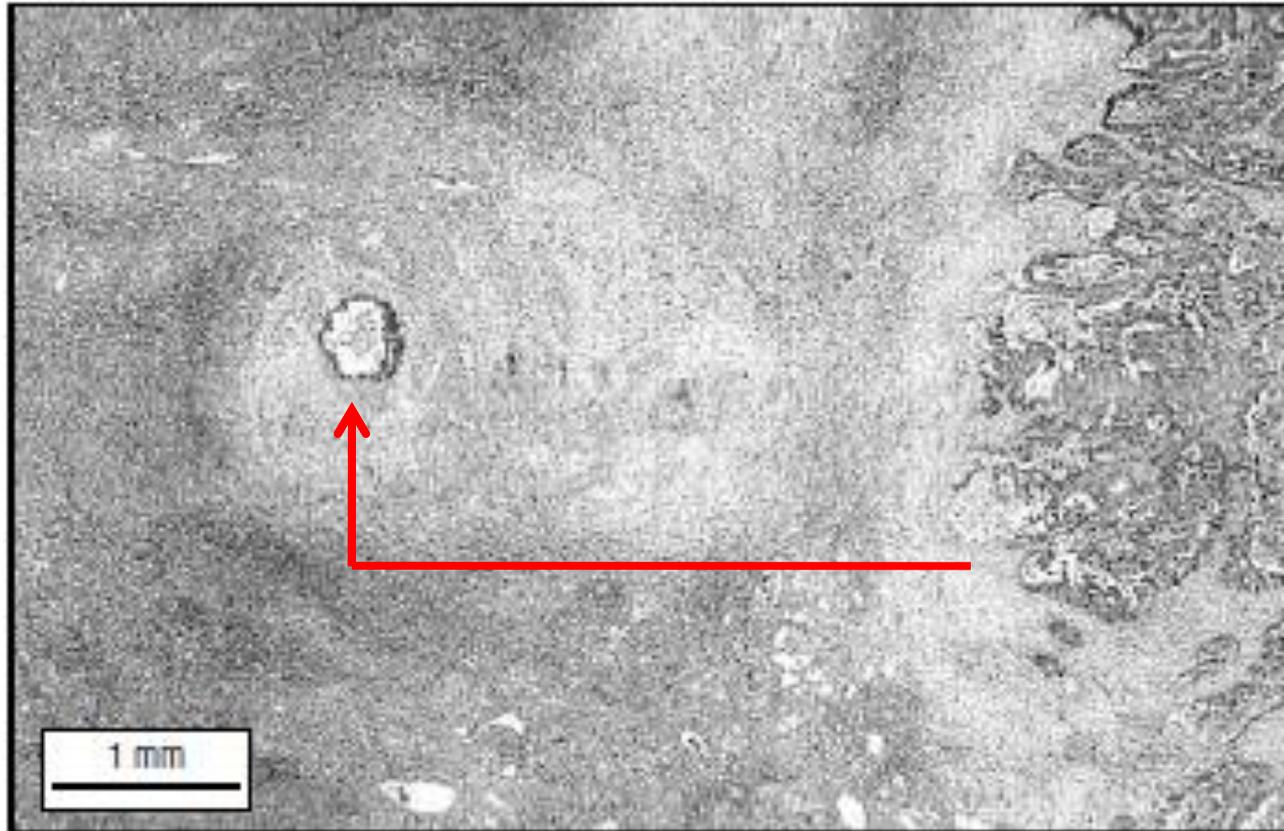
Conclusão:

Embora o percentual de redução seja pequeno, talvez seja importante quando considerar a margem de ressecção.

Avaliação genética (K-ras e p53)



