

17 de maio de 2019



Castro's Park Hotel - Goiânia

Ressecção de metástases hepáticas: nodulectomias

Orlando Jorge M. Torres MD, PhD

Full Professor and Chairman
Department of Gastrointestinal Surgery
Hepatopancreatobiliary Unit
Universidade Federal do Maranhão - Brazil

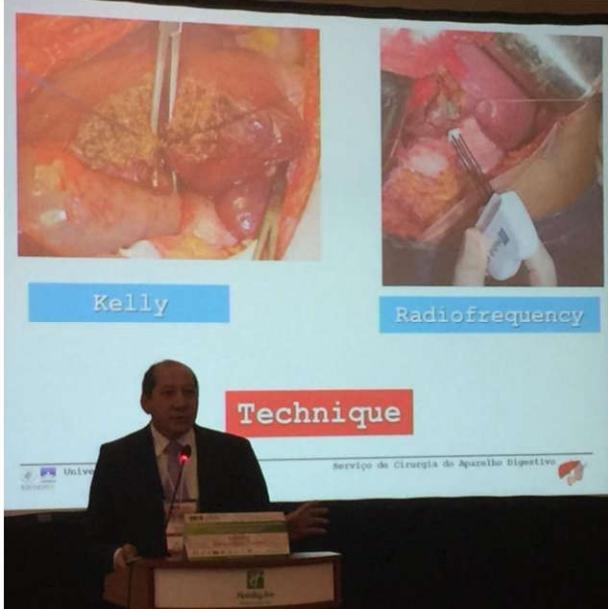
II Eurasian Hepatobiliary Oncology Forum

Holiday Inn Lesnaya
Moscow, Russian Federation

February 22 - 24, 2019



Ativar o Windows



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 irresecáveis*

Orlando Jorge Martins **TORRES**^{1,2,6}, Márcio Carmona **MARQUES**^{2,6}, Fabio Nasser **SANTOS**¹, Igor Correia de **FARIAS**^{2,6},
Anelisa Kruschewsky **COUTINHO**³, Cássio Virgílio Cavalcante de **OLIVEIRA**^{1,4,5}, Antonio Nocchi **KALIL**^{1,2,4,6},
Celso Abdon Lopes de **MELLO**³, Jaime Arthur Pirola **KRUGER**^{1,4,5,6}, Gustavo dos Santos **FERNANDES**³,
Claudemiro **QUIREZE JR**^{1,4,5,6}, André M. **MURAD**³, Milton José de **BARROS E SILVA**³,
Charles Edouard **ZURSTRASSEN**¹, Helano Carioca **FREITAS**³, Marcelo Rocha **CRUZ**³, Rui **WESCHENFELDER**³,
Marcelo Moura **LINHARES**^{1,4,5,6}, Leonaldson dos Santos **CASTRO**^{1,2,6}, Charles **VOLLMER**⁶,
Elijah **DIXON**⁶, Héber Salvador de Castro **RIBEIRO**^{1,2,6}, Felipe José Fernandez **COIMBRA**^{1,2,5,6}

MARGINS STATUS

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

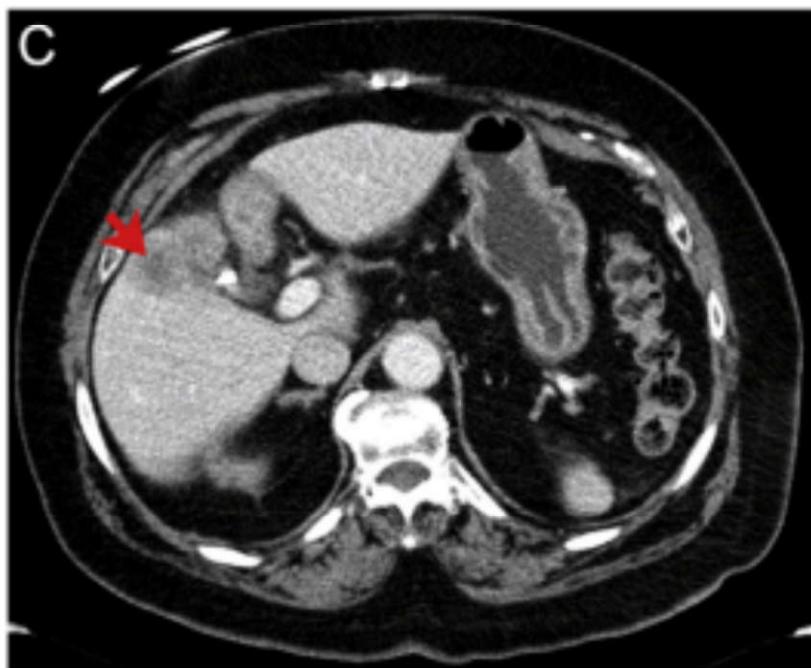
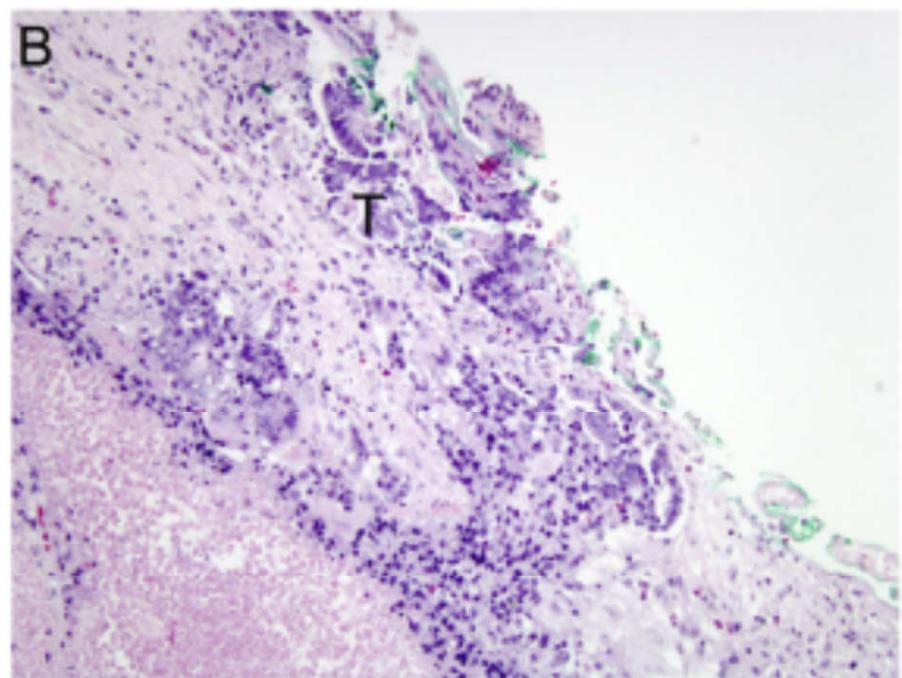
Analysis of 1001 Consecutive Cases

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	p
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



- Tumor in seg 4 (resected by laparoscopy).
- Histology of the resection margin (positive).
- CT after 10 months (clear signs of recurrence).



Av

journal homepage: www.elsevier.com/locate/suronc

Positive (R1) resection margin

REVIEW

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

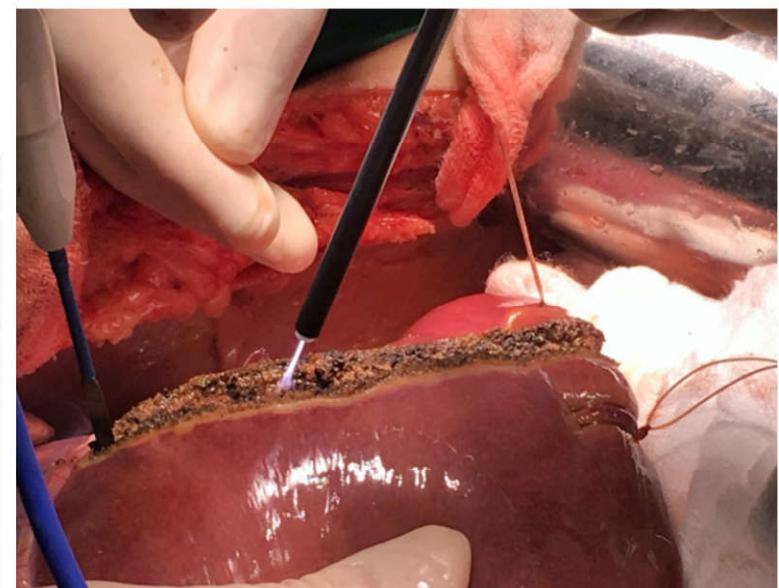
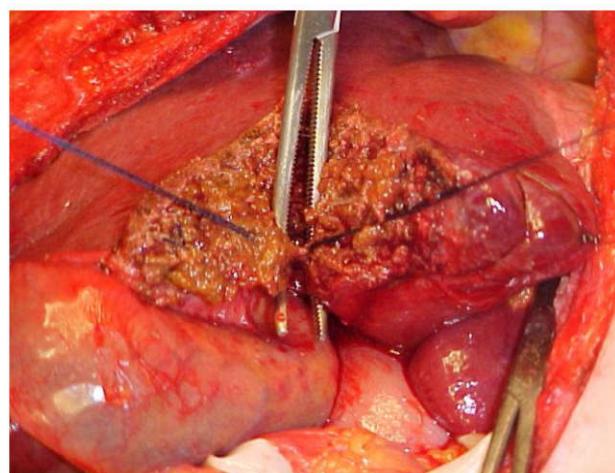
Fenella K.S. Welsh^{a,*}, Paris P. Tekkis^b, Tom O'Rourke^a,
Timothy G. John^a, Myrddin Rees^a

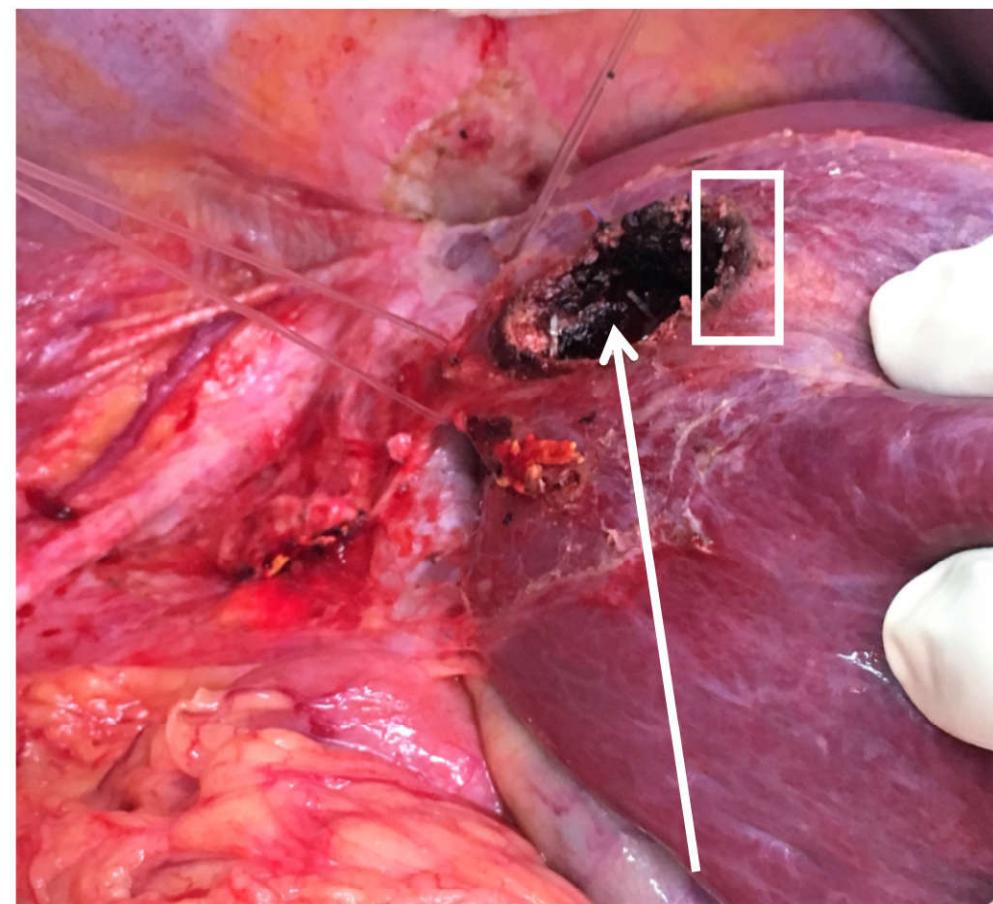
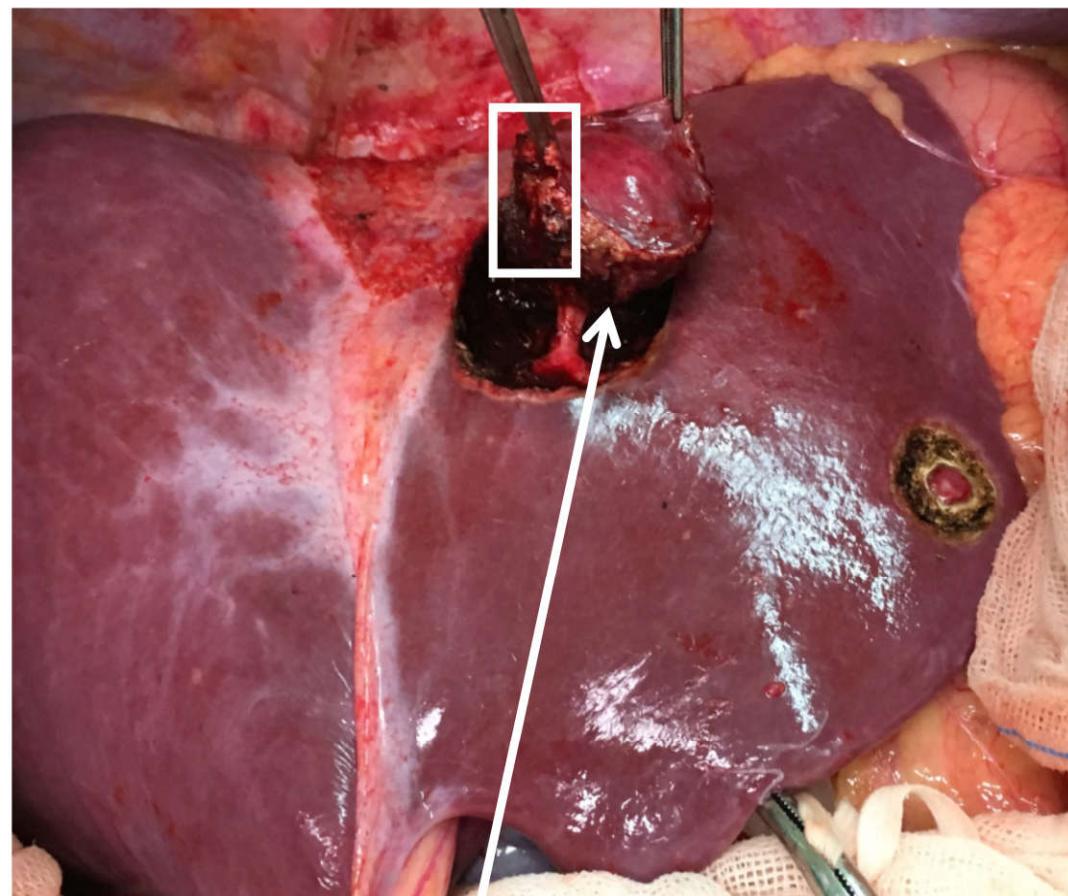
- Non-anatomical resection**
- Extended resection**
- >3 hepatic metastases involving >50% of the liver**
- Repeat hepatic resection**
- Bilobar disease**
- Abnormal pre-operative LFTs**

Risk

ACCURATE ASSESSMENT OF MARGINS STATUS

- Vaporize
- Aspirate
- Ablate
- Fracture
- Coagulate

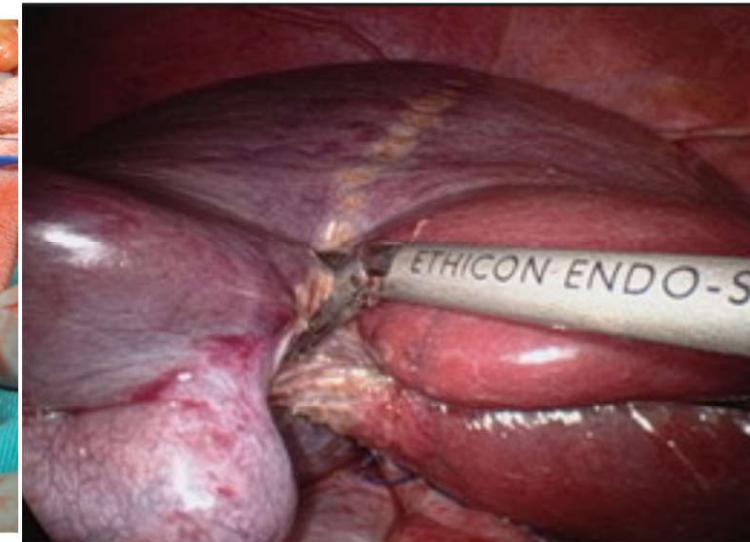
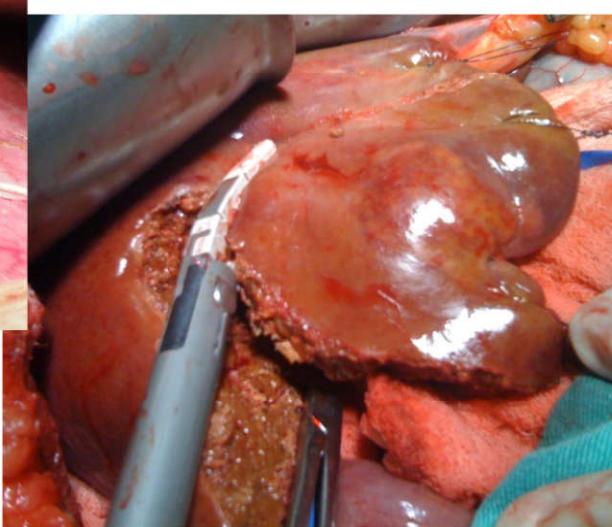
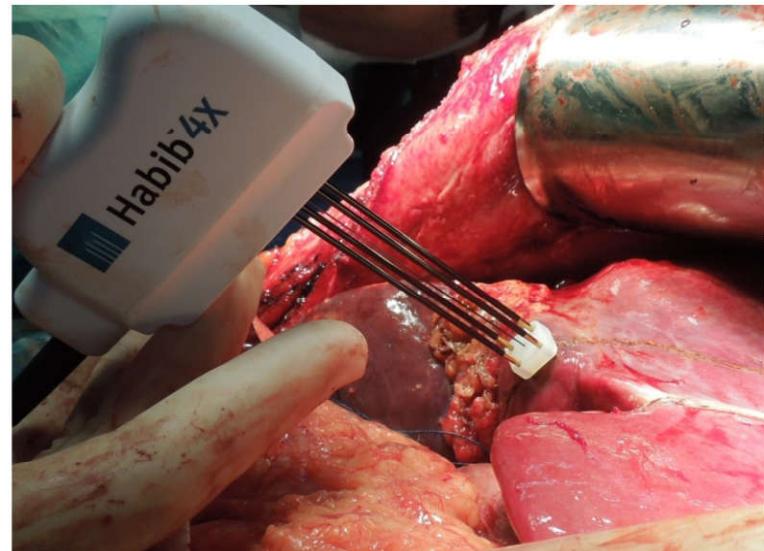




