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Margin status in liver resections for colorectal metastases

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ABCDDV/1235

ABCD Arq Bras Cir Dig 2016;29(3):173-179 DOI: /10.1590/0102-6720201600030011 **Original Article**

BRAZILIAN CONSENSUS FOR MULTIMODAL TREATMENT OF COLORECTAL LIVER METASTASES. MODULE 3: CONTROVERSIES AND UNRESECTABLE METASTASES

Consenso brasileiro de tratamento multidisciplinar de metástase hepática de origem colorretal Módulo 3: Controvérsias e metástases irressecáveis

Orlando Jorge Martins TORRES^{1,2,6}, Márcio Carmona MARQUES^{2,6}, Fabio Nasser SANTOS¹, Igor Correia de FARIAS^{2,6}, Anelisa Kruschewsky COUTINHO³, Cássio Virgílio Cavalcante de OLIVEIRA^{1,4,5}, Antonio Nocchi KALIL^{1,2,4,6}, Celso Abdon Lopes de MELLO³, Jaime Arthur Pirola KRUGER^{1,4,5,6}, Gustavo dos Santos FERNANDES³, Claudemiro QUIREZE JR^{1,4,5,6}, André M. MURAD³, Milton José de BARROS E SILVA³, Charles Edouard ZURSTRASSEN^{*}, Helano Carioca FREITAS³, Marcelo Rocha CRUZ³, Rui WESCHENFELDER³, Marcelo Moura LINHARES^{1,4,5,6}, Leonaldson dos Santos CASTRO^{1,2,6}, Charles VOLLMER⁶, Elijah DIXON⁶, Héber Salvador de Castro RIBEIRO^{1,2,6}, Felipe José Fernandez COIMBRA^{1,2,5,6}

MARGINS STATUS

Torres OJ, et al. Arq Bras Cir Dig 2016;29:173-9

Clinical Score for Predicting Recurrence After Hepatic Resection for Metastatic Colorectal Cancer

Analysis of 1001 Consecutive Cases

Yuman Fong, MD,*† Joseph Fortner, MD,† Ruth L. Sun, BA,*† Murray F. Brennan, MD,† and Leslie H. Blumgart, MD, FRCS*†

IN OUR HANDS

Table 4. MULTIVARIATE PREDICTORS OF RECURRENCE

	Hazard	Coefficient	р
Positive margin	1.7	0.5	0.004
Extrahepatic disease	1.7	0.5	0.003
>1 tumor	1.5	0.4	0.0004
Carcinoembryonic antigen >200 ng/ml	1.5	0.4	0.01
Size >5 cm	1.4	0.3	0.01
Node-positive primary	1.3	0.28	0.02
Disease-free interval <12 months	1.3	0.25	0.03
Bilateral tumor	0.9	-0.1	0.4

Fong Y, et al. Ann Surg 1999;230:309-21







Tumor in seg 4 (resected by laparoscopy).

Histology of the resection margin (positive).

CT after 10 months (clear signs of recurrence).



REVIEW

Quantification of risk of a positive (R1) resection margin following hepatic resection for metastatic colorectal cancer: An aid to clinical decision-making

Fenella K.S. Welsh^{a,*}, Paris P. Tekkis^b, Tom O'Rourke^a, Timothy G. John^a, Myrddin Rees^a

Non-anatomical resection

- Extended resection
- >3 hepatic metastases involving >50% of the liver
- Repeat hepatic resection
- 🖵 Bilobar disease
- Abnormal pre-operative LFTs



Welsh FKS, et al. Surg Oncol 2008;17:3-13

ACCURATE ASSESSMENT OF MARGINS STATUS





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Pathology

EBSERH









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Radiofrequency











Surgical Oncology 26 (2017) 229-235

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The impact of radiofrequency-assisted transection on local hepatic recurrence after resection of colorectal liver metastases



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^d BioMIT, Electronic Engineering Department, Universitat Politècnica de València, Valencia, Spain



Quesada R, et al. Surg Oncol 2017;26:229-35

Radiofrequency assisted transection ... associated with a deep thermal lesions may reduce local hepatic recurrence, especially in case of margin invasion during transection.

