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INTERVENTIONAL

Ablation of colorectal liver metastasis: Interaction of ablation margins and *RAS* mutation profiling on local tumour progression-free survival

Marco Calandri[1] · Suguru Yamashita[2] · Carlo Gazzera[1] · Paolo Fonio[1] · Andrea Veltri[3] · Sara Bustreo[4] · Rahul A. Sheth[5] · Steven M. Yevich[5] · Jean-Nicolas Vauthey[2] · Bruno C. Odisio[5]

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Abstract

Objectives To investigate effects of ablation margins on local tumour progression-free survival (LTPFS) according to *RAS* status in patients with colorectal liver metastases (CLM).

Methods This two-institution retrospective study from 2005–2016 included 136 patients (91 male, median age 60 years) with 218 ablated CLM. LTPFS was performed using the Kaplan–Meier method and evaluated with the log-rank test. Uni/multivariate analyses were performed using Cox-regression models.

Results Three-year LTPFS rates for CLM with minimal ablation margin ≤10 mm were significantly worse than those with >10 mm in both mutant-*RAS* (29% vs. 48%, p=0.038) and wild-type *RAS* (70% vs. 94%, p=0.039) subgroups. Three-year LTPFS rates of mutant-*RAS* were significantly worse than wild-type *RAS* in both CLM subgroups with minimal ablation margin ≤10 mm (29% vs. 70%, p<0.001) and >10 mm (48% vs. 94%, p=0.006). Predictors of worse LTPFS were ablation margins ≤10 mm (HR: 2.17, 95% CI 1.2–4.1, p=0.007), CLM size ≥2 cm (1.80, 1.1–2.8, p=0.017) and mutant-*RAS* (2.85, 1.7–4.6, p<0.001).

Conclusions Minimal ablation margin and *RAS* status interact as independent predictors of LTPFS following CLM ablation. While minimal ablation margins >10 mm should be always the procedural goal, this becomes especially critical for mutant-*RAS* CLM.

Key Points

- *RAS and ablation margins are predictors of local tumour progression-free survival.*
- *Ablation margin > 10 mm, always desirable, is crucial for mutant RAS metastases.*
- *Interventional radiologists should be aware of RAS status to optimize LTPFS.*

Keywords Colorectal neoplasms · Metastasis · DNA mutational analysis · Interventional radiology · Ablation techniques

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✉ Bruno C. Odisio
bcodisio@mdanderson.org

[1] Radiology Institute, Department of Surgical Sciences, University of Turin, Città della Salute e della Scienza, Via Genova 3, 10126 Torino, Italy

[2] Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Houston, Texas, USA

[3] Radiology Unit, Oncology Department, San Luigi Gonzaga Hospital, University of Turin, Regione Gonzole, 10043 Orbassano, Italy

[4] Department of Medical Oncology 1, Città della Salute e della Scienza, Via Genova 3, 10126 Torino, Italy

[5] Department of Interventional Radiology, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Houston, Texas, USA

Abbreviations

CLM	Colorectal liver metastases
LTP	Local tumour progression
LTPFS	Local tumour progression-free survival
RAS	Rat sarcoma viral oncogene

Introduction

Percutaneous thermal ablation is an effective and widely utilized local treatment for patients with colorectal cancer liver metastases (CLM), usually reserved for poor surgical candidates [1–4]. Accordingly, in recognition of its role in the multidisciplinary management of colorectal oligometastatic disease, the recent consensus guidelines for metastatic colorectal cancer of the European Society for Medical Oncology classify both surgical resection and thermal ablation as 'local ablative treatments' [5].

In order to achieve optimal outcomes with respect to hepatic-progression-free and overall survival, a low rate of local tumour progression (LTP) following percutaneous ablation is of paramount importance [1, 3, 6]. In addition to known local factors such as small lesion size, adequate minimal ablation margins, absence of adjacent large blood vessels promoting a heat-sink effect and non-subcapsular tumour location [1, 7–9], other intrinsic tumour biomarkers have also been recently linked to improved LTP rates following percutaneous ablation [10].