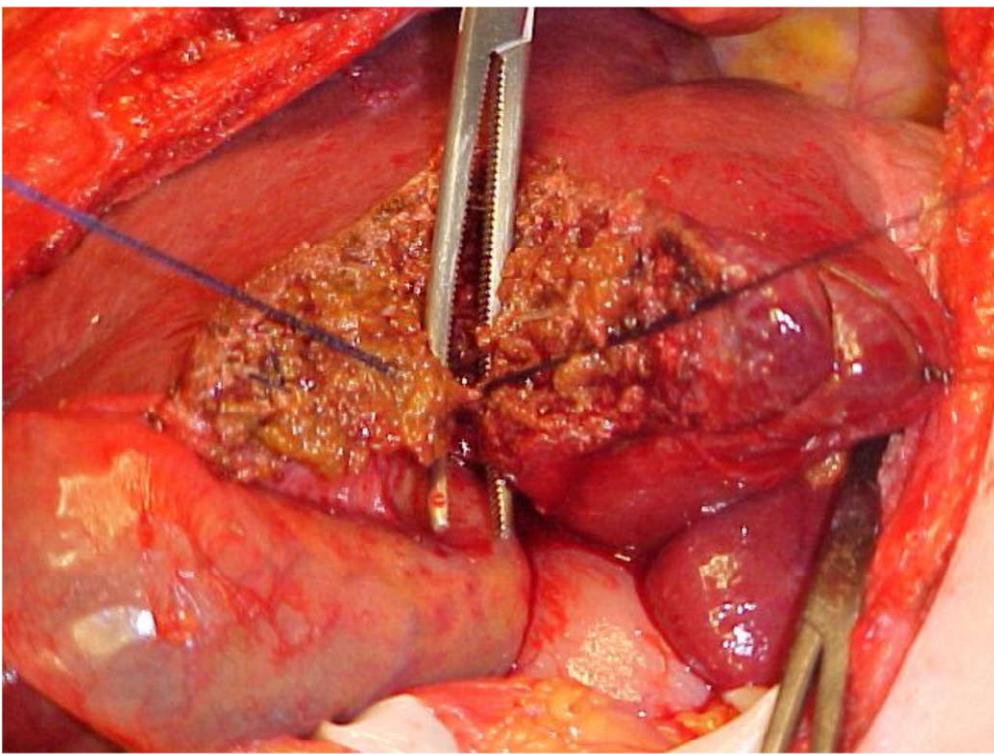
Pathology

Surgical

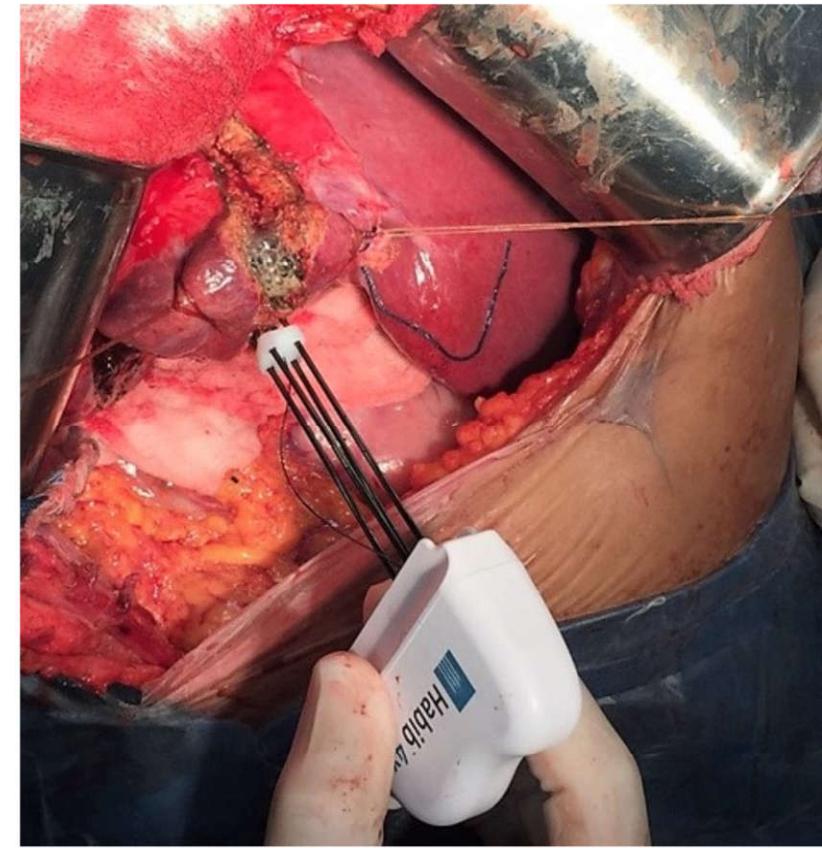
A NEW PERSPECTIVE



- Bipolar coagulator (Ligasure®)
- Ultrasonic dissector:
 - SonoSurg®
 - Harmonic®
- Ultrasonic surgical Aspirator (CUSA®)
- Argon Beam
- Radiofrequency ablation

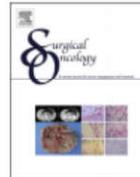


Kelly



Radiofrequency

Technique



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



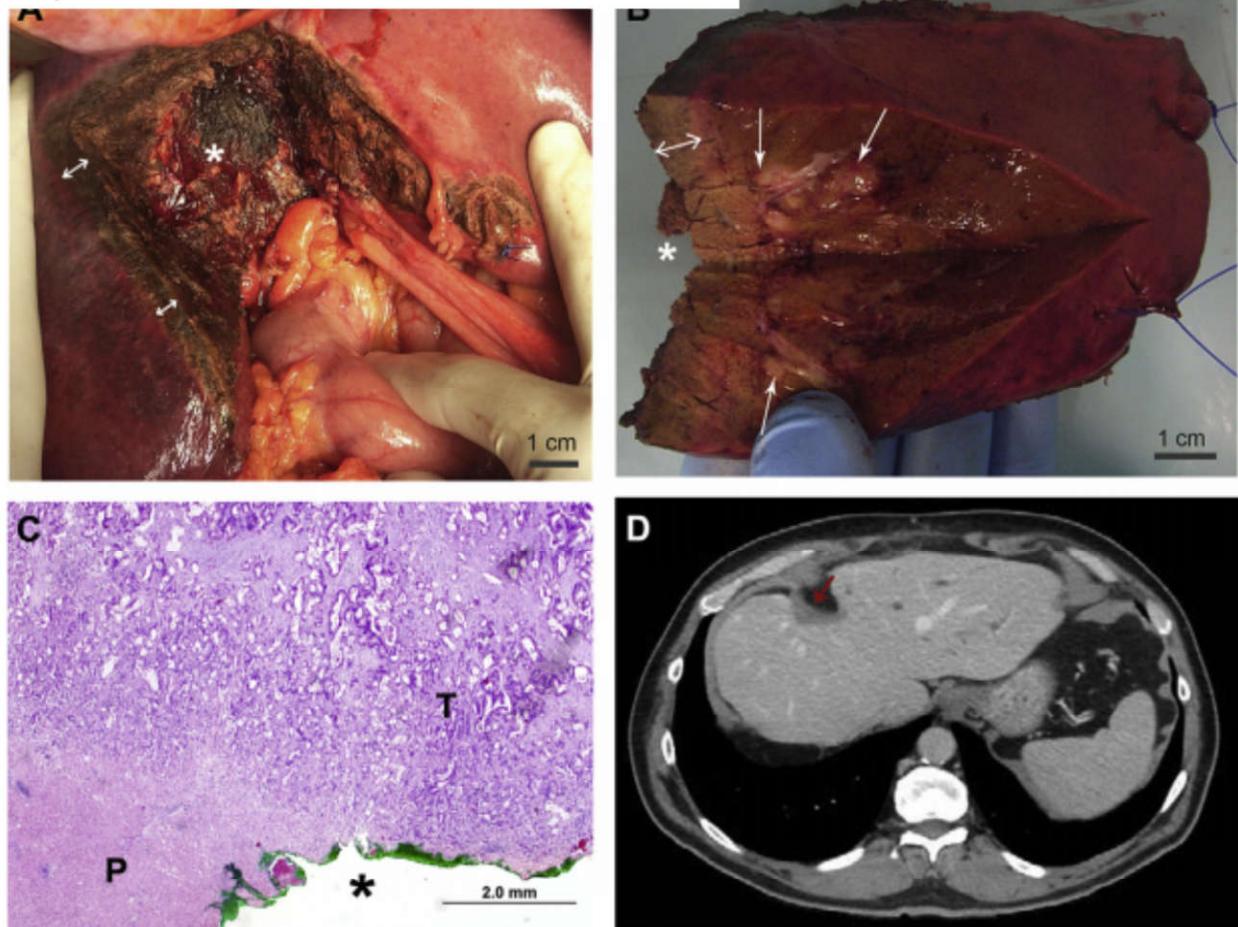
R. Quesada, MSc, PhD ^{a,*}, A. Moreno ^b, I. Poves ^{a,c}, E. Berjano ^d, L. Grande ^c, F. Burdío ^{a,c}

^a Cancer Research Group HBP, Institut Hospital del Mar d'Investigacions Mèdiques, Barcelona, Spain

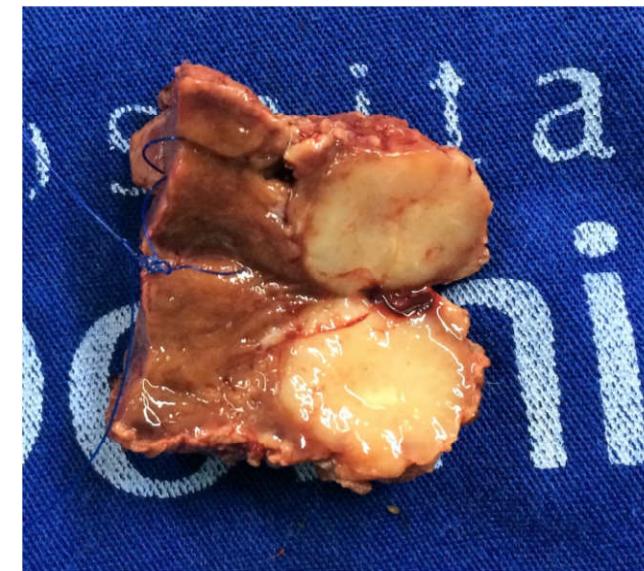
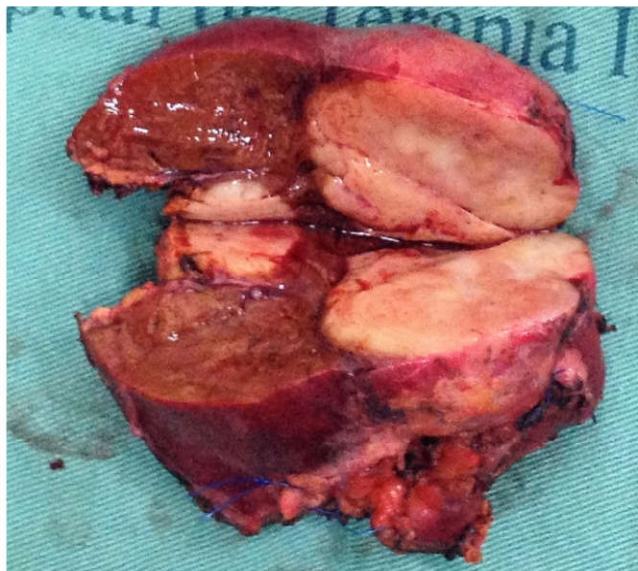
^b School of Medicine, Universitat Pompeu Fabra and UAB, Barcelona, Spain

^c Department of Surgery, Hospital del Mar, Barcelona, Spain

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



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



$\geq 10\text{mm}$

$\geq 4\text{mm}$

$\geq 1\text{mm}$

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

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

Wakai T, et al. Ann Surg Oncol 2008;15:2472-81

1

Microsatellite lesions

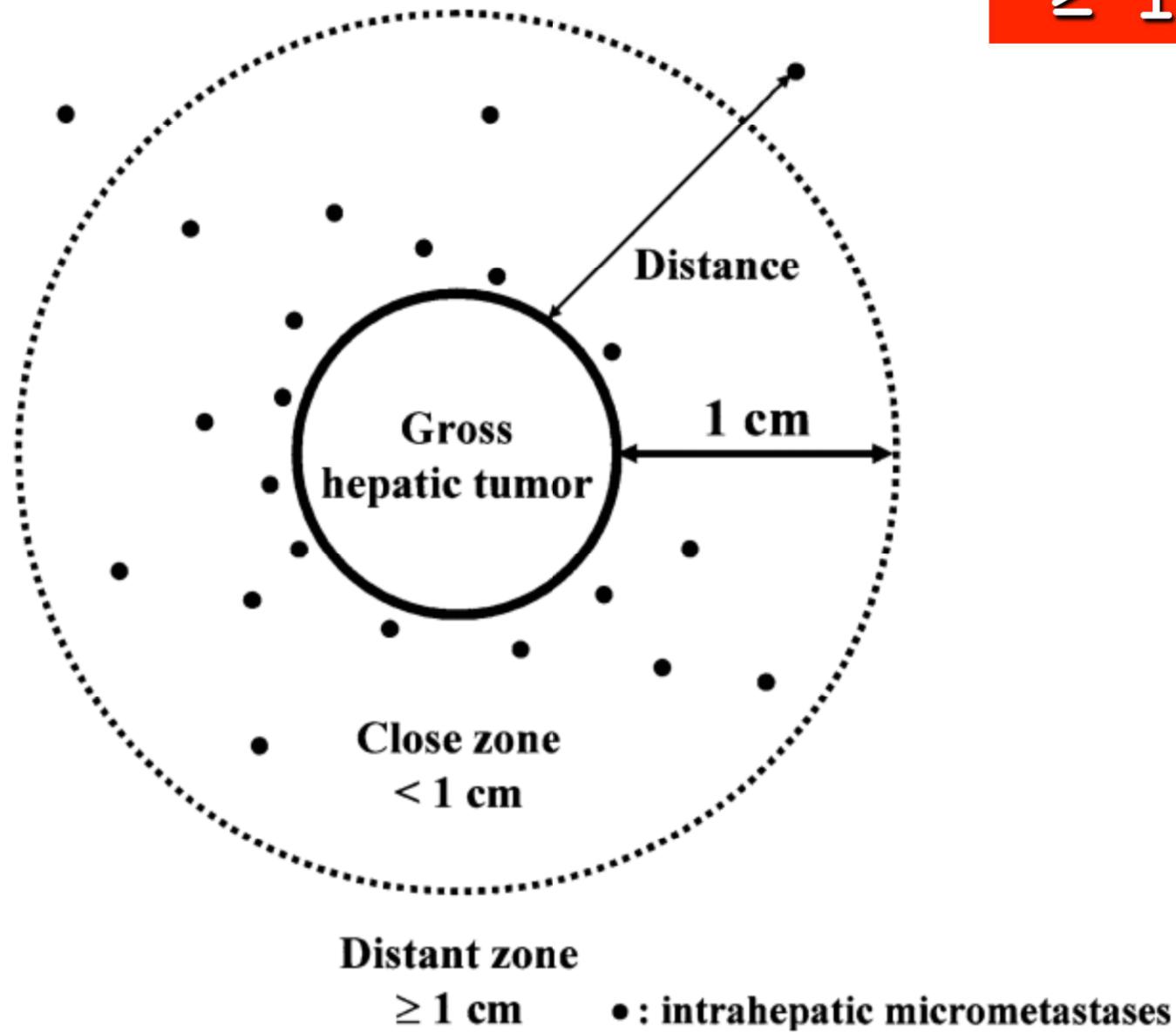
Annals of Surgical Oncology 15(9):2472–2481
DOI: 10.1245/s10434-008-0023-y

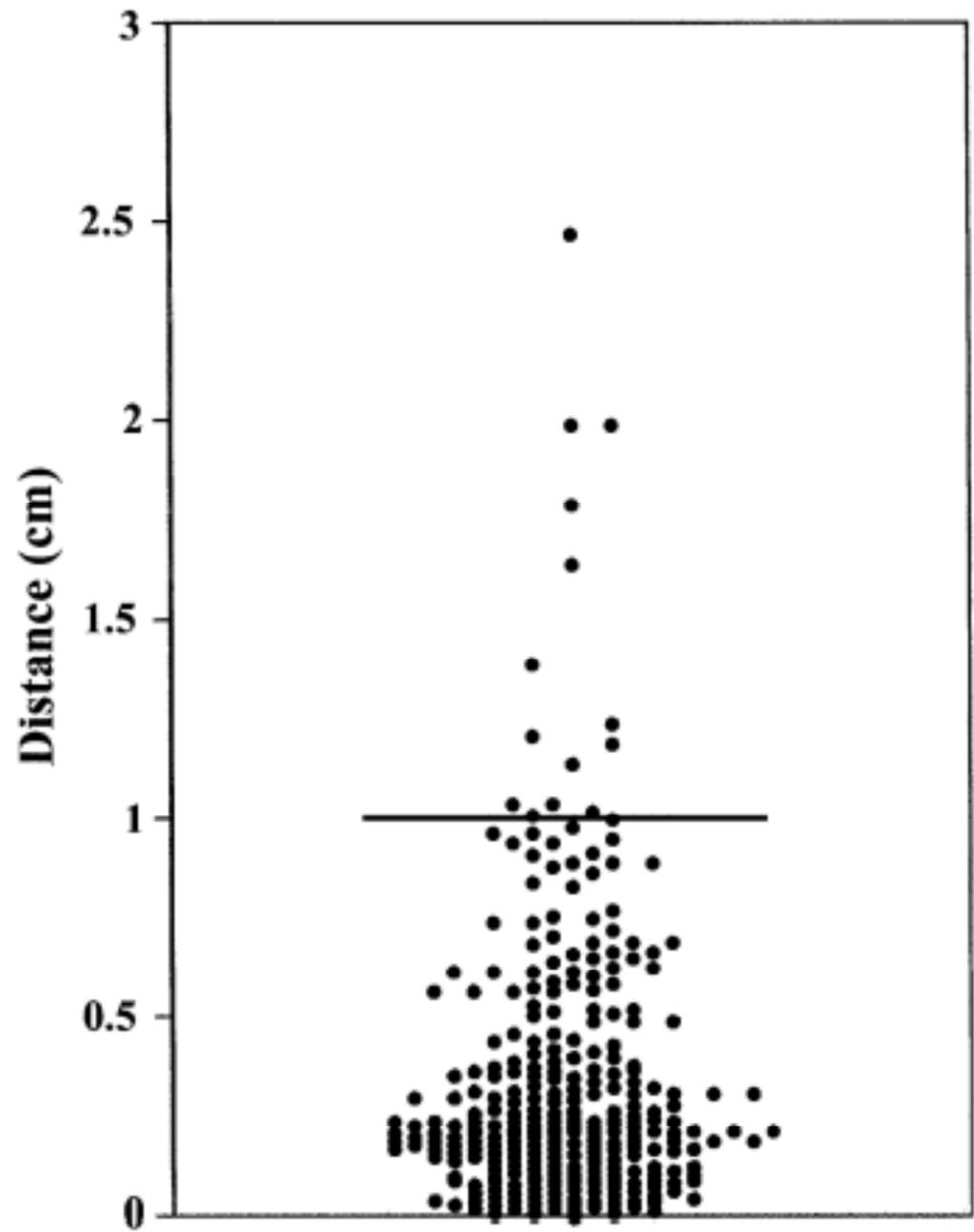
Appraisal of 1 cm Hepatectomy Margins for Intrahepatic Micrometastases in Patients with Colorectal Carcinoma Liver Metastasis