Quesada R, et al. Surg Oncol 2017;26:229-35



Hamady ZZR, et al. Ann Surg 2014;259:543-8

Hayashi H, et al. Oncol Rep 2009;21:601-7



Annals of Surgical Oncology 15(9):2472–2481 DOI: 10.1245/s10434-008-0023-y

Appraisal of 1 cm Hepatectomy Margins for Intrahepatic Micrometastases in Patients with Colorectal Carcinoma Liver Metastasis

Toshifumi Wakai, MD, PhD,¹ Yoshio Shirai, MD, PhD,¹ Jun Sakata, MD, PhD,¹ Vladimir A. Valera, MD, PhD,¹ Pavel V. Korita, MD,¹ Kouhei Akazawa, PhD,² Yoichi Ajioka, MD, PhD,³ and Katsuyoshi Hatakeyama, MD, PhD, FACS¹















 \Box The current recommendation of \geq 1 cm hepatectomy margin should remain the goal for patients with colorectal liver metastases.

Microsatellite lesions

Presence of microsatellite lesions with colorectal liver metastases correlate with intrahepatic recurrence after surgical resection

HIROYUKI HAYASHI^{1,2}, KAZUKI NABESHIMA¹, MAKOTO HAMASAKI¹, YUICHI YAMASHITA², TAKAYUKI SHIRAKUSA³ and HIROSHI IWASAKI¹

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Hayashi H, et al. Oncol Rep 2009;21:601-7



Hayashi H, et al. Oncol Rep 2009;21:601-7



Hayashi H, et al. Oncol Rep 2009;21:601-7

- Microsatellite metastases were detected in 55.5% of the cases.
- 🖵 Worse overall survival
 - Found within 4 mm from the main metastases
- 70% were located within 2 mm of the tumor border

Hayashi H, et al. Oncol Rep 2009;21:601-7

One-Millimeter Cancer-Free Margin Is Curative for Colorectal Liver Metastases

A Propensity Score Case-Match Approach

Zaed Z. R. Hamady, PhD, FRCS,* † J. Peter A. Lodge, MD, FRCS, † Fenella K. Welsh, FRCS,* Giles J. Toogood, DM, FRCS, † Alan White, MRCS, † Timothy John, FRCS,* and Myrddin Rees, FRCS*



TABLE 2. Overall Disease-Free Survival (DFS) Stratified by Resection Margin Clearance and Illustration of Univariate and Multivariate Analyses

		Median DFS Mo	(%) Disease-Free Survival		Univariate Analysis		Multivariate Analysis				
Margin	Number (2715)	(95% CI)	1-Yr	3-Yr	5-Yr	10-Yr	Р		HR (95% CI)	Р	
<1 mm	663	19.8 (17.4-22)	69	34	25	21	Ref			Rof	
1-4.9 mm	852	24.2 (21-27)	72	42	33	27	< 0.001	Ref		1.5(1.3-1.7)	< 0.001*
5–9.9 mm	439	24 (21-27)	73	40	32	28	0.007	0.998	Ref	1.0(0.9-1.2)	0.285**
≥10 mm	761	26 (21–31)	77	42	33	29	< 0.001	0.331	0.445	1.0 (0.8–1.2)	0.487***

*Compared with <1 mm, **compared with 1-4.9 mm, ***compared with 5-9.9 mm.



Hamady ZZR, et al. Ann Surg 2014;259:543-8

This study provides evidence that achievement of 1-mm margin width should <u>be considered the standard of care</u> for patients with CRLM in the modern liver resection practice, at least when ultrasonic dissection is used.

Hamady ZZR, et al. Ann Surg 2014;259:543-8







ORIGINAL ARTICLE

Margin Status Remains an Important Determinant of Survival After Surgical Resection of Colorectal Liver Metastases in the Era of Modern Chemotherapy

Andreas Andreou, MD,* Thomas A. Aloia, MD, FACS,* Antoine Brouquet, MD,* Paxton V. Dickson, MD,* Giuseppe Zimmitti, MD,* Dipen M. Maru, MD,† Scott Kopetz, MD, PhD,‡ Evelyne M. Loyer, MD,§ Steven A. Curley, MD, FACS,* Eddie K. Abdalla, MD, FACS,* and Jean-Nicolas Vauthey, MD, FACS*



Andreou A, et al. Ann Surg 2013;257: 1079-88







Andreou A, et al. Ann Surg 2013;257: 1079-88

- Continued emphasis on achieving R0 resection in patients with CLMs.
- Modern chemotherapy combined with aggressive surgical strategies has resulted in improved long-term OS.

For patients with unfavorable tumor biology, only if R0 resection is deemed feasible.