Micrometástase a 3 mm do tumor principal



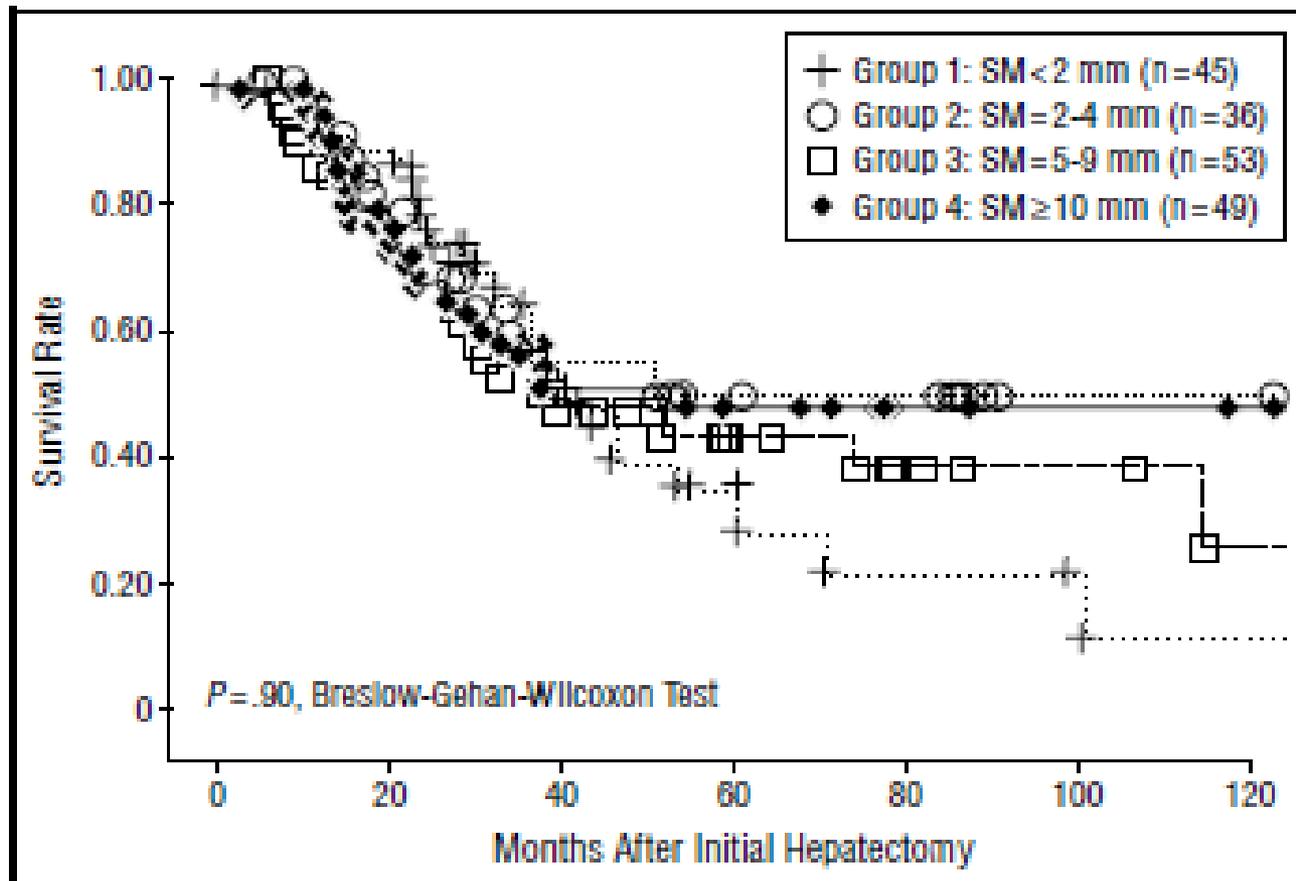
Kokudo N, et al – Arch Surg 2002, 137:833-40

Recorrência de acordo com a margem

Table 2. Pattern of Recurrence According to Macroscopic Surgical Margin (SM)