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

2008

$\geq 10\text{mm}$

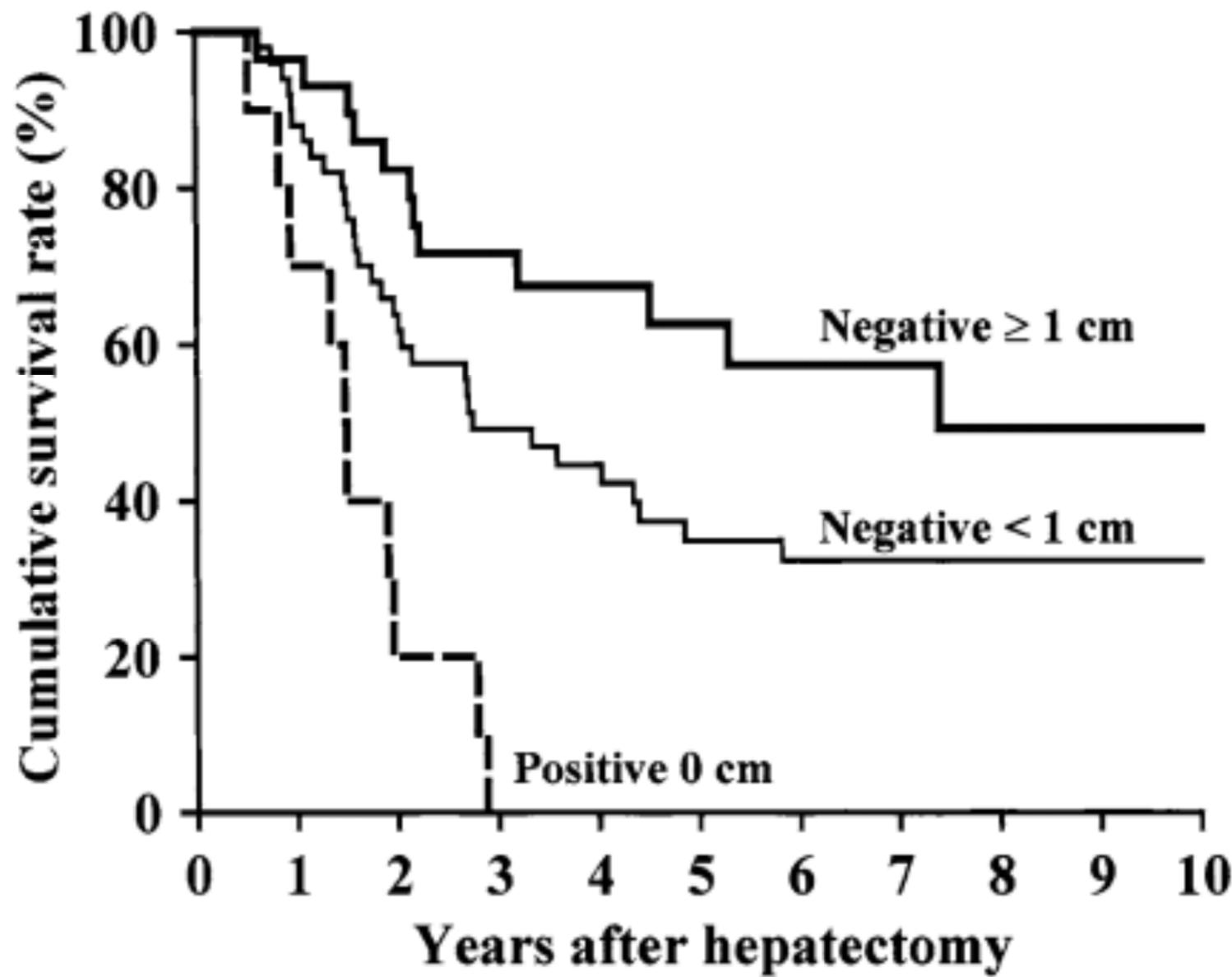




◻ 95% - 1 cm

$\geq 10\text{mm}$

$\geq 10\text{mm}$



$\geq 10\text{mm}$

- The current recommendation of ≥ 1 cm hepatectomy margin should remain the goal for patients with colorectal liver metastases.

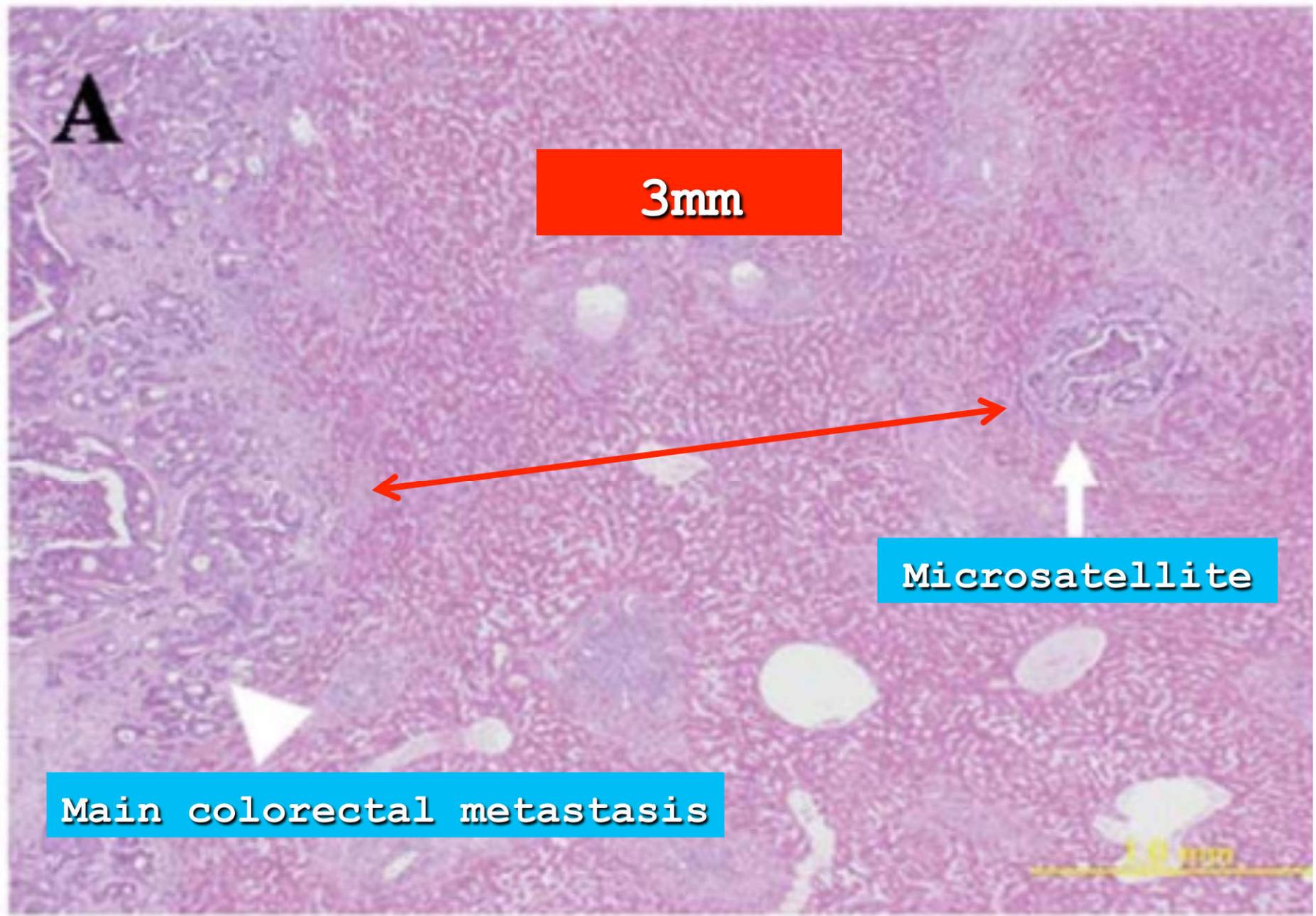
Microsatellite lesions

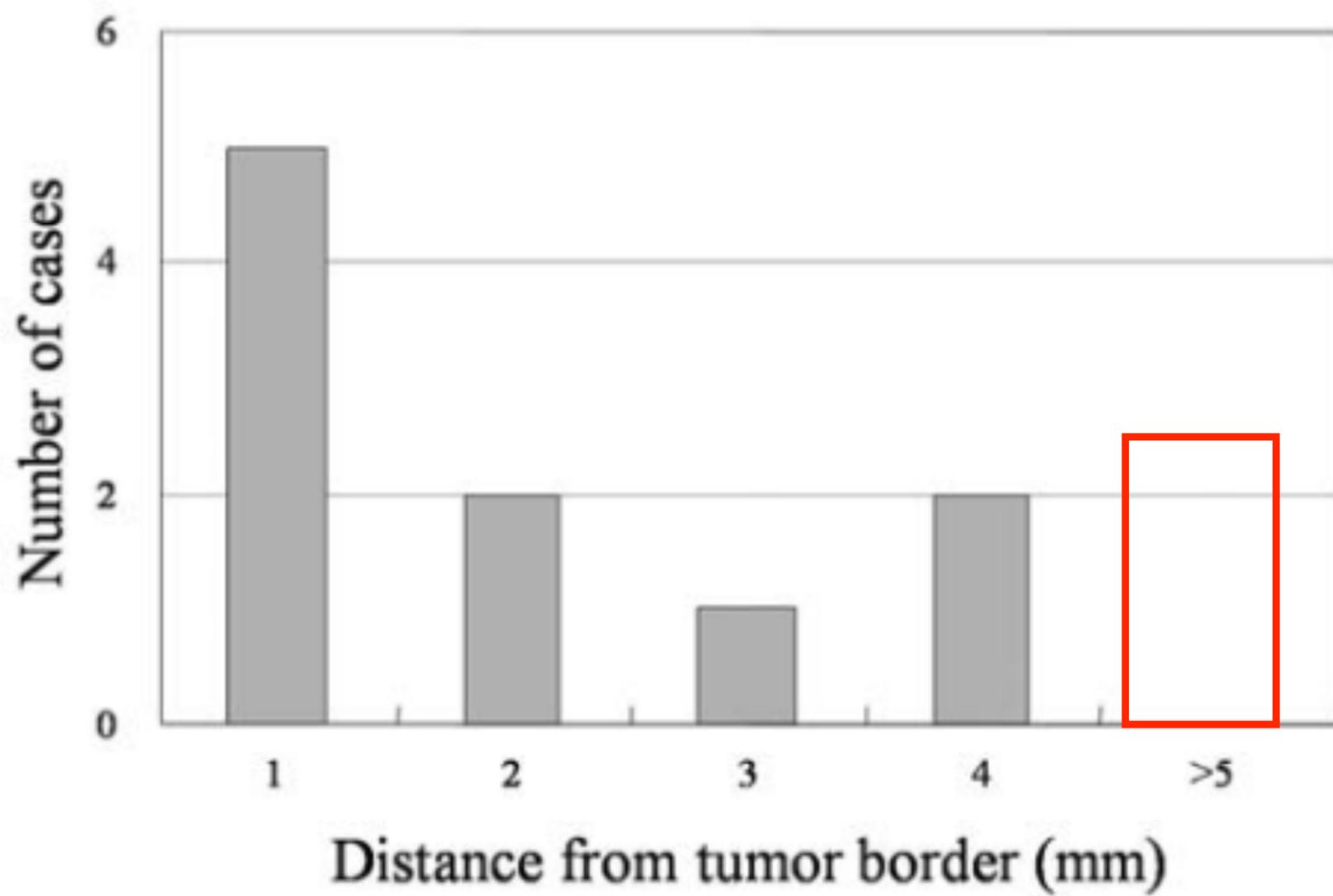
Presence of microsatellite lesions with colorectal liver metastases correlate with intrahepatic recurrence after surgical resection

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

Departments of ¹Pathology, ²Gastroenterological Surgery and ³Thoracic, Endocrine and Pediatric Surgery,
Fukuoka University Hospital and School of Medicine, 7-45-1 Nanakuma, Jonan-ku, Fukuoka 814-0180, Japan

2009





- 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

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*

2014

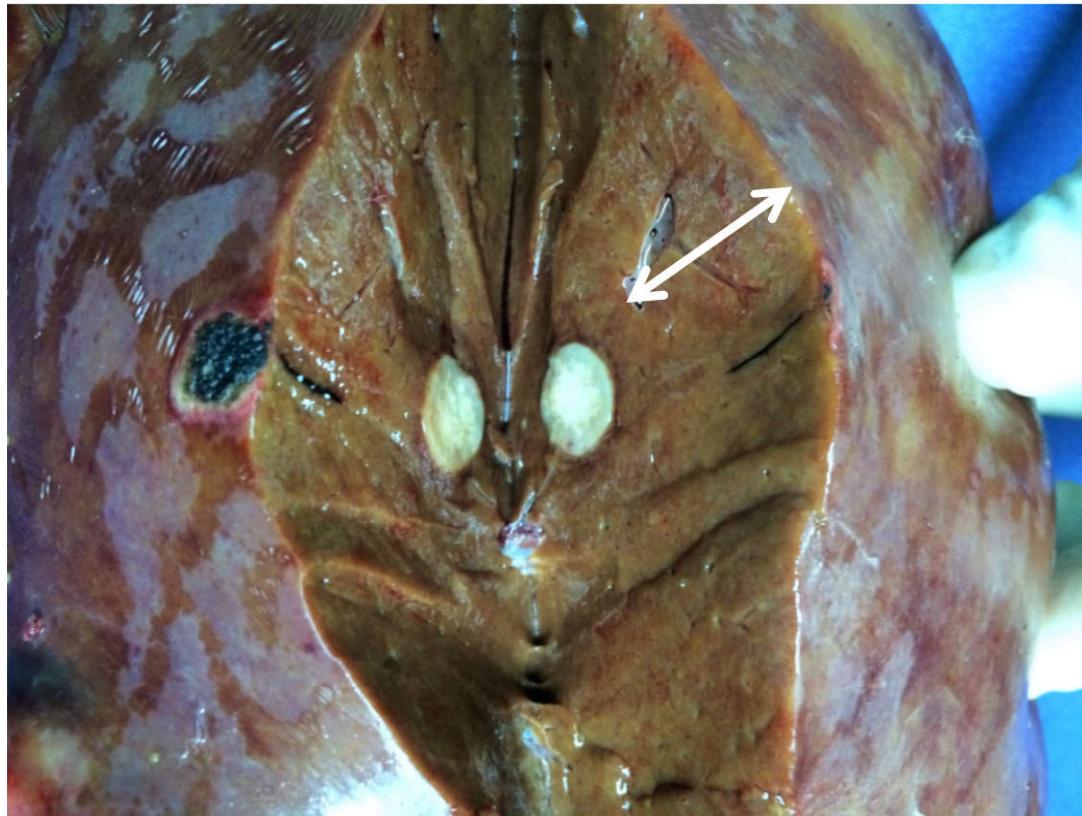
TABLE 2. Overall Disease-Free Survival (DFS) Stratified by Resection Margin Clearance and Illustration of Univariate and Multivariate Analyses

Margin	Number (2715)	Median DFS, Mo (95% CI)	(%) Disease-Free Survival				Univariate Analysis		Multivariate Analysis		
			1-Yr	3-Yr	5-Yr	10-Yr	P	HR (95% CI)	P		
<1 mm	663	19.8 (17.4–22)	69	34	25	21	Ref	Ref	Ref		
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.

≥ 1mm

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



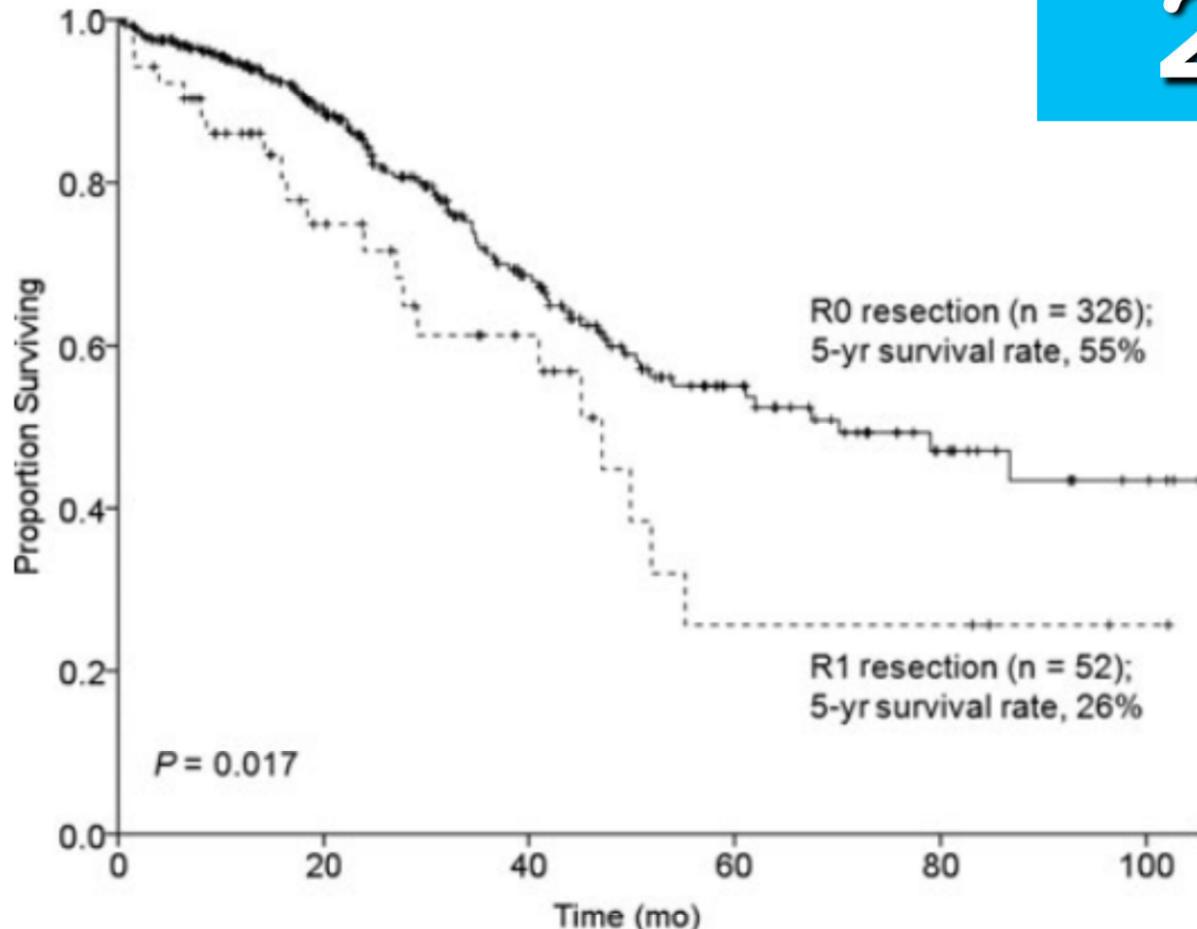
Margin Status Remains an Important Determinant of Survival After Surgical Resection of Colorectal Liver Metastases in the Era of Modern Chemotherapy