Andreou A, et al. Ann Surg 2013;257: 1079-88



Prognostic Impact of Positive Surgical Margins After Resection of Colorectal Cancer Liver Metastases: Reappraisal in the Era of Modern Chemotherapy

Hadrien Tranchart · Mircea Chirica · Matthieu Faron · Pierre Balladur · Leila Bengrine Lefevre · Magali Svrcek · Aimery de Gramont · Emmanuel Tiret · François Paye





Tranchart H, et al. World J Surg 2013;37:2647-54

A positive surgical margin after LR of CRLM remains a significant negative prognostic factor in the era of effective chemotherapy regimens.

Postoperative chemotherapy reduces recurrence rates after R1 resection of CRLM.

Tranchart H, et al. World J Surg 2013;37:2647-54

Annals of

SURGICAL ONCOLOGY OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

Impact of Margin Status and Neoadjuvant Chemotherapy on Survival, Recurrence After Liver Resection for Colorectal Liver Metastasis

Sanjay Pandanaboyana, MBBS, MS, MPhil, FRCS, Alan White, MBChB, MRCS, Samir Pathak, BSc, MBChB, MSc, MRCS, Ernest L. Hidalgo, FRCS, Giles Toogood, FRCS, J. P. Lodge, FRCS, and K. R. Prasad, MBBS, MS, FRCS



Neoadjuvant chemotherapy

Positive margin

Does not seem to improve survival
Does not have impact on recurrence
Does not reduce the need for redo

Pandanaboyana S, et al. Ann Surg Oncol 2015;22:173-9

J Gastrointest Surg (2017) 21:1831–1840 DOI 10.1007/s11605-017-3557-0

ORIGINAL ARTICLE



Prognostic Significance of Surgical Margin Size After Neoadjuvant FOLFOX and/or FOLFIRI for Colorectal Liver Metastases

Cynthia L. Miller^{1,2} • Martin S. Taylor³ • Motaz Qadan¹ • Vikram Deshpande³ • Steven Worthington⁴ • Robert Smalley² • Chey Collura¹ • David P. Ryan⁵ • Jill N. Allen⁵ • Lawrence S. Blaszkowsky⁵ • Jeffrey W. Clark⁵ • Janet E. Murphy⁵ • Aparna R. Parikh⁵ • David Berger¹ • Kenneth K. Tanabe¹ • Keith D. Lillemoe¹ • Cristina R. Ferrone¹

Table 2Disease-free and overall survival according to margin size(95% confidence interval)

	3-year	5-year	10-year
Disease-free survi	ival		
\geq 1–< 5 mm	10% (3–20%)	6% (2–17%)	_
\geq 5–< 10 mm	28% (16-41%)	16% (7–28%)	16% (7–28%)
$\geq 10 \text{ mm}$	46% (34–57%)	41% (29–53%)	39% (26–50%)
Overall survival			
< 1 mm	66% (42-82%)	33% (11–57%)	_
\geq 1–< 5 mm	74% (59–84%)	41% (24–57%)	14% (1–40%)
\geq 5–< 10 mm	79% (65–88%)	60% (44–74%)	22% (8–41%)
$\geq 10 \text{ mm}$	78% (67–86%)	64% (51–74%)	44% (27–60%)

Miller CL, et al. J Gastrointest Surg 2017;21:1831-40


Miller CL, et al. J Gastrointest Surg 2017;21:1831-40

Positive margins had a 3.3-fold increased risk of death.

Chemotherapy

No significant difference in risk of death between patients with positive and negative margins. R0 resection for CRLM in the era of modern chemotherapy is important

Patients with positive margins should receive additional post-liver resection chemotherapy for improved survival.

No evidence of a long-term survival benefit from wider margins.

Miller CL, et al. J Gastrointest Surg 2017;21:1831-40

Int J Colorectal Dis https://doi.org/10.1007/s00384-017-2916-3

ORIGINAL ARTICLE



Chemotherapy

Prognostic influence of hepatic margin after resection of colorectal liver metastasis: role of modern preoperative chemotherapy



Makowiec F, et al. Int J Colorectal Dis 2017

Table 4Multivariate survival analysis of 334 patients after firstresection of isolated colorectal liver metastases

Parameter	p	RR	95% CI
Positive hepatic margin	< 0.001	3.2	2.0-5.2
Age > 65 years	0.005	1.6	1.1–2.1
Size (metastasis) > 30 mm	(0.07)	(1.3)	—

Makowiec F, et al. Int J Colorectal Dis 2017

Margin status remains the strongest independent prognostic factor.

- Despite a liver-only metastatic disease, survival was relatively poor in patients with positive margins.
- In our series, this prognostic effect was equally present after neoadjuvant chemotherapy for CLM.