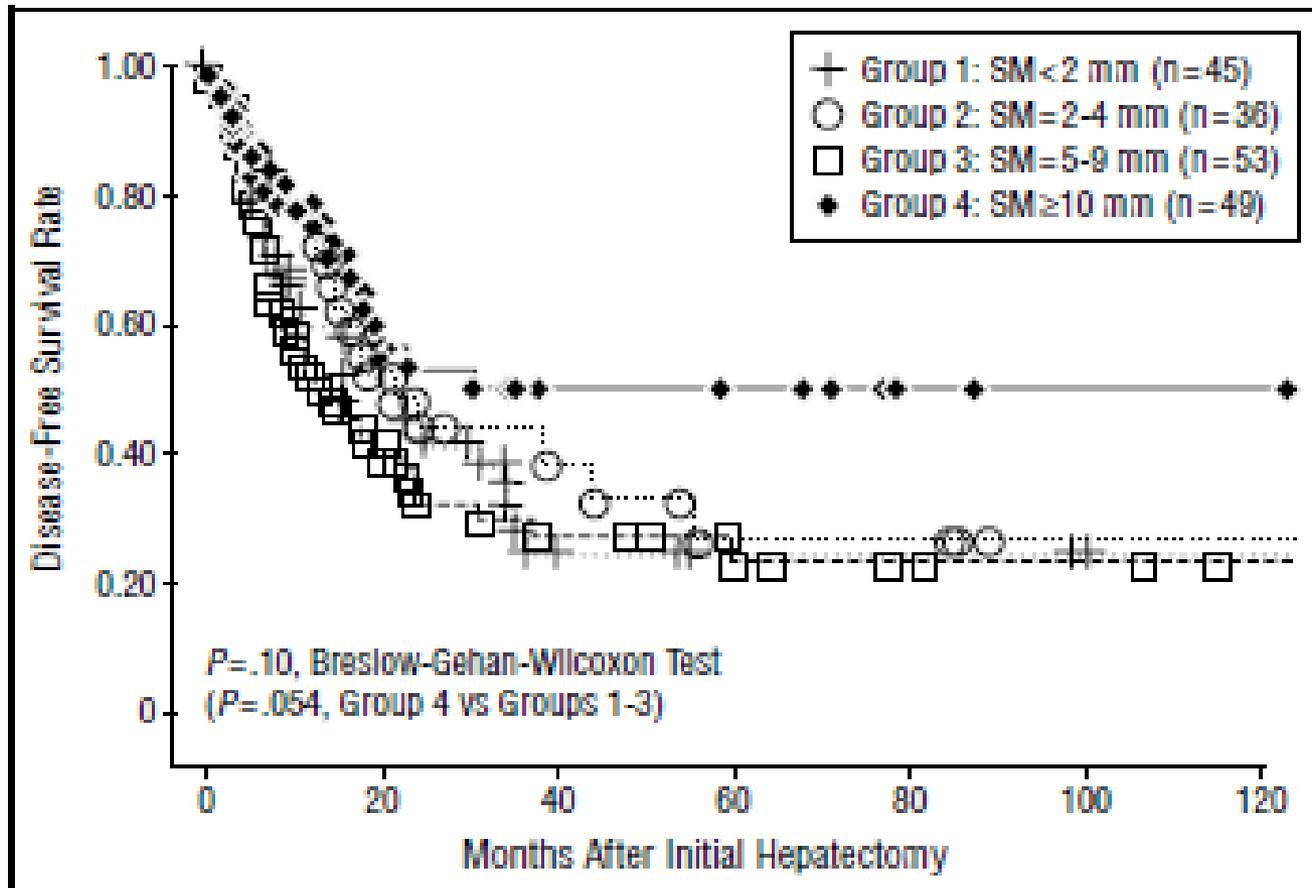
Group	SM, mm	No. of Cases	Total Recurrence, %	Recurrence in the Liver, %	Cut-End Recurrence		Cut-End Only, %*
					Suspected	Definite	
1	<2	45	28 (62.2)	20 (44.4)	3	6	9 (20.0)
2	2-4	36	21 (58.3)	12 (33.3)	3	1	2 (5.6)
3	5-9	53	38 (71.7)	24 (45.3)	6	0	4 (7.5)
4	≥10	49	20 (40.8)	13 (26.5)	0	0	0
Total	...	183	107 (58.5)	69 (37.7)	12	7	15 (8.2)