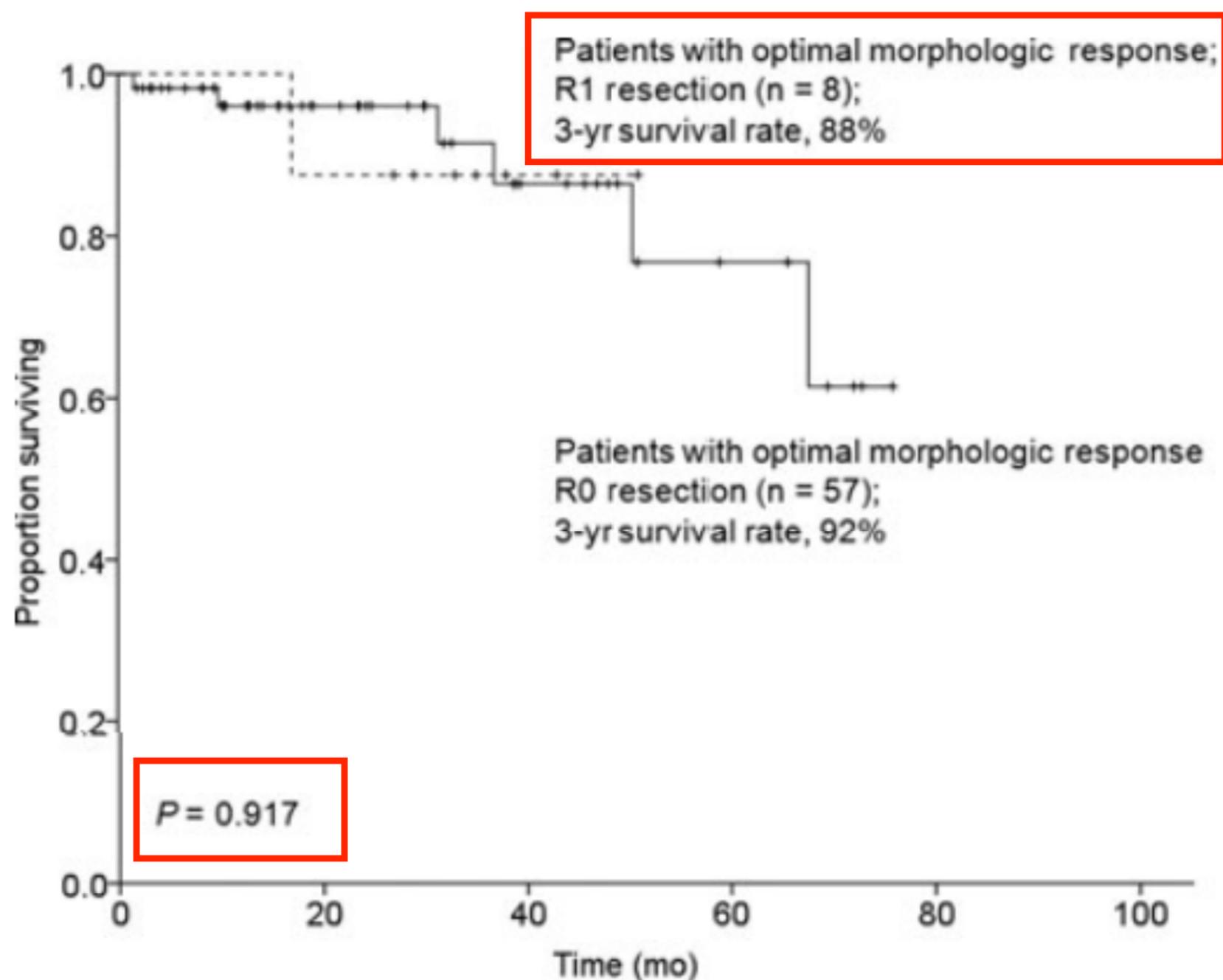
Andreas Andreou, MD,* Thomas A. Aloia, MD, FACS,* Antoine Brouquet, MD,* Paxton V. Dickson, MD,*

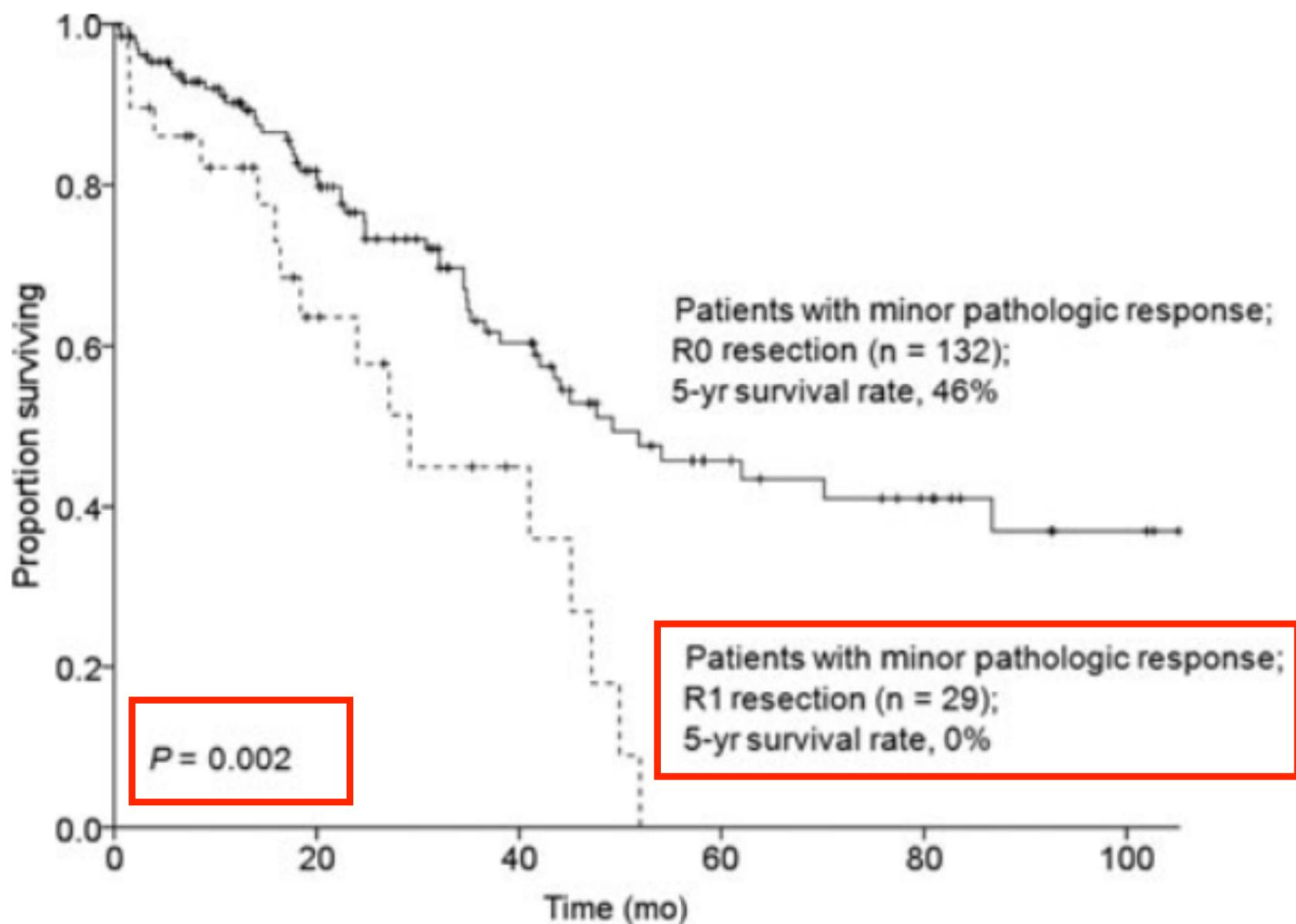
Giuseppe Zimmitti, MD,* Dipen M. Maru, MD,† Scott Kopetz, MD, PhD,‡ Evelyne M. Loyer, MD,§

Steven A. Curley, MD, FACS,* Eddie K. Abdalla, MD, FACS,* and Jean-Nicolas Vauthey, MD, FACS*

2



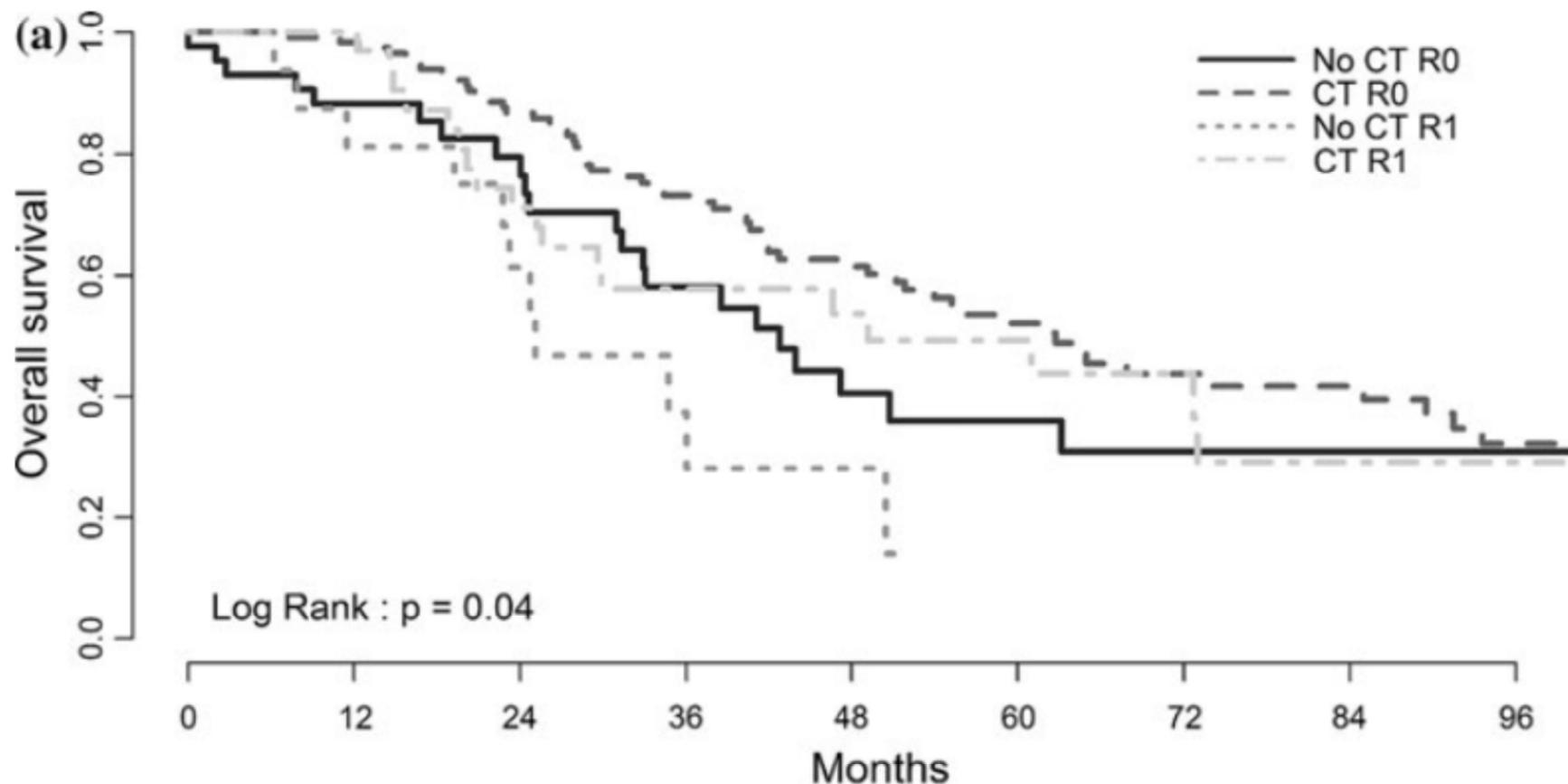


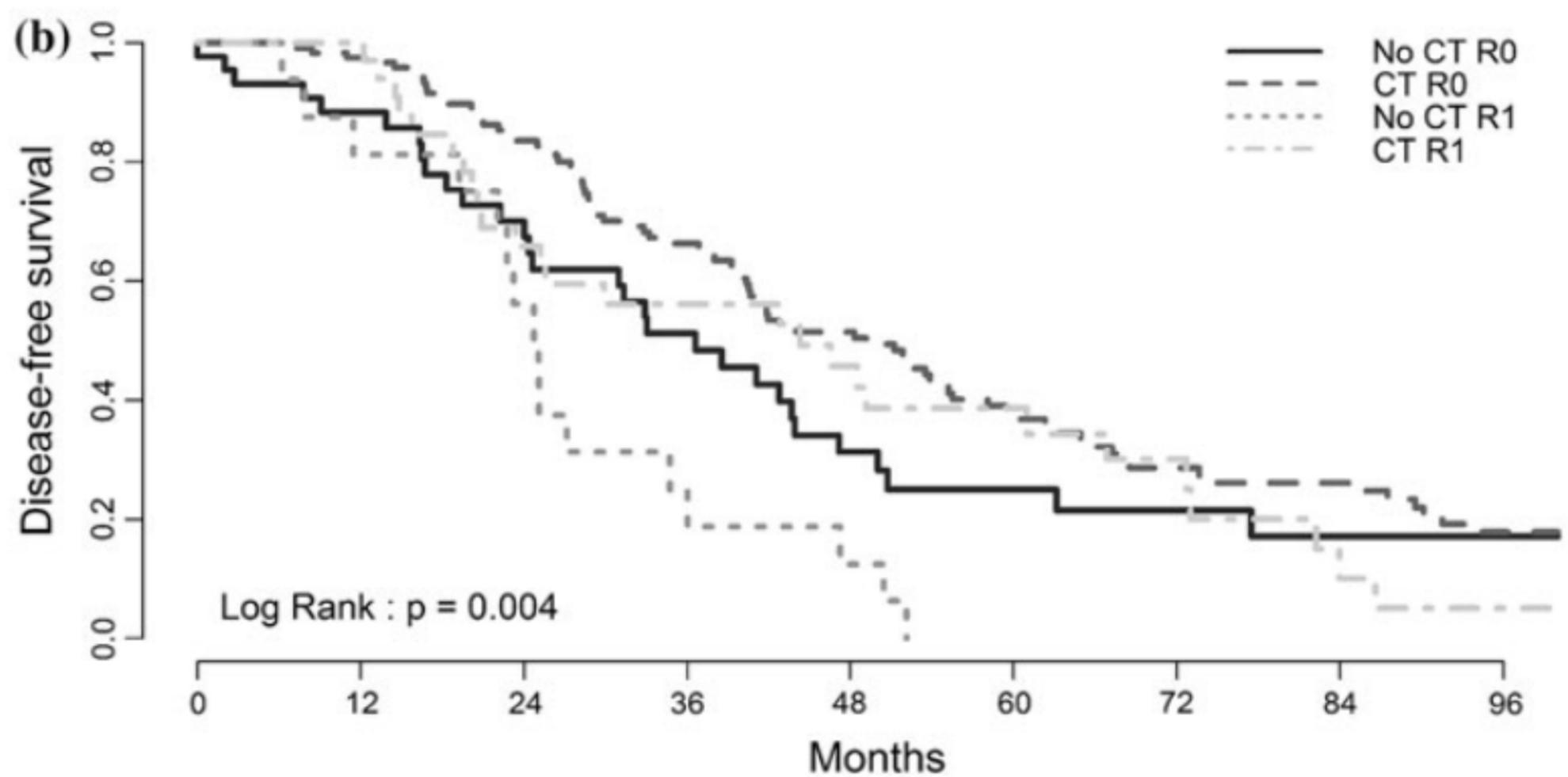


- ❑ Continued emphasis on achieving R0 resection in patients with CLMs.
- ❑ Modern chemotherapy combined with aggressive surgical strategies has resulted in improved long-term OS.
- ❑ For patients with unfavorable tumor biology, only if R0 resection is deemed feasible.

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

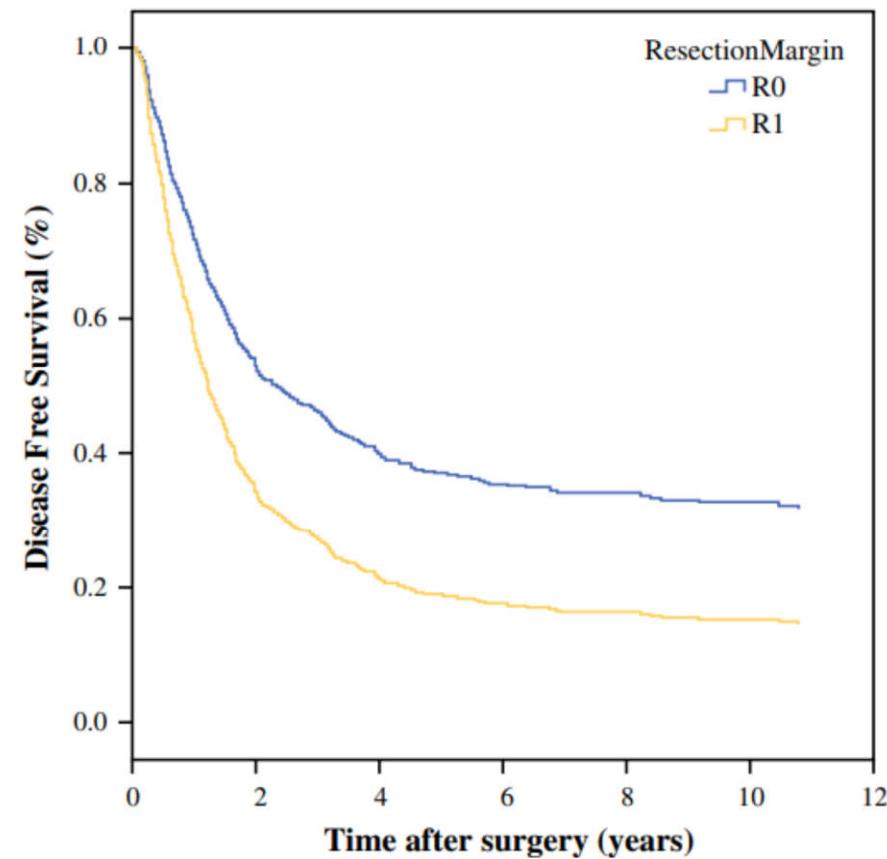
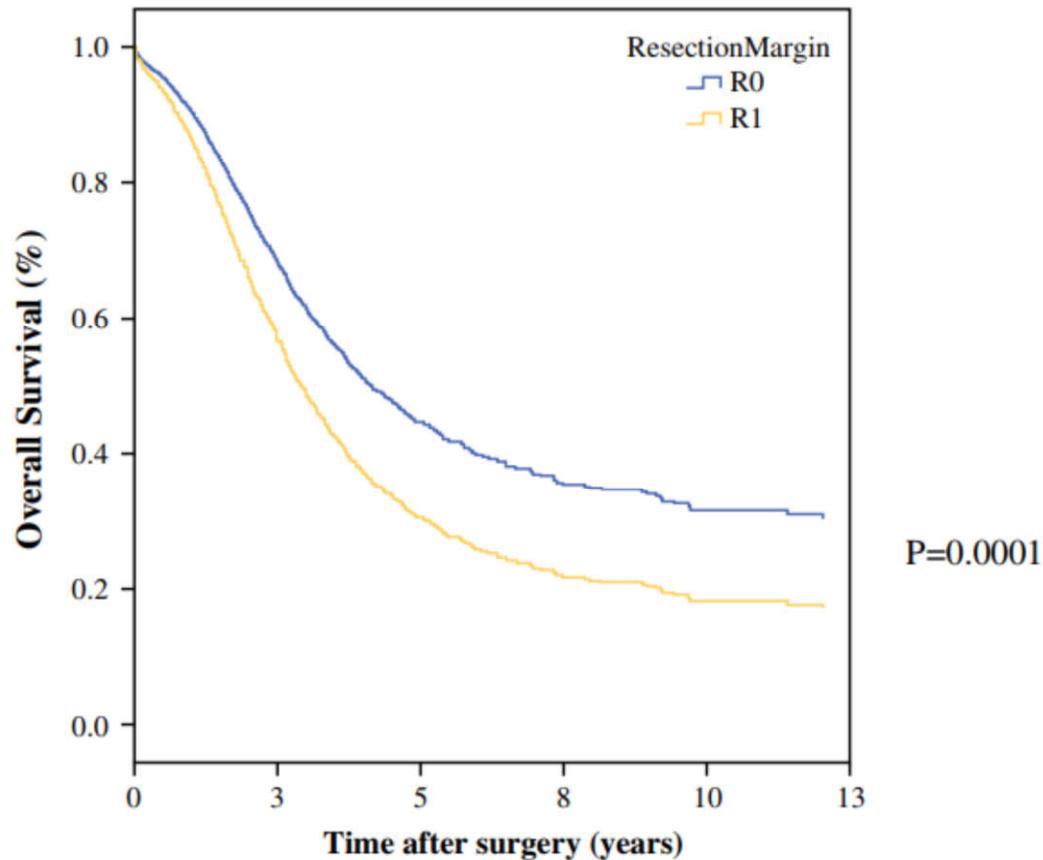




- A positive surgical margin after LR of CRLM remains a significant negative prognostic factor in the era of effective chemotherapy regimens.
- Postoperative chemotherapy reduces recurrence rates after R1 resection of CRLM.