Makowiec F, et al. Int J Colorectal Dis 2017

Prognostic impact of margin status in liver resections for colorectal metastases after bevacizumab

K. Sasaki¹, G. A. Margonis¹, N. Andreatos¹, A. Wilson¹, M. Weiss¹, C. Wolfgang¹, T. N. Sergentanis², G. Polychronidis³, J. He¹ and T. M. Pawlik¹



b P = 0.010

c P = 0.081



Sasaki K, et al. Br J Surg 2017

Although the impact of resection margin status on long-term oncological outcomes appears to vary depending on the receipt of preoperative bevacizumab, achieving a macroscopically and microscopically negative (R0) resection should remain a fundamental operative goal.



Ann Surg Oncol DOI 10.1245/s10434-016-5187-2 Annals of <u>SURGICALONCOLOGY</u> OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY



ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

RAS Mutation Predicts Positive Resection Margins and Narrower Resection Margins in Patients Undergoing Resection of Colorectal Liver Metastases

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Brudvik KW et al - Ann Surg Oncol 2016





Brudvik KW et al - Ann Surg Oncol 2016

RAS mutations are associated with positive margins in patients undergoing resection of CLM. Tumors with RAS mutation should prompt careful efforts to achieve negative resection margins.

Brudvik KW et al - Ann Surg Oncol 2016

Laparoscopic hepatectomy

Impact of surgical margins on overall and recurrence-free survival in parenchymal-sparing laparoscopic liver resections of colorectal metastases

Roberto Montalti · Federico Tomassini · Stéphanie Laurent · Peter Smeets · Marc De Man · Karen Geboes · Louis J. Libbrecht · Roberto I. Troisi



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Montalti R, et al. Surg Endosc 2015



Montalti R, et al. Surg Endosc 2015



Montalti R, et al. Surg Endosc 2015

Laparoscopic parenchymal-sparing surgery of CRLM does not compromise the oncological outcome.

R1 margins are a risk factor for tumor recurrence but not for overall survival.

The presence of multiple lesions is the only independent risk factor of R1 margins and also the major disadvantage of this technique.

ORIGINAL ARTICLE

Margin status after laparoscopic resection of colorectal liver metastases: does a narrow resection margin have an influence on survival and local recurrence?

Nadya Postriganova^{1,2}, Airazat M. Kazaryan^{1,3}, Bård I. Røsok⁴, Åsmund A. Fretland^{1,4}, Leonid Barkhatov¹ & Bjørn Edwin^{1,4,5}

¹Intervention Centre and ⁴Department of Hepatopancreatobiliary Surgery, Oslo University Hospital – Rikshospitalet, Oslo, Norway, ²Department of Hospital Surgery, Moscow State University of Medicine and Dentistry, Moscow, Russia, ³Department of Surgery, Telemark Hospital, Skien, Norway, and ⁵Institute of Clinical Medicine, Medical Faculty, University of Oslo, Oslo, Norway

Bipolar coagulator (Ligasure®) Ultrasonic dissector: AutoSonix® SonoSurg® Harmonic® Ultrasonic surgical Aspirator (CUSA®)

Parameters	Group 1 (<i>n</i> = 33)		Group 2	Group 3	Group 4	P-value	Total
	1a (positive margin) (n = 17)	1b (margin: > 0 mm to < 1 mm) (<i>n</i> = 16)	(margin: ≥ 1 mm to < 3 mm) (<i>n</i> = 31)	(margin: ≥ 3 mm to < 10 mm (<i>n</i> = 55)	(margin: ≥ 10 mm) (<i>n</i> = 36)		(n = 155)
Overall recurrence, n (%)	17 (51.5%)		11 (35.5%)	28 (50.9%)	17 (47.2%)	0.316	73 (47.1%)
	8 (47.1%)	9 (56.3%)	_				
Recurrence in the liver, n (%)	14 (42.4%)		10 (32.3%)	19 (34.5%)	8 (22.2%)	0.349	51 (32.9%)
	7 (41.2%)	7 (43.7%)	-				
Recurrence including local (margin), n (%)	2 (6	6.1%)	0	1 (1.8%)	0	0.232	3 (1.9%)
	1 (5.9%)	1 (6.3%)	_				
Re-resection for recurrence in the liver, n (%)	13 (92.9% of all recurrences in the liver)		5 (50.0%)	9 (47.4%)	3 (37.5%)	0.023	30 (58.8%)
	6 (85.7%)	7 (100%)	_				
Ablation for recurrence in the liver, <i>n</i> (%)	1 (7.1% of all recurrences in the liver)		1 (10.0%)	1 (5.3%)	3 (37.5%)	0.102	6 (11.8%)

Table 4 Recurrence in the liver in patients submitted to laparoscopic liver resection for colorectal metastasis

Postriganova N, et al. HPB 2014;16:822-9

Patients with margins of < 1 mm achieved survival comparable with that in patients with margins of ≥ 10 mm.