Sobrevida global



$P = NS$

Sobrevida livre de doença

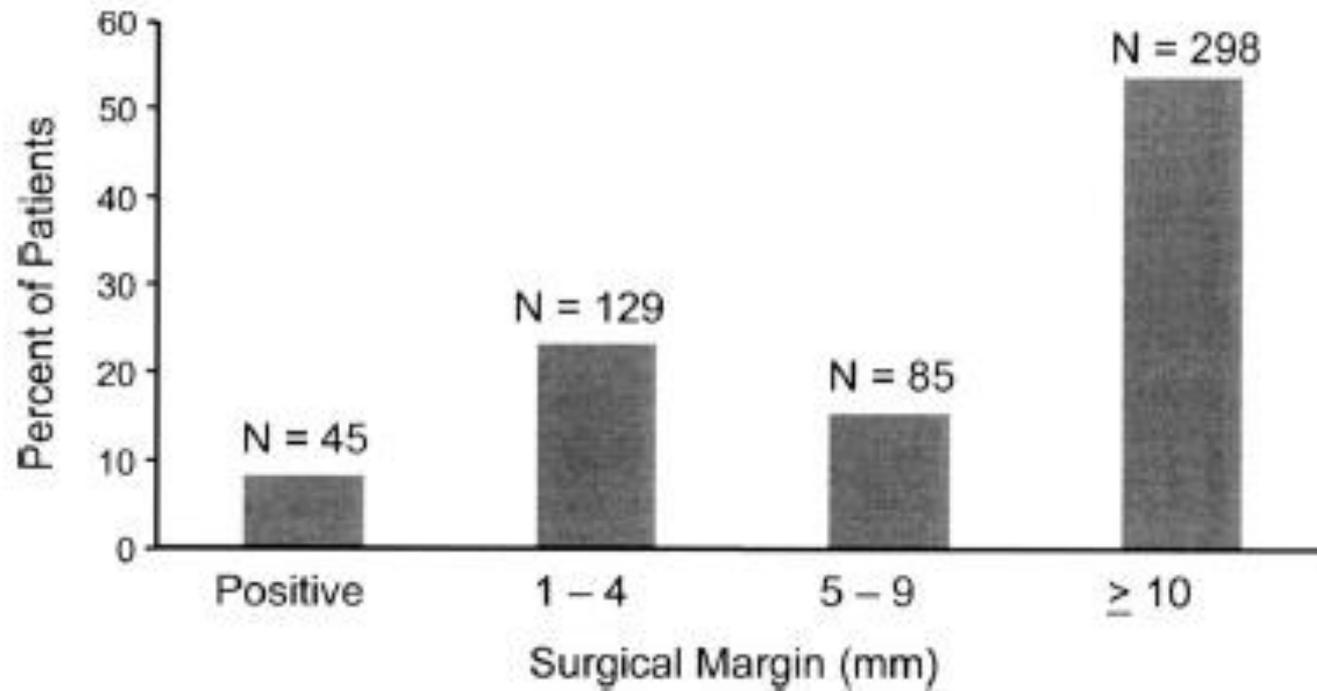


P= 0,054 grupo 4 vs grupo 1-3

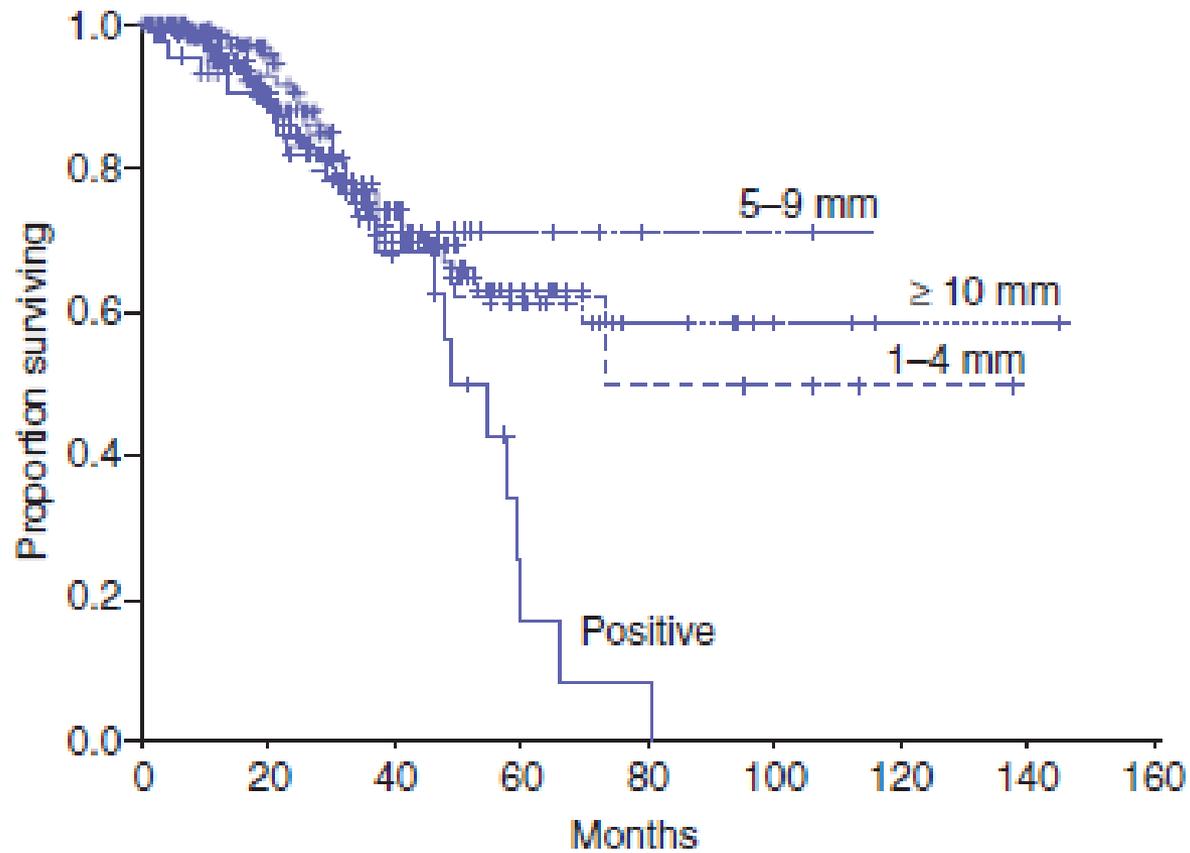
Conclusões

- Micrometástases em torno do fígado são incomuns
- Maioria confinada às margens do tumor
- Sugerem margem de 2 mm (risco de 6% de recorrência)
- Margem mínima está justificada quando inevitável

Margem cirúrgica



Sobrevida global



Padrão de recorrência de acordo com a margem cirúrgica (n= 225)

Type of recurrence	No. (%) of Patients With Recurrence			
	Positive (n = 45)	1–4 mm (n = 129)	5–9 mm (n = 85)	≥1 cm (n = 298)
Surgical margin	5 (11)	7 (5)	2 (2)	7 (2)
Other intrahepatic	5 (11)	13 (10)	9 (11)	29 (10)
Extrahepatic	8 (18)	15 (12)	14 (16)	45 (15)
Intra- + extrahepatic	5 (11)	15 (12)	10 (12)	36 (12)
Any recurrence	23 (51)	50 (39)	35 (41)	117 (39)