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



Positive margin

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

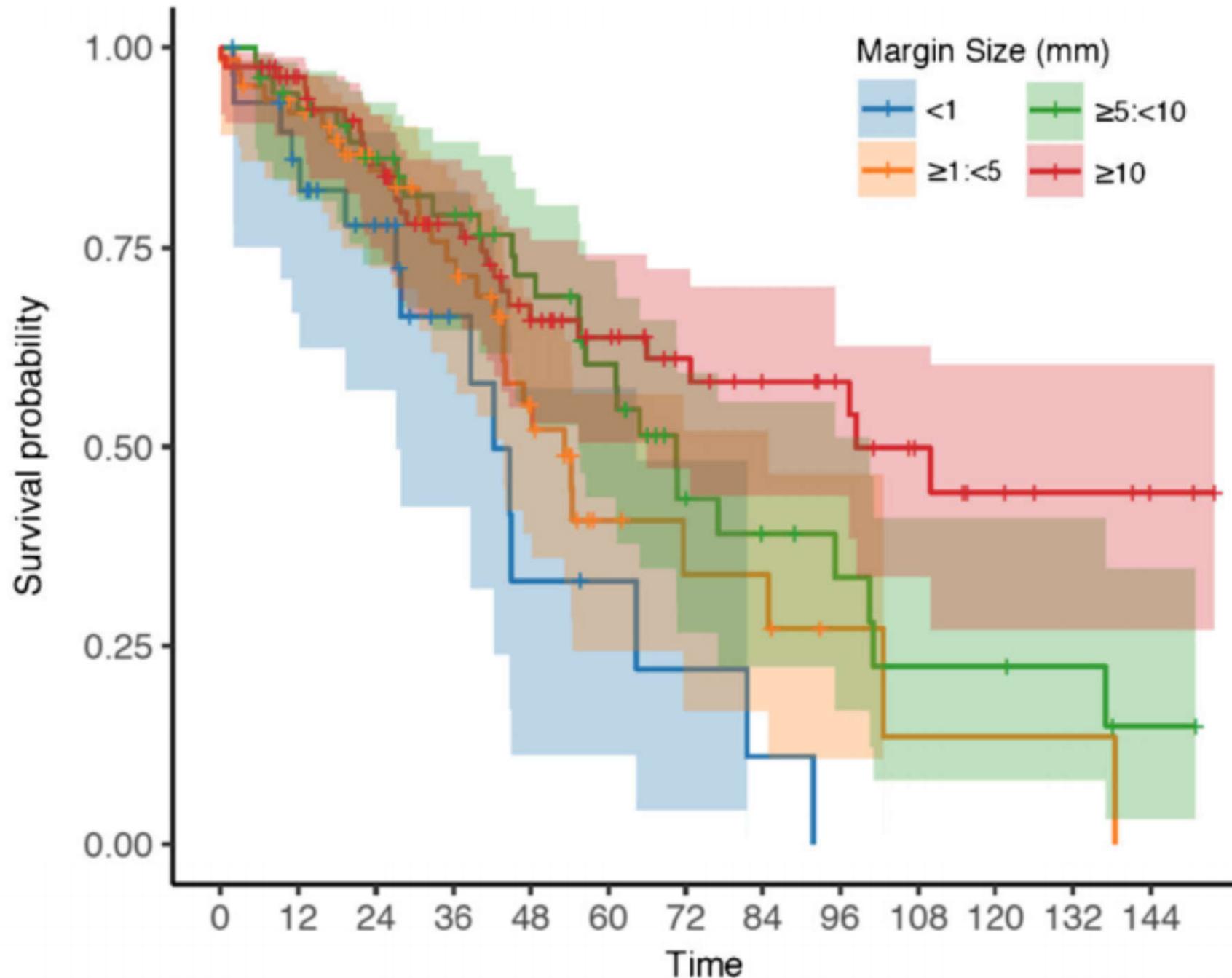


Prognostic Significance of Surgical Margin Size After Neoadjuvant FOLFOX and/or FOLFIRI for Colorectal Liver Metastases

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

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



No chemotherapy

- 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.

Chemotherapy

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

Frank Makowiec^{1,2}  · Peter Bronsert^{2,3} · Andrea Klock¹ · Ulrich T. Hopt¹ ·
Hannes P Neeff^{1,2}

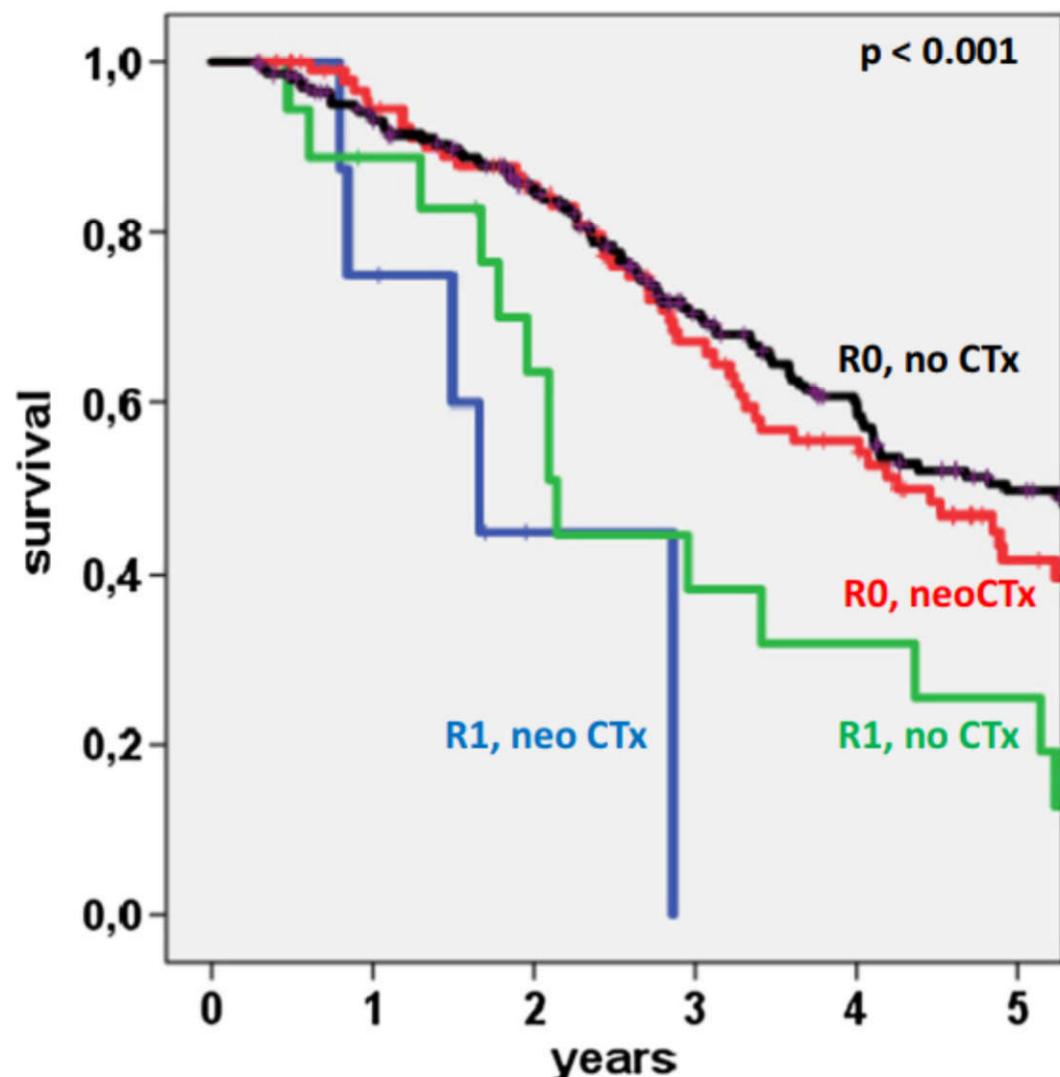


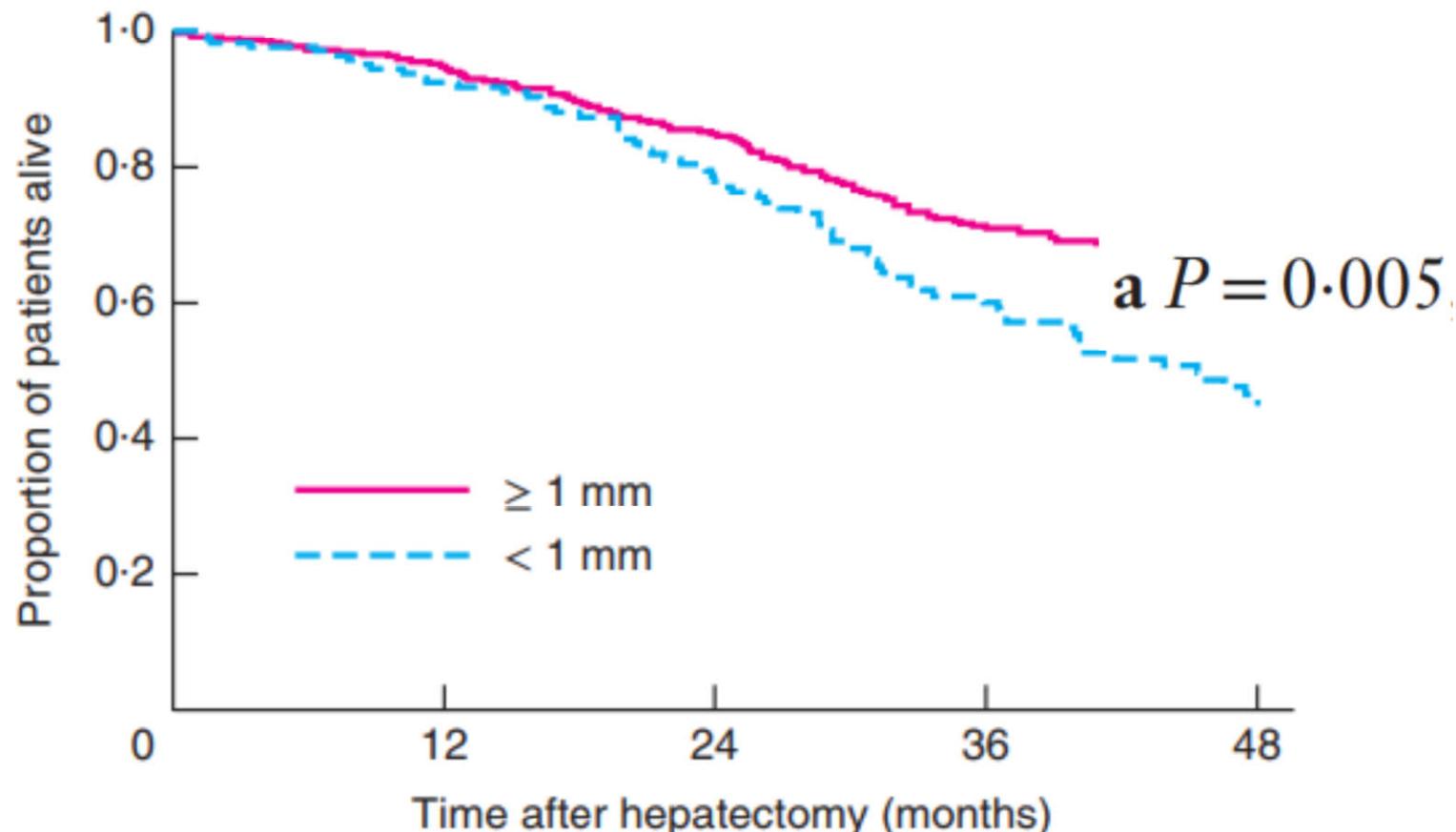
Table 4 Multivariate survival analysis of 334 patients after first resection of isolated colorectal liver metastases

Parameter	<i>p</i>	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)	—

- 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.

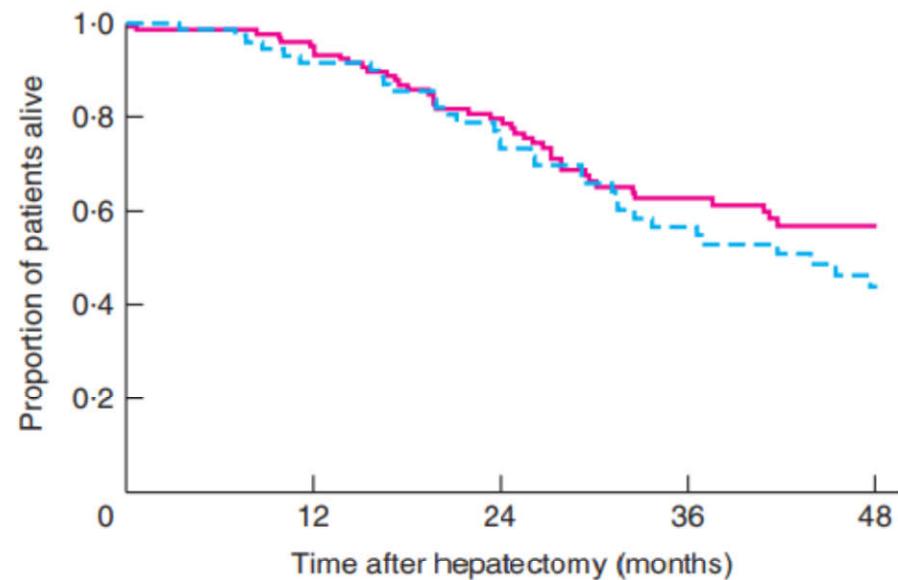
Prognostic impact of margin status in liver resections for colorectal metastases after bevacizumab

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



3

b $P = 0.010$

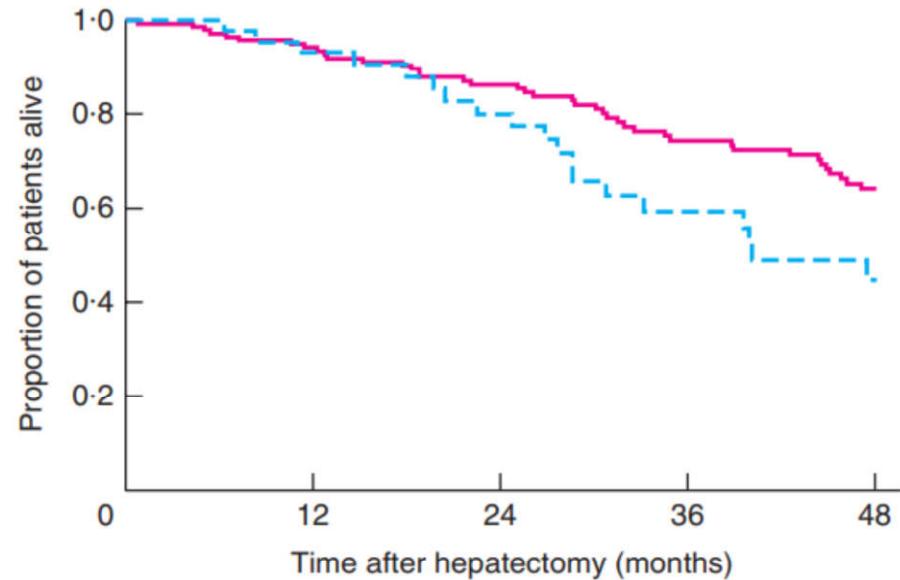


No. at risk

$\geq 1\text{ mm}$	154	124	102	79	61
$< 1\text{ mm}$	49	40	30	18	11

b Preoperative chemotherapy without bevacizumab

c $P = 0.081$



No. at risk

$\geq 1\text{ mm}$	136	106	77	47	36
$< 1\text{ mm}$	78	62	41	30	17

c Preoperative chemotherapy with bevacizumab

- 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.



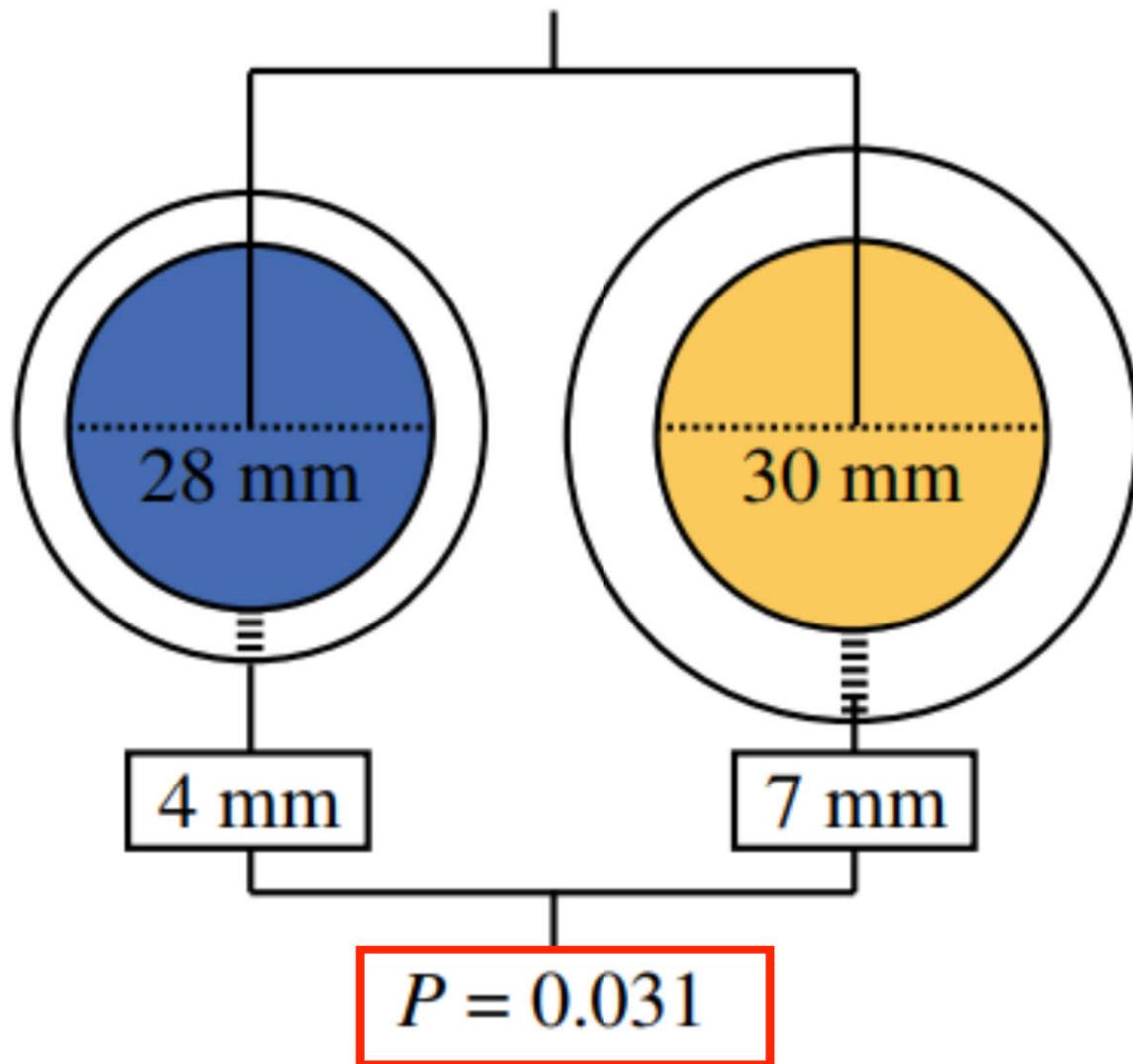
ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