When modern surgical equipment that generates an additional coagulation zone is applied, the association between resection margin and survival may not be apparent.

Postriganova N, et al. HPB 2014;16:822-9

ORIGINAL ARTICLE

Vascular margin

Safety analysis of the oncological outcome after vein-preserving surgery for colorectal liver metastases detached from the main hepatic veins

Federico Tomassini^{1,5} • Italo Bonadio^{1,6} • Peter Smeets² • Karen De Paepe¹ • Giammauro Berardi¹ • Liesbeth Ferdinande³ • Stéphanie Laurent⁴ • Louis J. Libbrecht³ • Karen Geboes⁴ • Roberto I. Troisi¹

Pre-operative

A1. Preserving the Left Hepatic Vein (arrow)



Post-operative

A2. Follow-Up at 12 months (no edge recurrence)



Tomassini F, et al. Langenbechs Arch Surg 2015;400:683-91

6



B1. Preserving Middle HV and Right HV (arrows)

B2. Follow-Up at 15 months (fluid collection, no local recurrence)





Recurrence patterns	VP (14)	CG (28)	р
Tumor recurrence, n (%)	10 (71.4)	20 (71.4)	0.99
Site of recurrence			
Liver	2/10 (20)	5/20 (25)	0.99
Liver and other	6 (60)	8 (40)	0.442
Other	2 (20)	7 (35)	0.674
Tumor recurrence on the venous cutting edge	0/7 (0)	-	-
Tumor recurrence on the cutting edge	0/7 (0)	1/13 (7.7)	-
Second hepatectomy (repeat), n (%)	5/8 (62.5)	6/13 (46.0.3)	0.659
Third hepatectomy (redo-repeat), n (%)	2/5 (40)	0/6 (0)	0.182

In patients with a positive CT response, CRLM can be detached from the hepatic veins, as the oncological outcome is similar to that of a larger resection.

Ann Surg Oncol (2016) 23:1352–1360 DOI 10.1245/s10434-015-5009-y

GY CrossMark

Vascular margin

Is Tumor Detachment from Vascular Structures Equivalent to R0 Resection in Surgery for Colorectal Liver Metastases? An Observational Cohort

Annals of

SURGICAL

Luca Viganò, MD, PhD, Fabio Procopio, MD, Matteo Maria Cimino, MD, Matteo Donadon, MD, PhD, Andrea Gatti, MD, Guido Costa, MD, Daniele Del Fabbro, MD, and Guido Torzilli, MD, PhD, FACS



Vigano L, et al. Ann Surg Oncol 2016;23:1352-60

Parameter	Overall survival	Overall survival				
	5-year OS	Univariate analysis	Multivariate analysis			
	(%)	p	p	RR (95 % CI)		
Surgical margin						
R0	54.3	0.068		1		
R1Vasc	59.4		n.s.	1.372 (0.644-2.922)		
R1Par	32.5		0.034	1.627 (1.037-2.552)		
Adjuvant chemotherapy	у					
Y	53.5	0.008	0.023	0.605 (0.393-0.933)		
Ν	34.6			1		

TABLE 3 Univariate and multivariate analysis of prognostic factors of OS after LR

Vigano L, et al. Ann Surg Oncol 2016;23:1352-60



Vigano L, et al. Ann Surg Oncol 2016;23:1352-60



Vigano L, et al. Ann Surg Oncol 2016;23:1352-60



Courtesy from Prof. Guido Torzilli (Milan)



Courtesy from Prof. Guido Torzilli (Milan)

R1 Vascular surgery achieves outcomes equivalent to R0 resection.

CLM detachment from intrahepatic vessels can be pursued to increase patient resectability and resection safety (parenchymal sparing).

Conclusions

- Margin status remains the strongest independent prognostic factor.
- Postoperative chemotherapy reduces recurrence rates after R1 resection of CRLM, in patients with optimal morphologic response.
- Preoperative bevacizumab seems to have impact on resection margin status.
- R1 Vascular surgery achieves outcomes equivalent to R0 resection.

Conclusions

- RAS mutations are associated with positive margins in patients undergoing resection of CLM.
- Laparoscopic parenchymal-sparing surgery of CRLM does not compromise the oncological outcome.
- Radiofrequency assisted transection could be useful when R0 resection is difficult to obtain in order to enhance the margin.





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