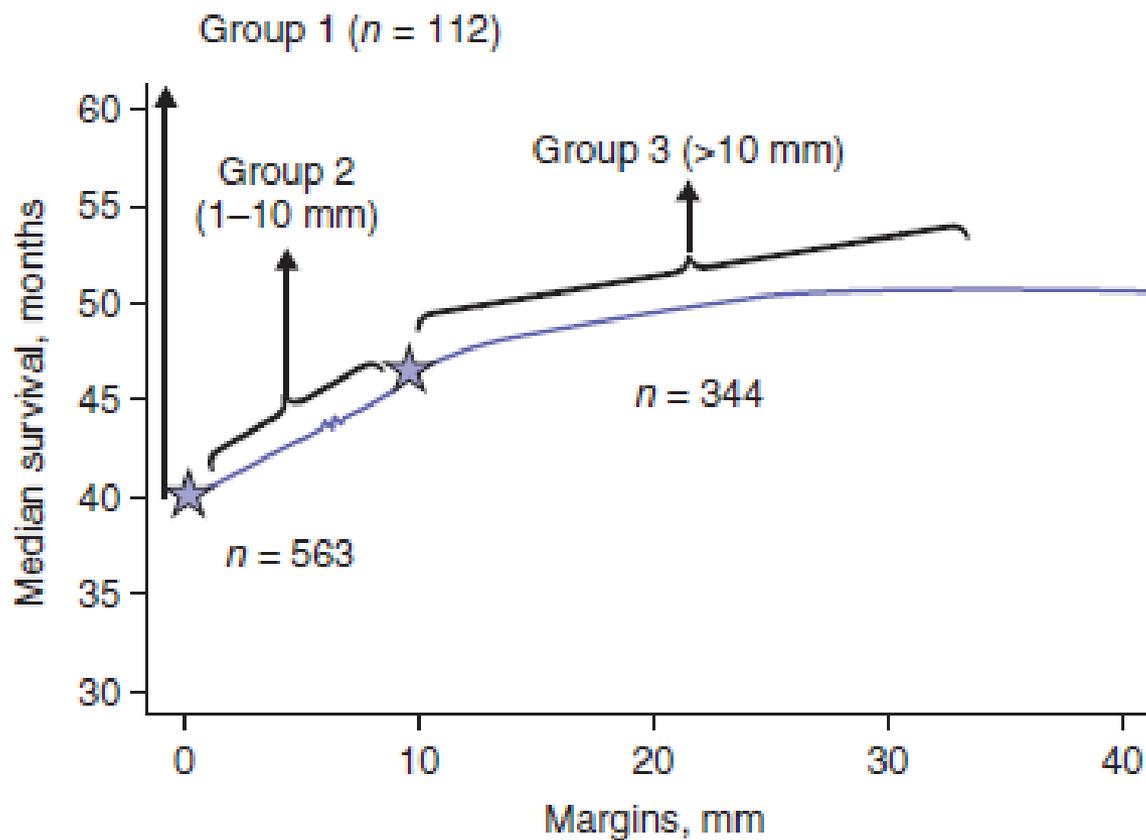
Recorrência na margem cirúrgica 3,8%

Fatores prognósticos para recorrência hepática

	No. of patients	Patients with hepatic recurrence	Cumulative hepatic recurrence, months (%)				Log-rank
			12	24	36	60	
Overall	545	177 (48) ^b	22	36	42	46	
Synchronous presentation							
Yes	248	92 (57)	28	42	51	55	0.0015
No	297	85 (41)	17	31	35	39	
Bilobar presentation							
Yes	201	84 (61)	32	50	57	60	<0.001
No	344	93 (41)	37	28	33	38	
No. of metastases							
1	257	58 (36)	11	23	29	32	<0.001
2-4	225	89 (57)	30	44	49	55	
≥5	63	30 (64)	39	61	64	64	
Resection margin							
<1 cm	206	75 (55)	27	41	49	54	0.0123
≥1 cm	339	102 (45)	19	32	37	41	
Extrahepatic disease at hepatectomy							
Yes	82	33 (64)	32	47	57	64	0.0037
No	463	144 (46)	20	34	39	43	

^aPatients with positive margin were excluded from the analysis.

^bValues in parentheses are percentages.



Margem de ressecção R0 vs R1

Table 1 Reported differences in overall survival based on margin status (R0 vs. R1 resection) after hepatic resection for colorectal liver metastases

Author(s)	Year	n	Study period	Follow-up, months	R1 rate	Survival				P-value
						5-year		Median, months		
						R0	R1	R0	R1	
Steele <i>et al.</i> ²⁰	1991	87	1984–1988	37	21%	–	–	37	21	<0.01
Cady <i>et al.</i> ⁸	1998	244	–	37	16%	–	–	18 ^a	9 ^a	<0.05 ^b
Fong <i>et al.</i> ⁵	1999	1001	1985–1998	–	11%	37%	20%	45	23	<0.001 ^b
Choti <i>et al.</i> ¹	2002	226	1984–1999	–	5%	–	–	46	24	0.04 ^b
Pawlik <i>et al.</i> ³	2005	557	1990–2004	29	8%	64%	17%	NR	49	0.01
Nuzzo <i>et al.</i> ¹⁹	2008	185	1992–2005	39	5%	39%	0%	48	22	0.01