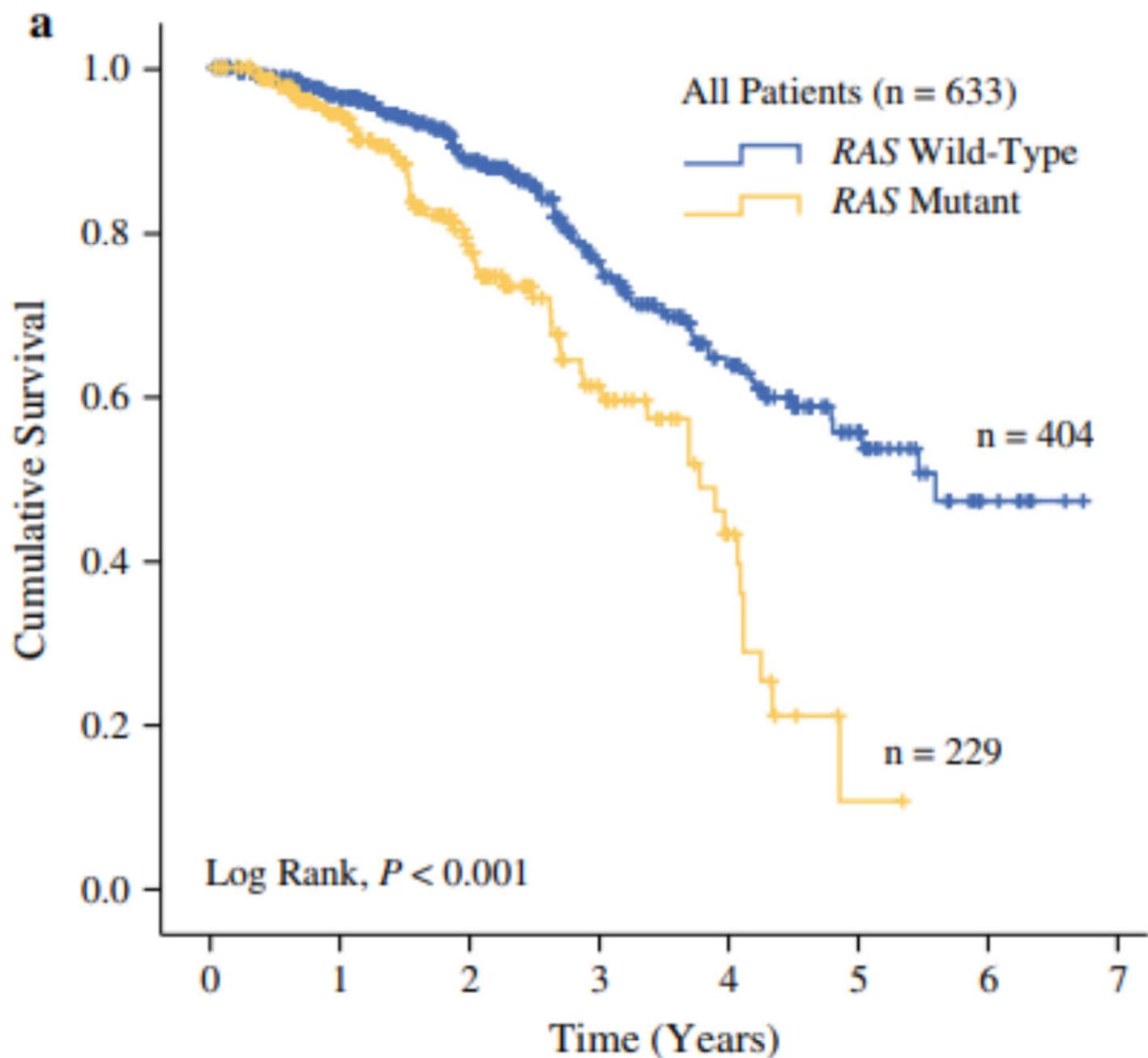
RAS Mutation Predicts Positive Resection Margins and Narrower Resection Margins in Patients Undergoing Resection of Colorectal Liver Metastases

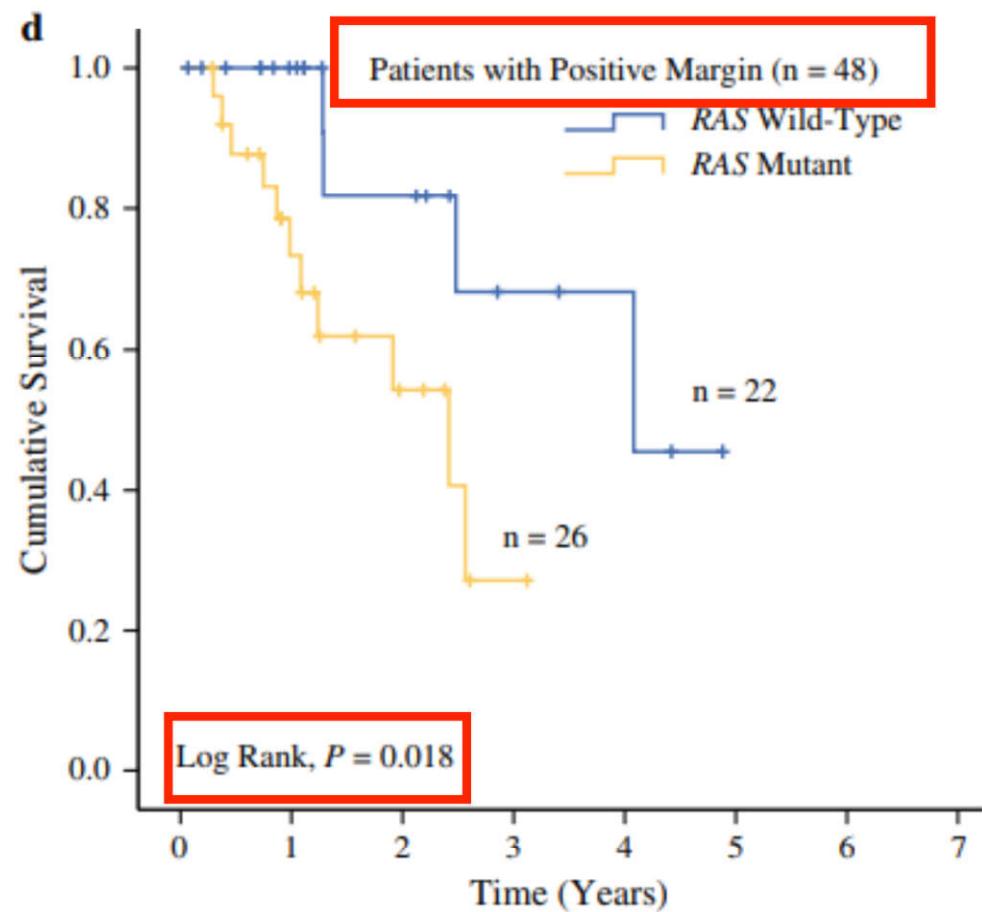
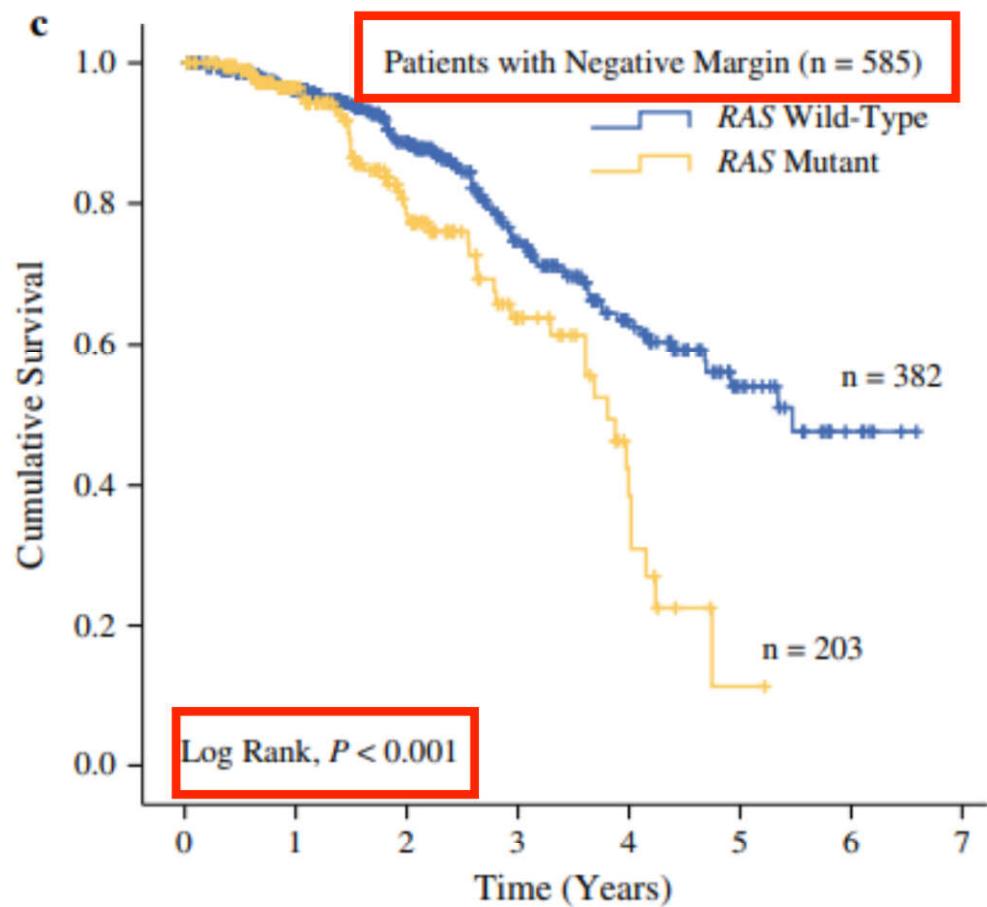
Kristoffer Watten Brudvik, MD, PhD¹, Yoshihiro Mise, MD, PhD¹, Michael Hsiang Chung, BS¹, Yun Shin Chun, MD¹, Scott E. Kopetz, MD², Guillaume Passot, MD, PhD¹, Claudius Conrad, MD, PhD¹, Dipen M. Maru, MD³, Thomas A. Aloia, MD¹, and Jean-Nicolas Vauthey, MD¹

¹Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; ²Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; ³Department of Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX

$P = 0.476$



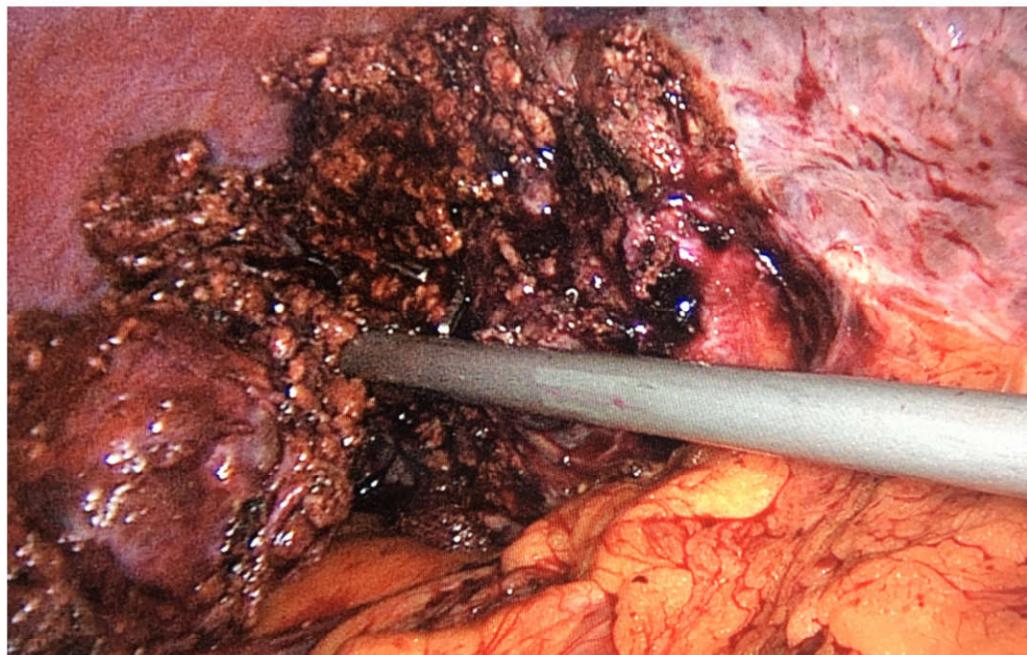


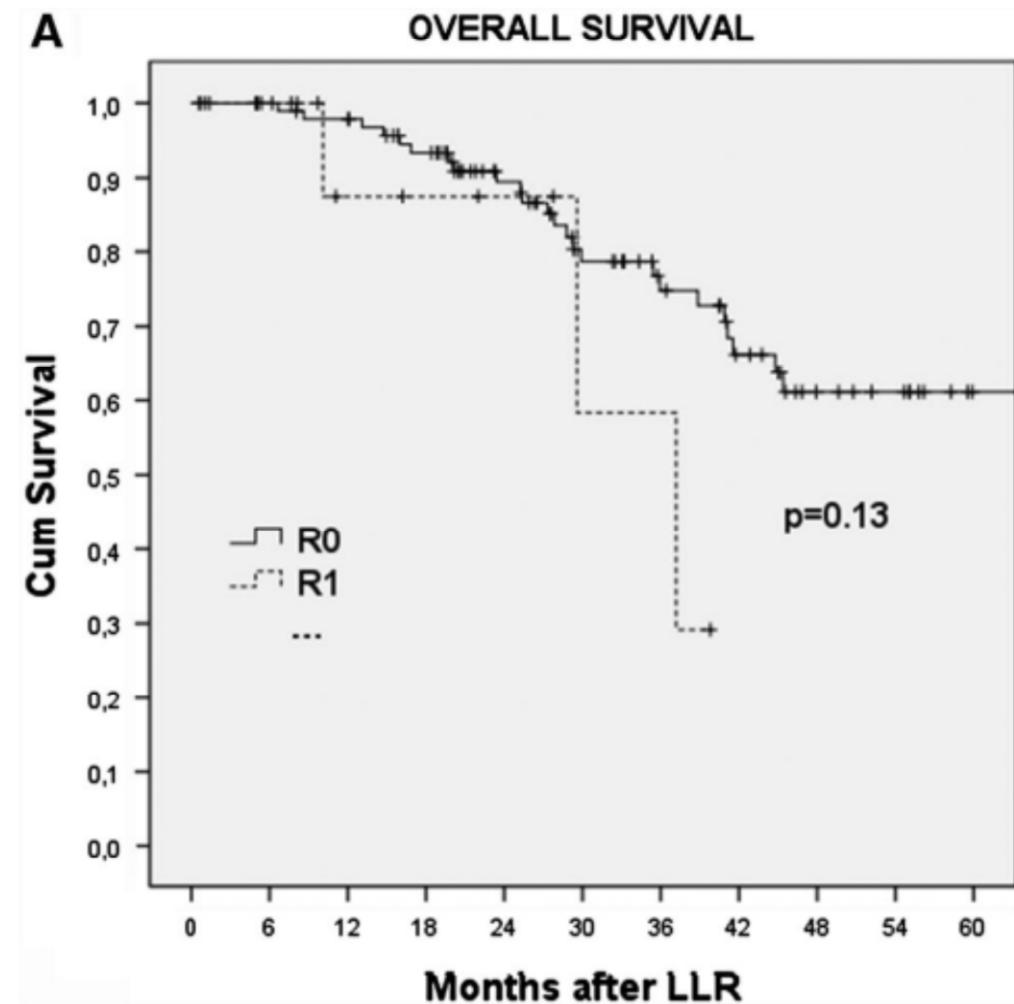
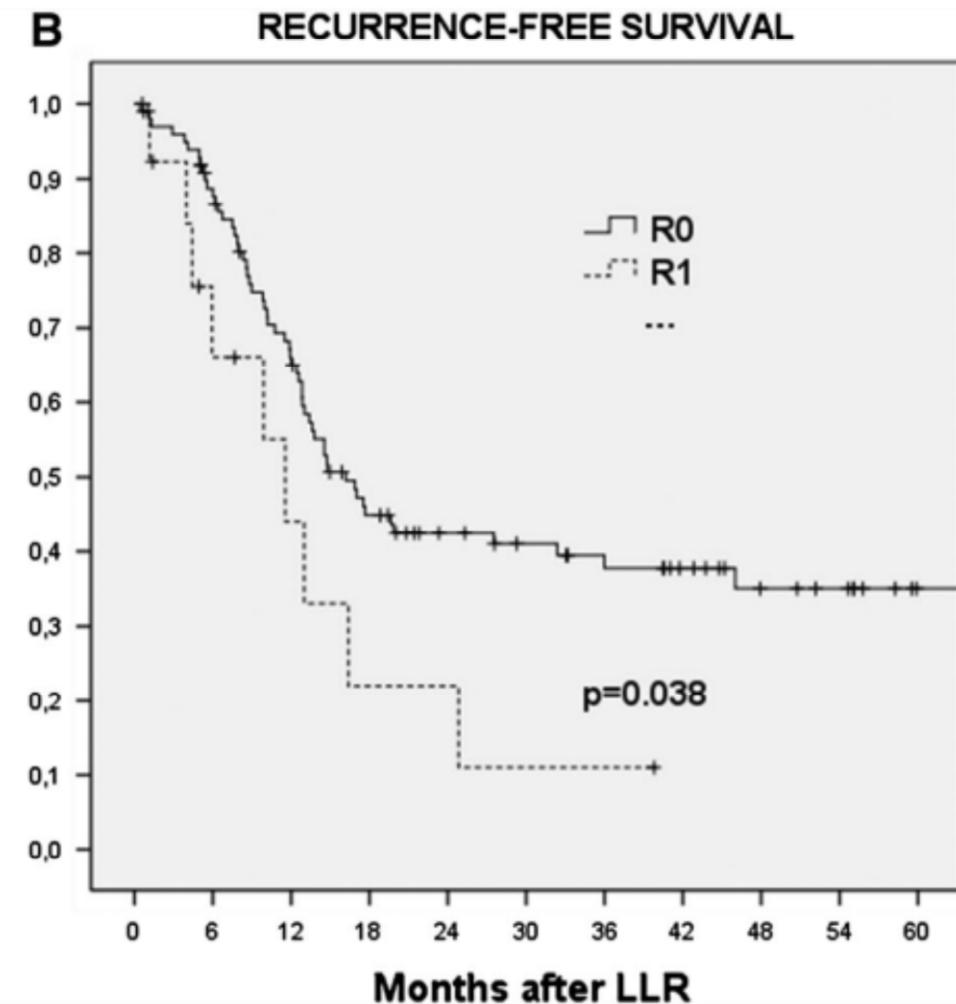