Specifically, mutation of the rat sarcoma viral oncogene (*RAS*), a well-known downstream component of the epidermal growth factor receptor (EGFR) signalling network, has been associated with resistance to treatment with EGFR antibodies [11, 12] and with more infiltrating/migratory tumour characteristics of colorectal cancer cells [13]. In a recent study of patients who underwent hepatic resection, mutant *RAS* was associated with an increased number of positive or narrower resection margins [14]. Similarly, another recent study demonstrated that CLM patients with mutant *RAS* had shorter LTP-free survival (LTPFS) following percutaneous liver ablation when compared to CLM patients with wild-type *RAS* [10]. To date, it has been unclear whether achieving larger ablation margins in CLM patients according to *RAS* mutational status could affect LTP rates, and definitions with respect to the minimal acceptable ablation margin for CLM according to *RAS* mutational status are lacking in the current literature.

We therefore aimed to investigate the effect of different minimal ablation margins on LTP rates according to *RAS* mutational status in patients with CLM treated with percutaneous ablation.

Patients and methods

Study design

This two-institution retrospective study was compliant with the Health Insurance Portability and Accountability Act (HIPAA) and approved by the Institutional Review Board (IRB) from Institution A (The University of Texas MD Anderson Cancer Center) with a waiver of informed consent; IRB approval from Institution B (The University of Torino) provided consent for data handling by Institution A, in full respect of the Declaration of Helsinki.

The prospectively compiled interventional radiology liver ablation registries of the two institutions were retrospectively evaluated and updated by review of the electronic medical records to identify consecutive patients with known *RAS* mutational status who underwent percutaneous liver ablation for the treatment of CLM from 2005 through 2016.

Ablation eligibility criteria, patient selection and technique

Patients were eligible for percutaneous ablation if presenting with fewer than five CLM, measuring ≤ 5 cm each. Indication for ablation was discussed at the institutions' multidisciplinary tumour boards. Patients underwent percutaneous image-guided ablation if not a surgical candidate or in case of refusal to surgery. No oncological criteria were utilized for ablation eligibility. A total of 152 consecutive patients with CLM and known *RAS* mutational status who underwent percutaneous liver ablation were identified. Among these, 16 patients were excluded (combined ablation and transarterial chemoembolization, n=4; surgical resection following ablation, n=3; absence of cross-sectional imaging following ablation, n=4; residual unablated tumour after the first ablation session that was not treated with another ablation session, n=5). Patients with CLM with residual disease following percutaneous ablation were excluded from the present study in order to focus on the impact of ablation margins on LTPFS. After these exclusions, a total of 136 patients (mean age 60 years [range 28–92]) who were deemed not to be surgical candidates (131/136) or refused surgery (5/136), with 218 CLM (median size 1.8 cm [range 0.6–5.2]) were included in the analysis. The median follow-up period was 25.1 months. Of the 136 patients, 91 were male (mean age 62 years [range 38–84]), and 45 were female (mean age 61 years [range 28–92]). All ablations were performed with the intent to completely cover the CLM, but no minimal ablation margin criteria were applied during the study period. Ablations at Institution A were performed under general anaesthesia and computed tomography guidance by one of four interventional radiologists with radiofrequency (Cool-tip Ablation System, Covidien), microwave (Certus probe, Certus 140 2.45-GHz ablation system, Neuwave), or cryoablation (SeedNet MRI Cryoablation System, Galil Medical Inc.) systems according to the operator's choice. At Institution B, ablations were done under conscious sedation by one of two interventional radiologists with radiofrequency (Med-Italia RF system) or microwave (Amica System, HS Hospital Service) systems under ultrasound guidance (MyLab Twice, Esaote). Contrast-enhanced ultrasound was performed at the operator's discretion in case of poor ultrasound conspicuity by injecting 2.5 ml of SonoVue (Bracco, Milan, Italy).

For immediate post-ablation imaging control, contrast medium-enhanced CT was performed at the end of the ablation at Institution A whereas US examination (and CEUS if required) was performed at Institution B. In both Institutions, additional ablation was performed in the same session, if deemed necessary.

Patients were discharged within 24 h after the treatment at both institutions.

Standardized terminology and reporting criteria for tumour ablation were utilized to determine ablation endpoints [15].