de Haas <i>et al.</i> ¹⁸	2008	436	1990–2006	40	46%	61%	57%	77	84	0.27

^aIndicates disease-free survival

^bP remained significant (<0.05) on multivariate analysis

P-values shown in bold indicate <0.05

NR, not reached

Margem de ressecção R0 vs R1

Table 2 Reported differences in marginal and overall intrahepatic recurrence based on margin status (R0 vs. R1 resection) after hepatic resection for colorectal metastases

Author(s)	Year	n	Study period	Median follow-up, months	R1 Rate	Recurrence					
						Marginal			Overall intrahepatic		
						R0	R1	P-value	R0	R1	P-value
Hughes <i>et al.</i> ²¹	1986	607	–	–	6%	–	–	–	38%	68%	<0.05 ^b
Cady <i>et al.</i> ⁶	1998	244	–	37	16%	–	–	–	23%	43%	0.03
Kokudo <i>et al.</i> ¹⁰	2002	183	1980–2000	29	25% ^a	6%	20%	–	–	–	–
Pawlik <i>et al.</i> ³	2005	557	1990–2004	29	8%	3%	11%	0.003	14%	22%	–
Wakai <i>et al.</i> ²²	2008	90	1989–2004	–	11%	3%	30%	0.001^b	–	–	–
Nuzzo <i>et al.</i> ¹⁹	2008	185	1992–2005	39	5%	4%	55%	<0.01	27%	78%	<0.01
de Haas <i>et al.</i> ¹⁸	2008	436	1990–2006	40	46%	8%	9%	0.72	17%	28%	0.004

^aR1 resection was defined in this study as margin clearance <2 mm

^bP remained significant (<0.05) on multivariate analysis

P-values shown in bold indicate <0.05

Margem de ressecção e sobrevida

Table 2 Resection margins and survival

Resection margin	<i>n</i>	Patient survival				<i>P</i>
		Median (months)	1 year	3 years	5 years	
Involved	28	25.8	81%	45%	19%	reference
0–1 mm	39	45.4	79%	63%	29%	ns
>1–<4 mm	44	54.5	91%	71%	47%	ns
4–<10 mm	63	51.7	86%	56%	38%	ns
≥10 mm	87	54.7	95%	65%	44%	<0.03
Overall	261	46.7	88%	61%	38%	