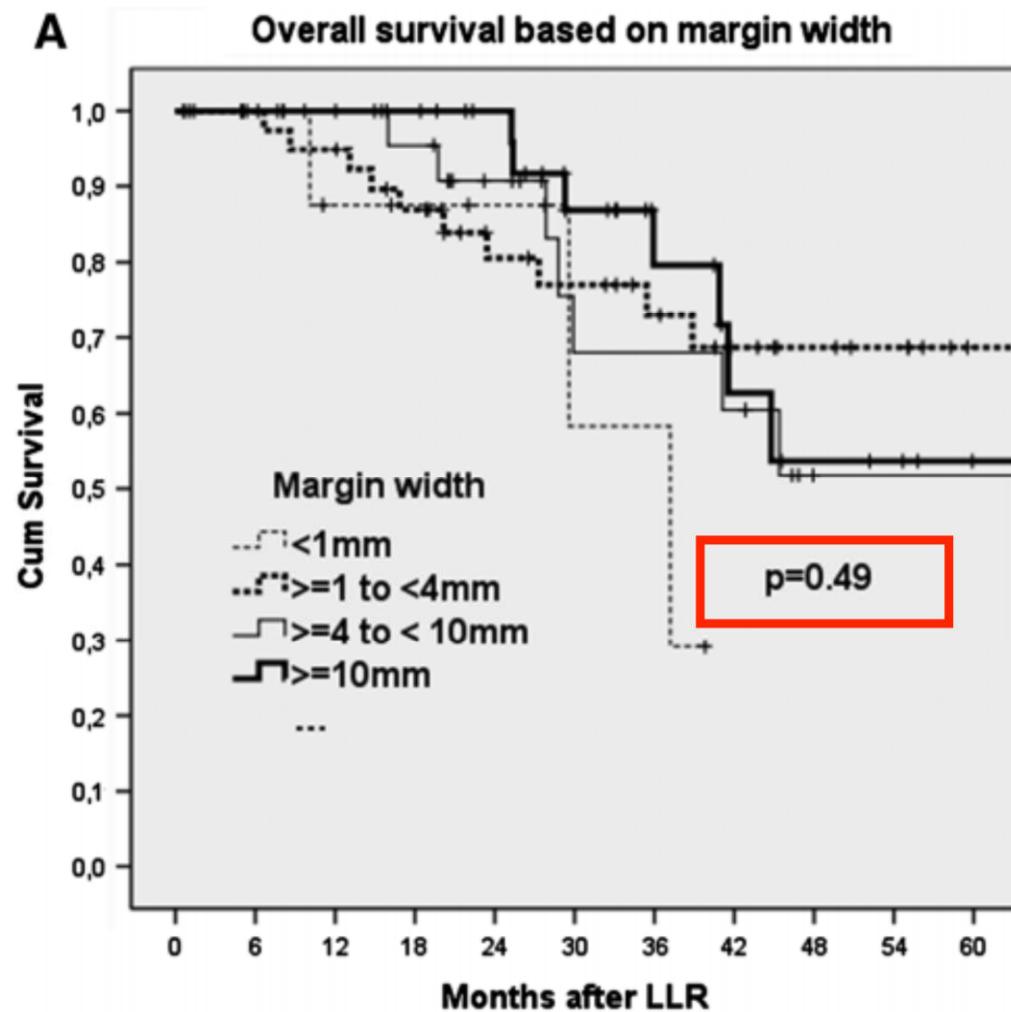
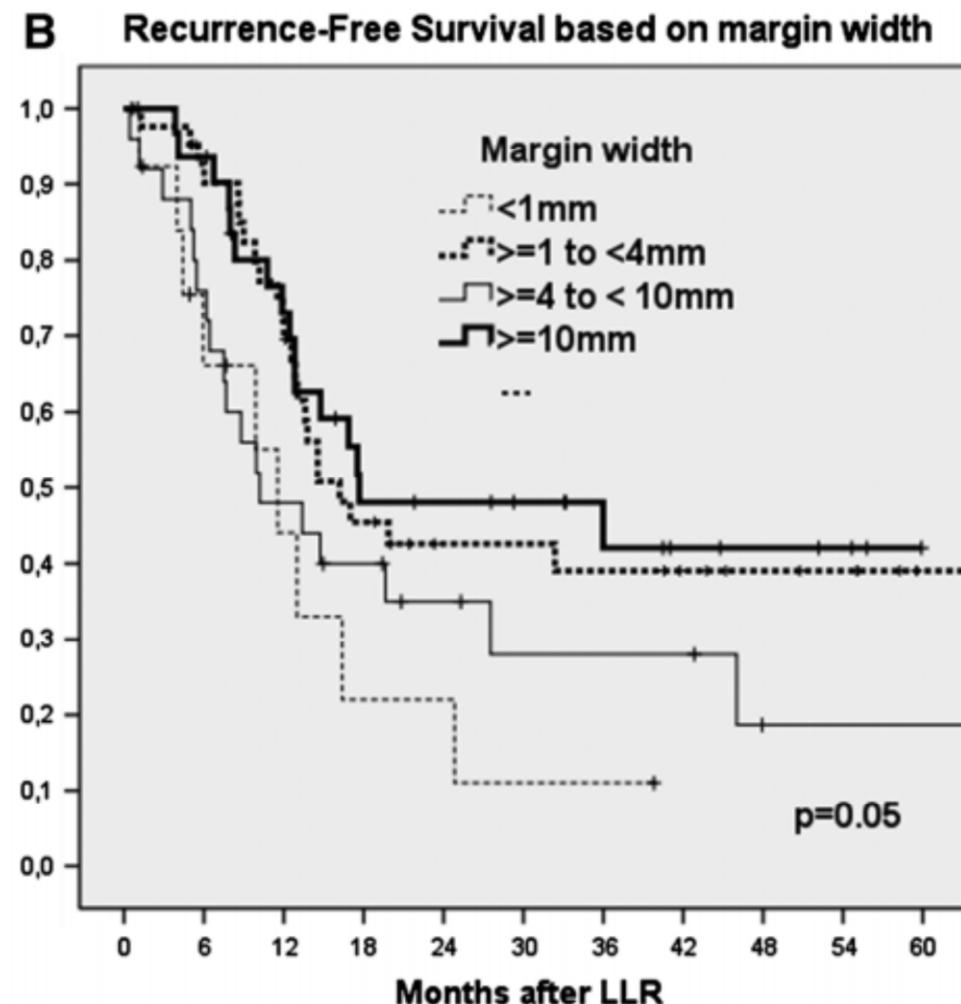
RAS mutations are associated with positive margins in patients undergoing resection of CLM. Tumors with RAS mutation should prompt careful efforts to achieve negative resection margins.

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



A**B**

A**B**

- 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®)

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

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

- ❑ 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.

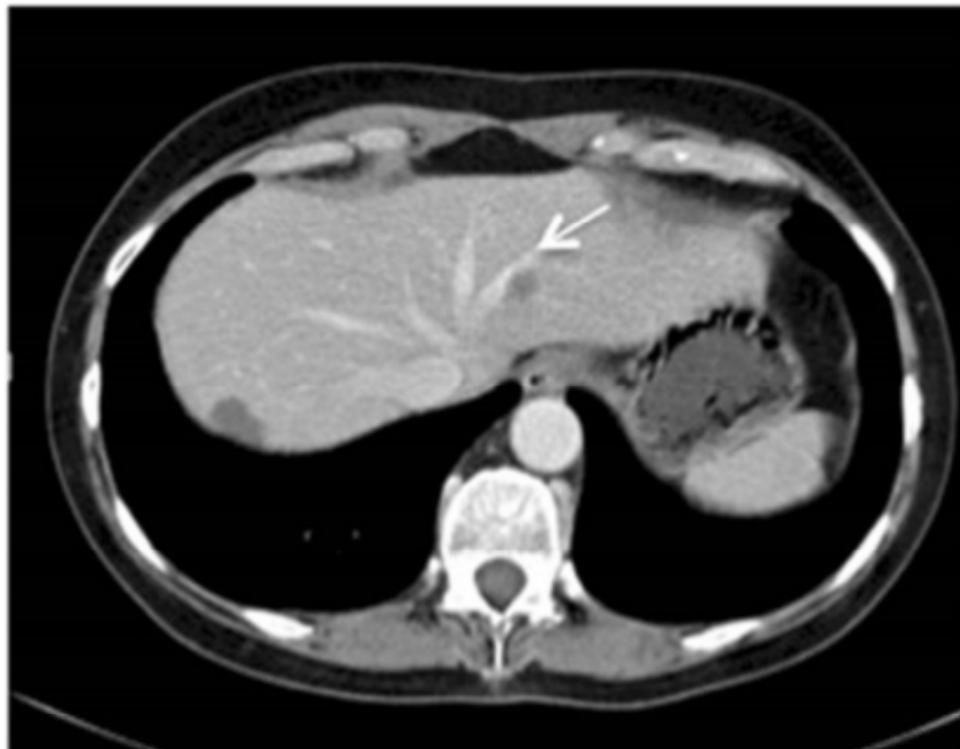
Safety analysis of the oncological outcome after vein-preserving surgery for colorectal liver metastases detached from the main hepatic veins

Federico Tomassini^{1,5} · Italo Bonadio^{1,6} · Peter Smeets² · Karen De Paepe¹ ·
Giampauro Berardi¹ · Liesbeth Ferdinand³ · Stéphanie Laurent⁴ ·
Louis J. Libbrecht³ · Karen Geboes⁴ · Roberto I. Troisi¹

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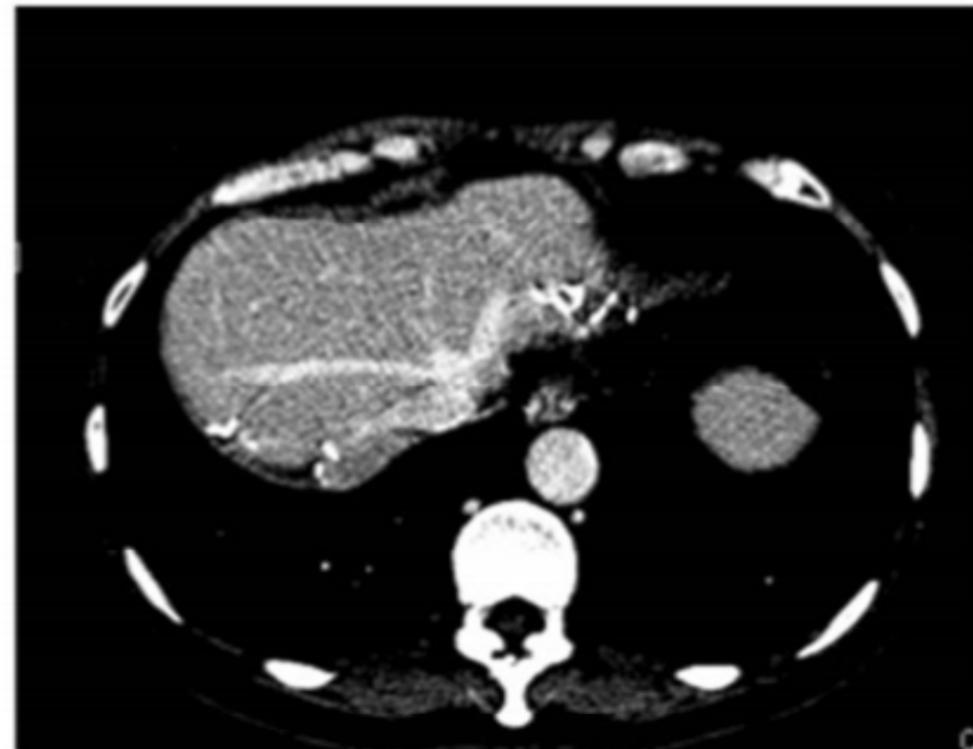
Pre-operative

A1. Preserving the Left Hepatic Vein (arrow)

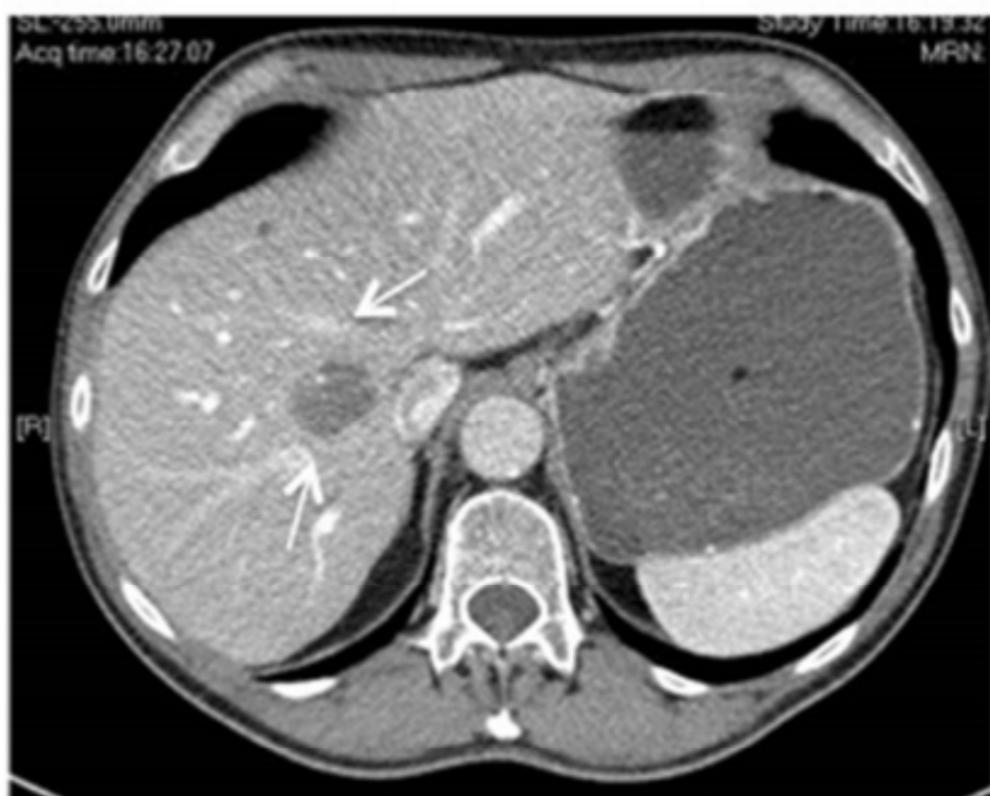


Post-operative

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

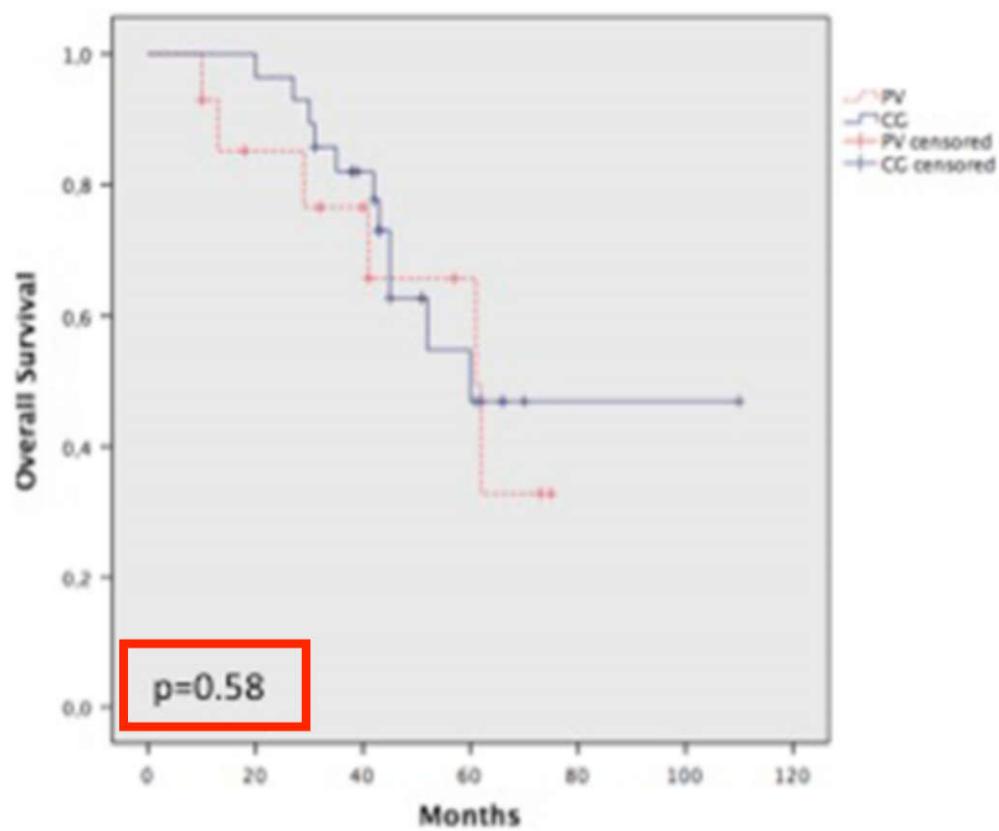
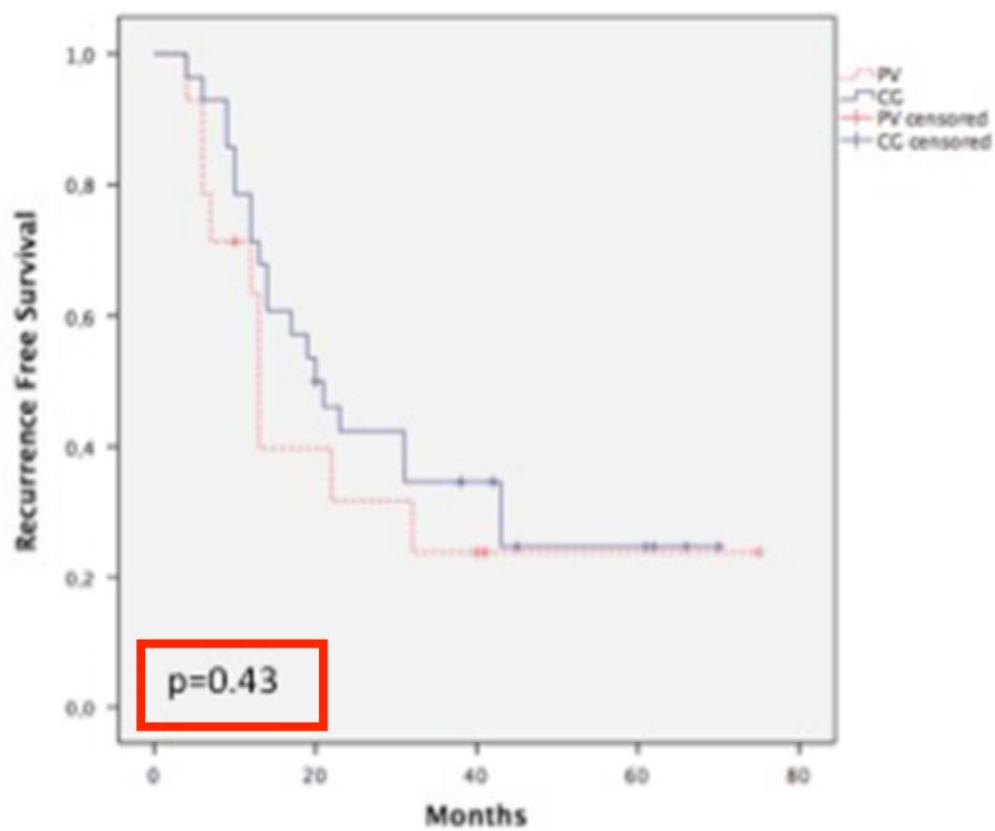


B1. Preserving Middle HV and Right HV (arrows)



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



a**b**

Recurrence patterns	VP (14)	CG (28)	<i>p</i>
Tumor recurrence, <i>n</i> (%)	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), <i>n</i> (%)	5/8 (62.5)	6/13 (46.0.3)	0.659
Third hepatectomy (redo-repeat), <i>n</i> (%)	2/5 (40)	0/6 (0)	0.182