Sobrevida livre de doença

Table 3 Analysis of impact of margin on disease-free survival

Resection margin	n	Disease free survival			P	
		Median (months)	1 year	3 years		5 years
Involved – 1 mm	67	10.1	41%	21%	17%	reference
>1 mm to <10 mm	107	16.8	58%	28%	20%	0.15
≥10 mm	87	24.1	64%	41%	29%	<0.02
Overall	261	17.5	58%	33%	22%	

Sobrevida global

Table 4 Analysis of impact of margin on overall survival

Resection margin	<i>n</i>	Patient survival				<i>P</i>
		Median (months)	1 year	3 years	5 years	
Involved – 1 mm	67	39	81%	45%	19%	reference
>1 mm to <10 mm	107	52	85%	63%	38%	0.081
≥10 mm	87	54	95%	65%	43%	<0.03
Overall	261	46	88%	61%	38%	

Sobrevida de acordo com a margem de ressecção

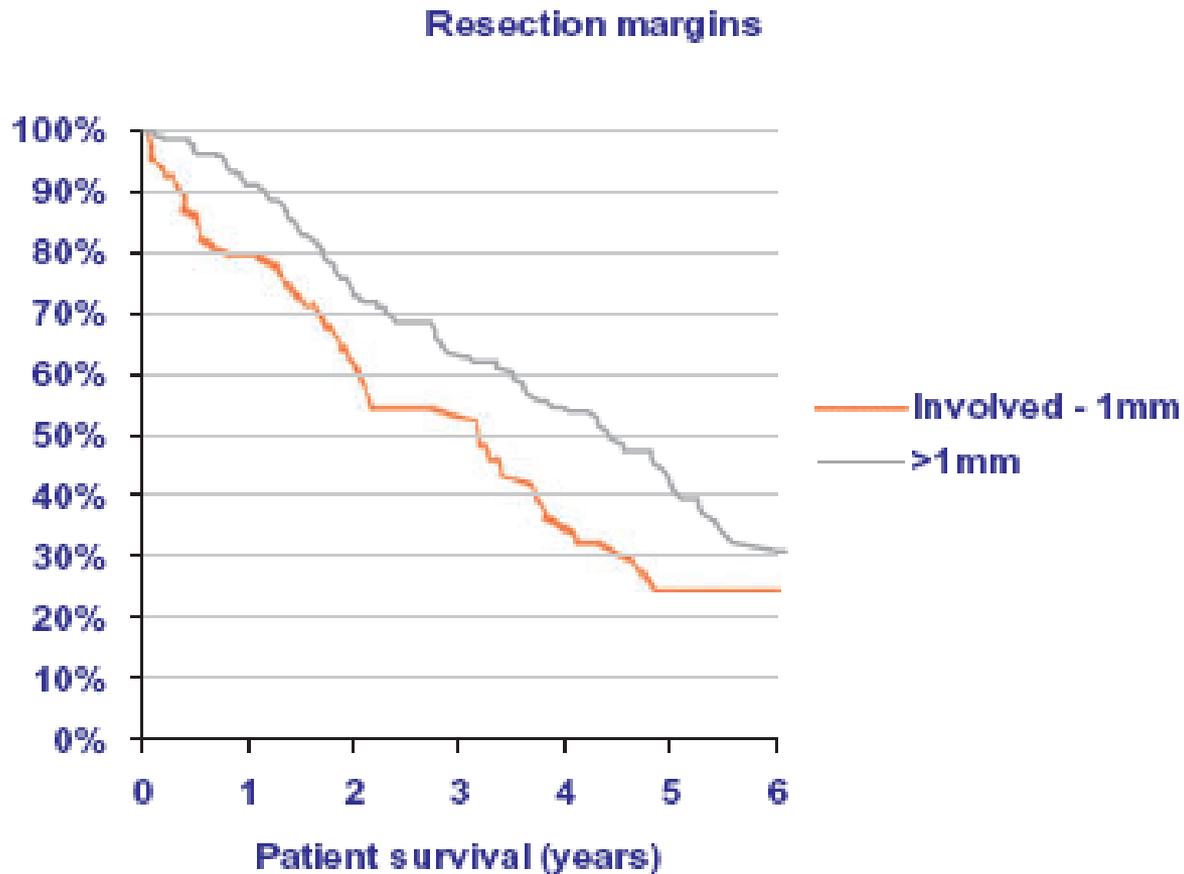
Table 5 Comparison of impact of resection margins ≤ 1 mm and >1 mm on overall survival