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

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

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

Vascular margin

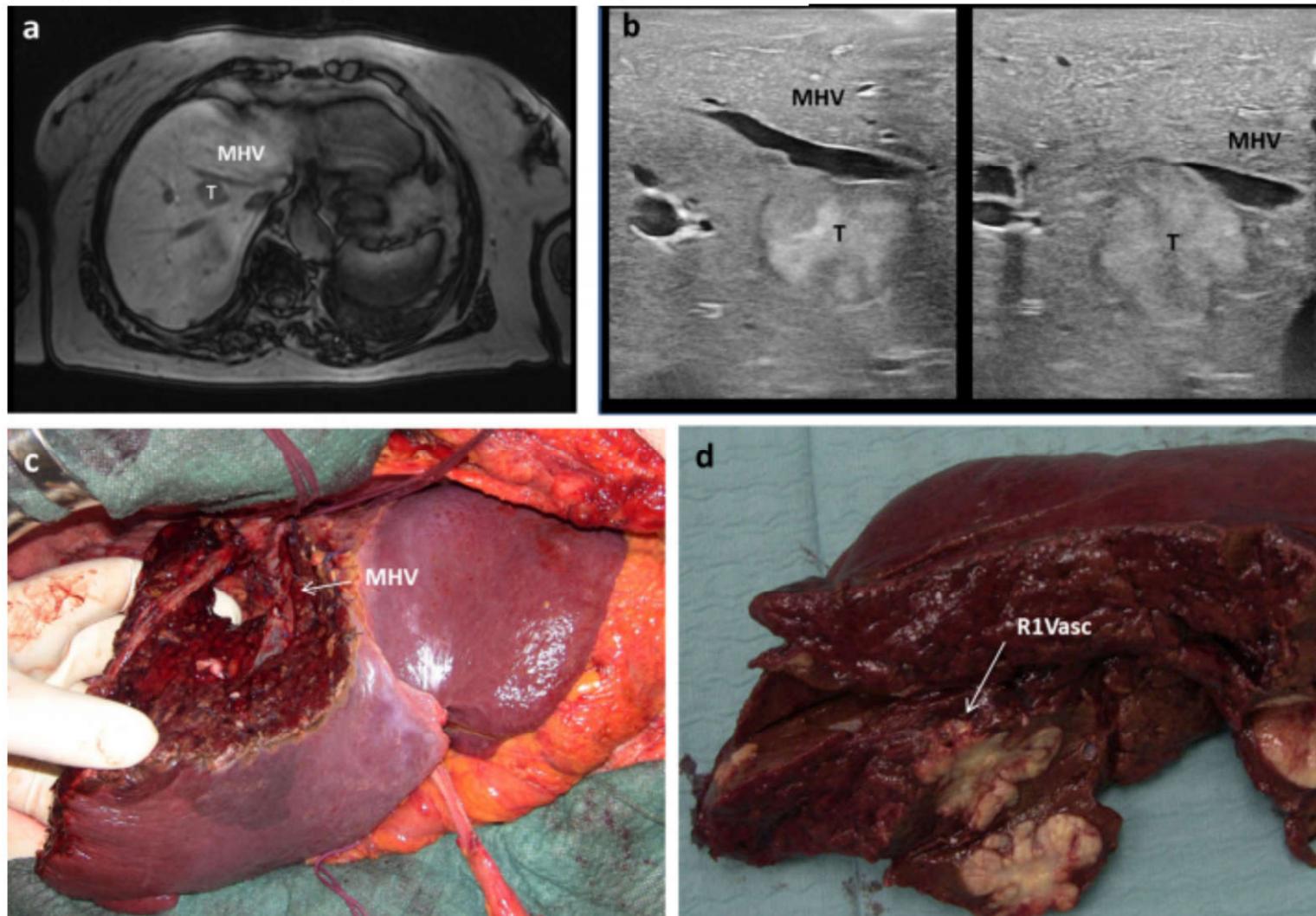
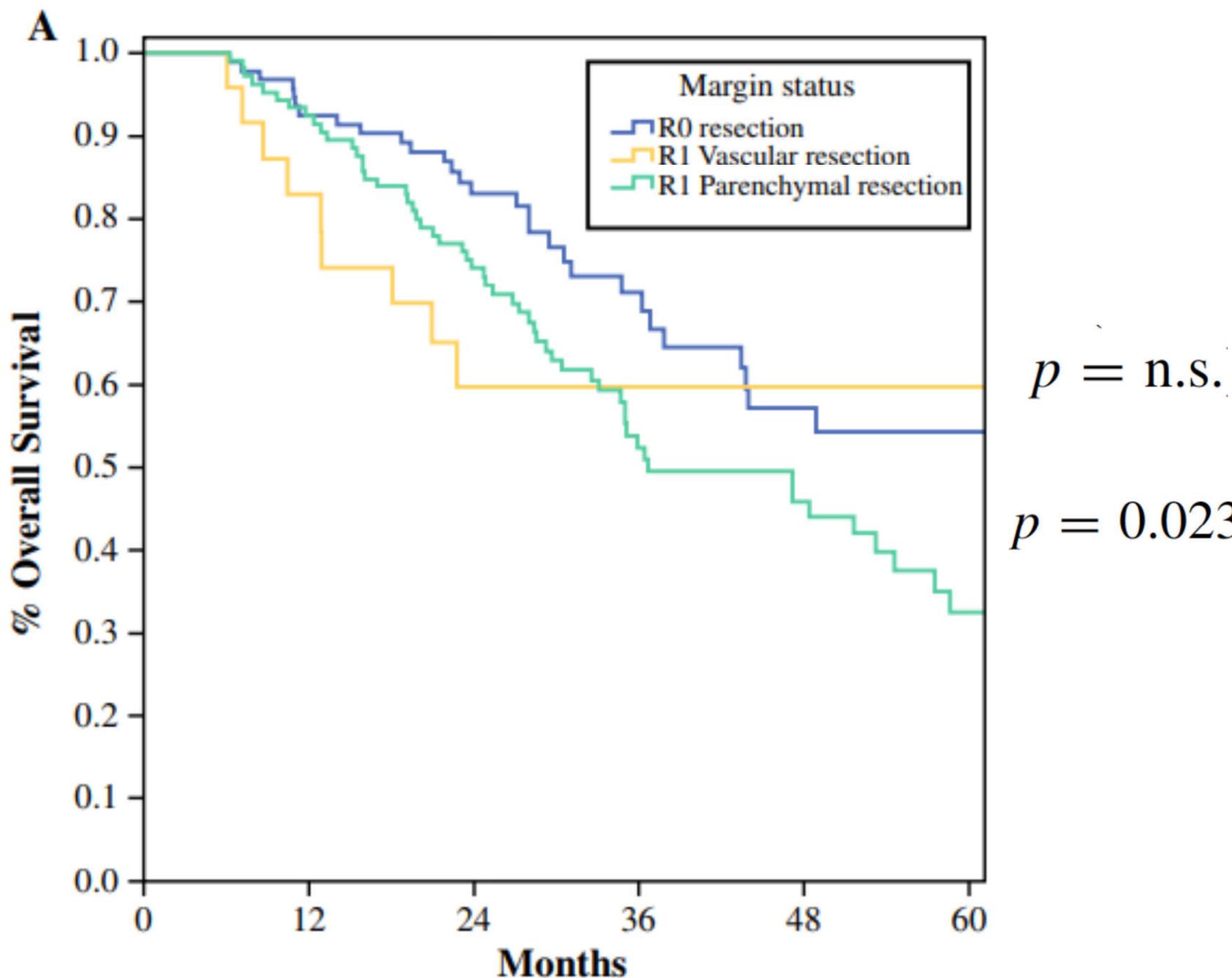
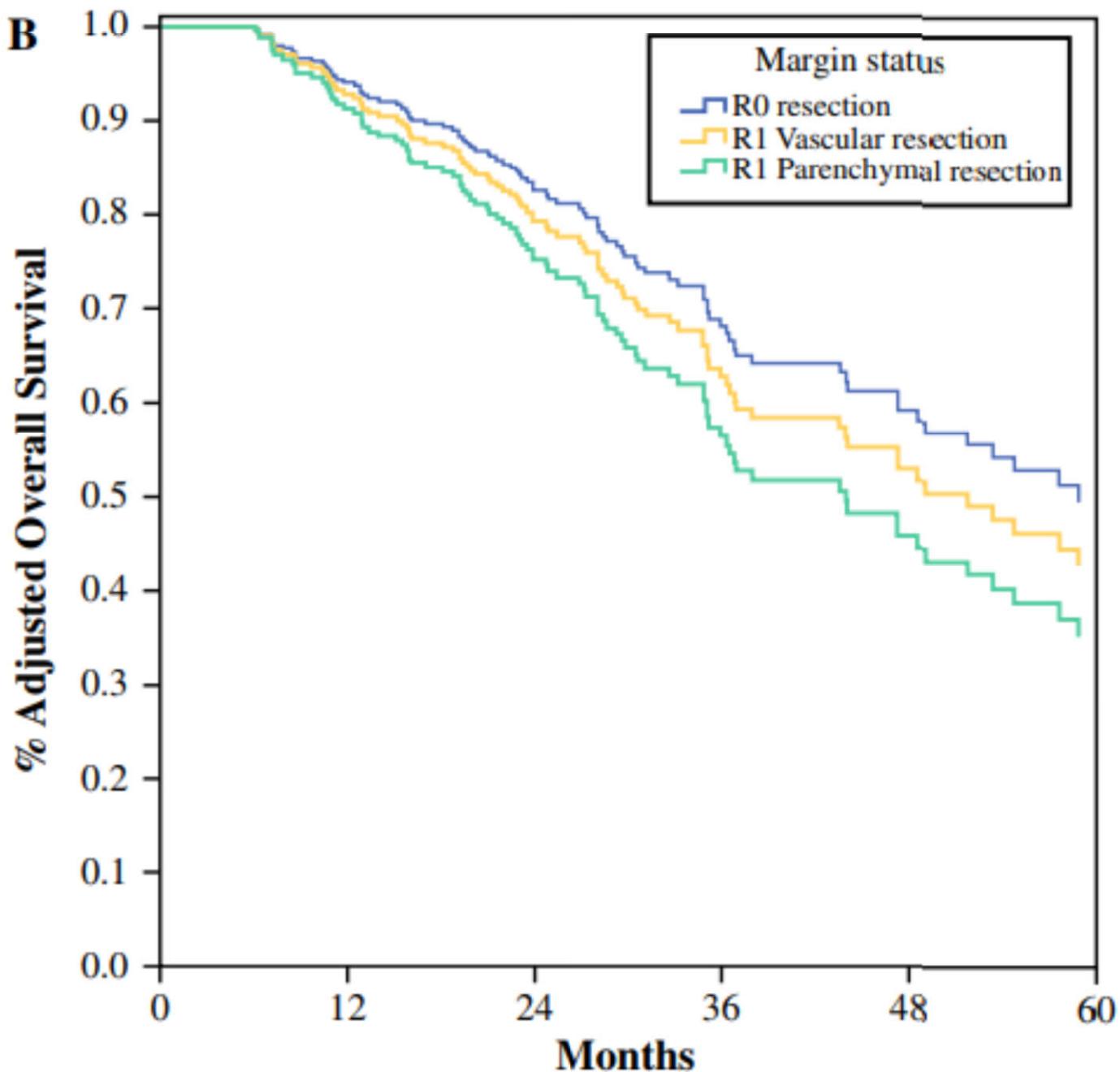
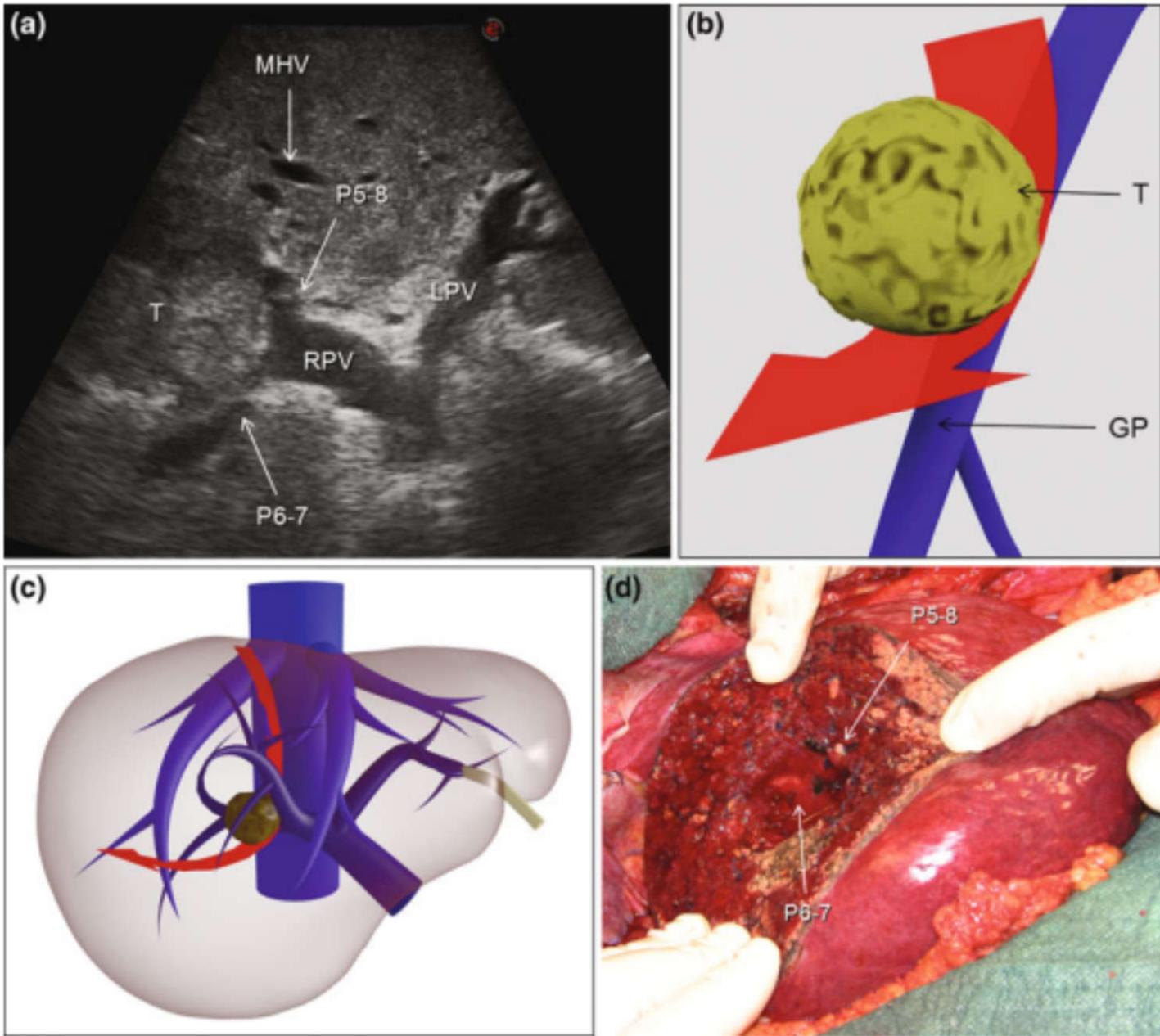


TABLE 3 Univariate and multivariate analysis of prognostic factors of OS after LR

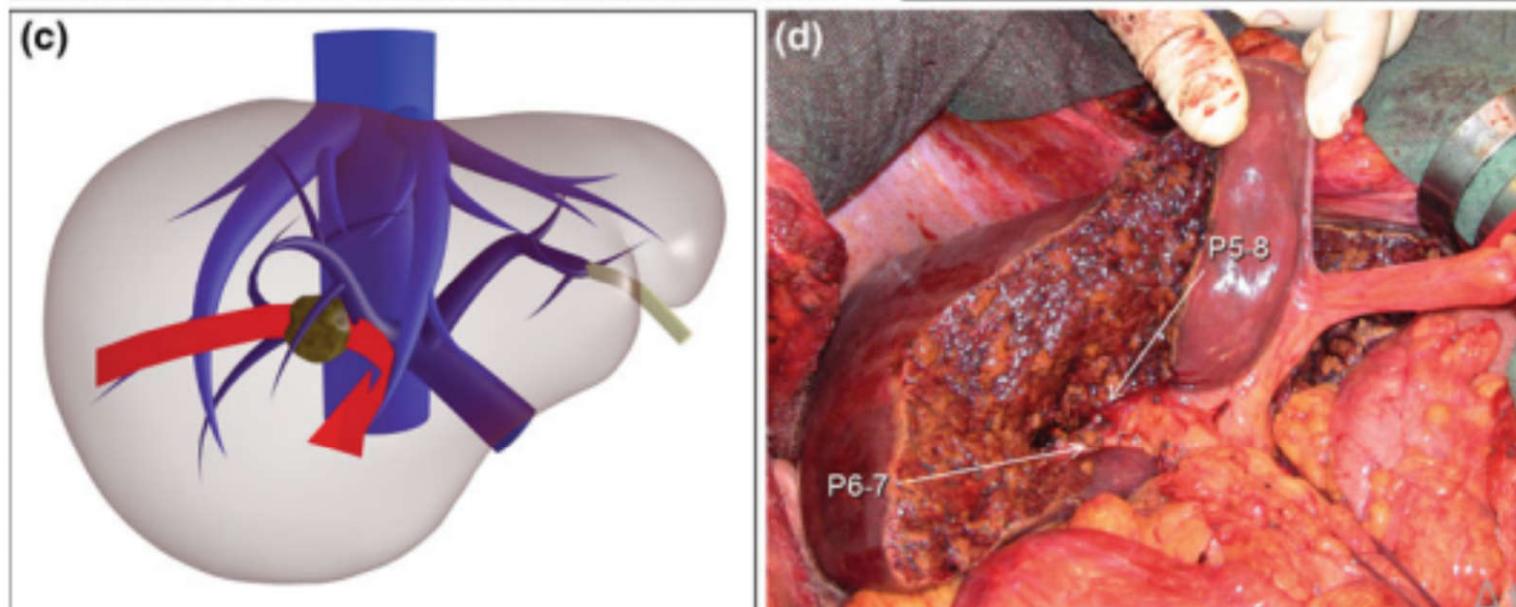
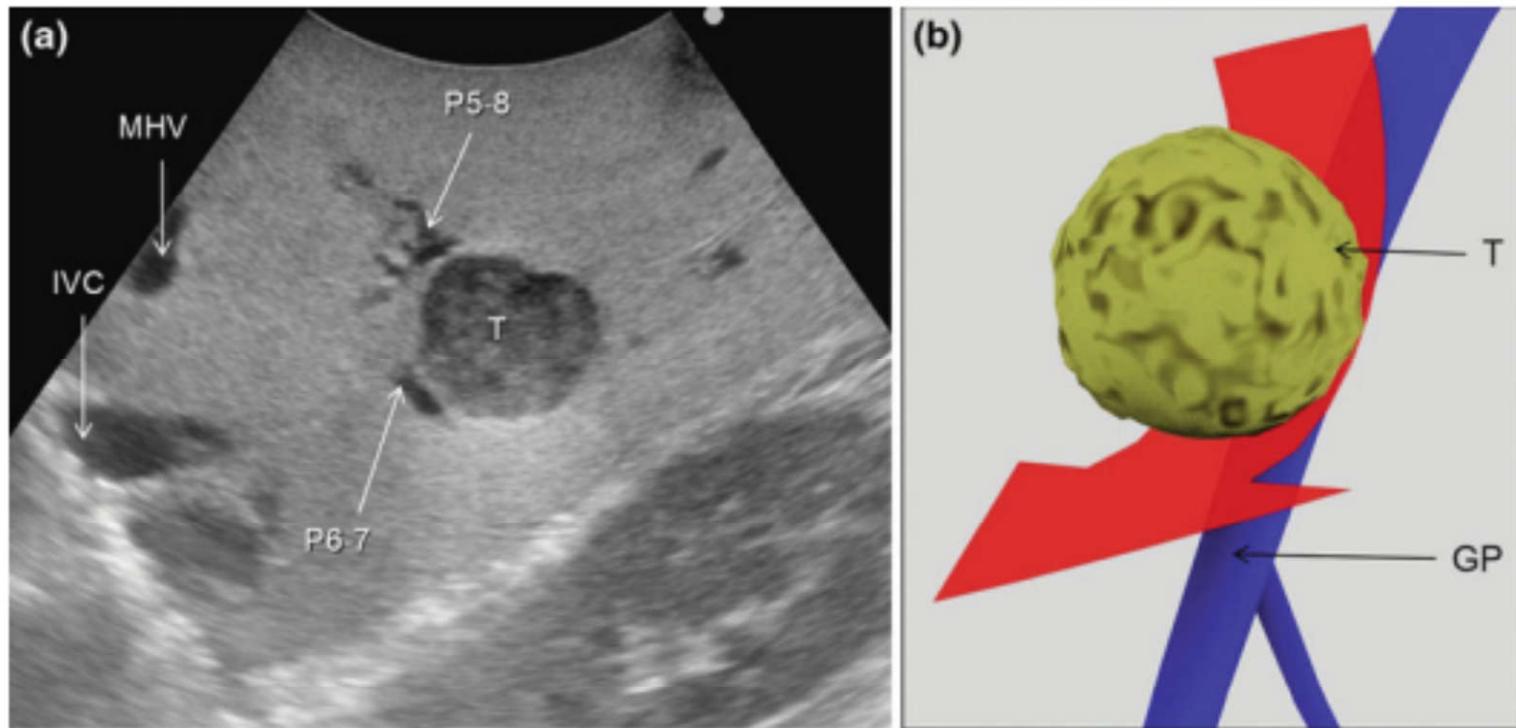
Parameter	Overall survival		Multivariate analysis <i>p</i>	RR (95 % CI)
	5-year OS (%)	Univariate analysis <i>p</i>		
Surgical margin				
R0	54.3	0.068		1
R1Vasc	59.4		n.s.	1.372 (0.644–2.922)
R1Par	32.5		0.034	1.627 (1.037–2.552)
Adjuvant chemotherapy				
Y	53.5	0.008	0.023	0.605 (0.393–0.933)
N	34.6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







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.



Thanks !



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