Resection margin	n	Patient survival		P
		3 years	5 years	
≤ 1 mm	67	55%	25%	reference
>1 mm	194	63.7%	42.7%	0.04

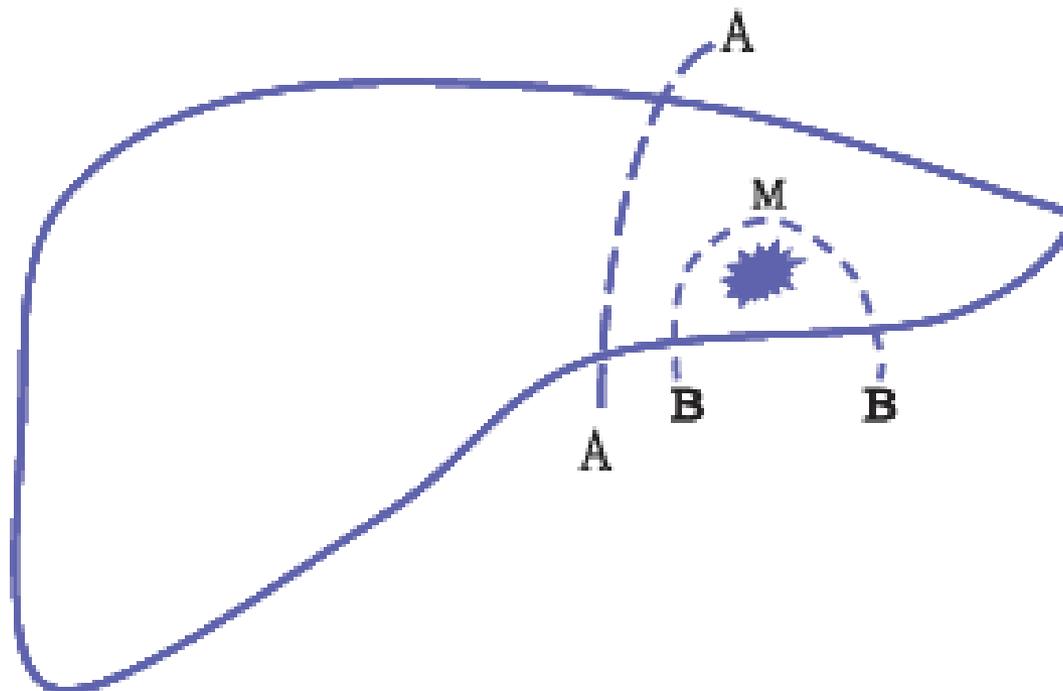
Table 6 Comparison of impact of resection margins ≤ 1 mm and >1 mm on disease-free survival

Resection margin	n	Disease-free survival		P
		3 years	5 years	
≤ 1 mm	67	27.5%	18.6%	reference
>1 mm	194	35%	23.6%	0.14

Sobrevida global de acordo com a margem de ressecção



Margem de ressecção laparoscópica



Mudança nos critérios de irressecabilidade em pacientes com metástase hepática colo-retal

Critério tradicional

- Quatro ou + metástases
 - Maior que 5 cm
 - Doença bilateral
 - Margem < 1 cm
 - Metástase extra-hepática
 - Escore de QT
-

Critério atual

- Incapacidade de realizar ressecção R0
 - Margem histológica positiva
 - Incapacidade de ressecar toda doença detectável
 - Progressão mesmo com QT
-

Suporte para ressecção limitada

- São histopatologicamente bem circunscritas
- Apenas 16% tem lesões satélites
- Extensão para a cápsula de Glisson é incomum (14,5%)
- Extensão é limitada (< 5 mm)
- Micrometástases são raras (2%)

Kokudo N, et al – Arch Surg 2002, 137:833-40

Pawlik TM, et al. Ann Surg 2005, 241:715-22

Figueras J, et al. Ann Oncol 2007,18:1190-5

Conclusões

Annals of Surgical Oncology 15(3):677–679
DOI: 10.1245/s10434-007-9703-2

Surgical Margins during Hepatic Surgery for Colorectal Liver Metastases: Complete Resection not Millimeters Defines Outcome

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Conclusões

❑ Margens menores que 1 centímetro na hepatectomia são insuficientes?

Não

Pode não ser alcançada

Exclui pacientes

Objetivar sempre margem negativa



Obrigado!