Residual unablated tumour was defined as the presence of peripheral or nodular enhancement within 1 cm of the ablated area at the first imaging follow-up (triple-phase contrast-enhanced computed tomography [CT] or magnetic resonance [MR]). LTP was defined as the appearance of tumour foci at the edge of the ablation zone or within 1 cm after at least one cross-sectional imaging had demonstrated complete ablation.

RAS mutational analysis

The specimens used for analysis originated either from the primary tumour or from the liver metastases; previous reports have shown a high concordance rate of *RAS* mutational status between those two sites [16, 17]. Formalin-fixed, paraffin-embedded tissue was used to extract DNA that subsequently underwent a routine PCR-based primer extension assay and mass spectrometry. Screening for mutations in *KRAS* codons 12 and 13 was performed in all patients, whereas screening for mutations in *KRAS* codons 59, 61, 117 and 146 and *NRAS* codons 12, 13, 18, 59, 61, 117 and 146 was performed in the majority of patients in the last 5 years of the study. *KRAS* and *NRAS* single mutations in the various codons were analysed together and reported as *RAS* mutations.

Assessment of tumour recurrence

All available pre- and post-ablation cross-sectional imaging was evaluated by two independent radiologists at each institution (B.C.O. and S.Y for institution A, with 8 and 7 years of experience, respectively; and C.G and M.C. for institution B, with 20 and 5 years of experience, respectively) blinded to the *RAS* mutational status. Disagreements in interpretation were resolved by consensus. The initial post-ablation cross-sectional contrast-enhanced imaging study to assess the efficacy of ablation was performed with CT or MR imaging within 4–6 weeks after the ablation procedures. Minimal ablation margin evaluation on the three orthogonal planes was performed as previously described [8] using the first cross-sectional contrast-enhanced imaging study following ablation. The minimal ablation margin achieved in all three-dimensional axes was utilized to categorize the ablated CLM as having ≤10 mm or >10 mm of minimal ablation margin, according to a recent panel of experts' recommendation [18]. After the first CT/MR post-ablation assessment, controls were performed every 3–6 months until patient death or loss to follow-up.

Statistical analysis

LTPFS was defined as the time interval between initial ablation and the first radiographic evidence of LTP for each ablated CLM. Continuous variables were compared using the Wilcoxon rank sum test, and categorical variables with the $\chi 2$ test. Survival curves were generated with the Kaplan-Meier method and evaluated with the log rank test. Univariable and multivariable analyses were performed using Cox regression models. Multivariable analysis was performed with the variables with $p<0.1$ at univariable analysis. In any case, an analysis was considered statistically significant if $p<0.05$. Statistical analysis was performed with JMP software (version 12.1.0; SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics

RAS mutation was detected in 54 (39.7 %) of the 136 patients, who harboured a total of 80 ablated CLM. At the time of analysis, 38 (17 %) of the total 218 ablated CLM demonstrated LTP (mutant RAS, n=22; wild-type RAS, n=16). Of those, ten CLM were retreated with ablation (mutant *RAS*, n=3; wild-type *RAS*, n=7), and 28 (mutant *RAS*, n=19; wild-type *RAS*, n=9) were not eligible for re-ablation due to either progression in an additional location (n=14) or technical infeasibility (n=14).

Baseline differences between the patient groups at Institutions A and B are reported in Supplementary Table 1. At Institution A, prior hepatic CLM resection was more frequent, the time from diagnosis of the primary tumour to discovery of the treated CLM was longer, and patients had received more lines of pre-ablation chemotherapy (all $p<0.001$). The median size of the CLM at the time of ablation was slightly larger at Institution B (1.8 vs. 1.5 cm, $p=0.007$) (Supplementary Table 2). Institution A used different percutaneous thermal ablation modalities depending on tumour location and adjacent vascular structures, whereas radiofrequency was by far the most used technology at Institution B ($p<0.001$) (Supplementary Table 2). No differences were noted in terms of the site of the lesion (subcapsular or in proximity to vessels), frequency of minimal ablation margins or frequency of *RAS* mutational status.

The overall baseline patient characteristics and primary tumour stratification according to *RAS* mutational status are described in Table 1. The mutant *RAS* group trended for a less frequent history of hepatic resection prior to ablation and, in those cases with prior hepatic resection, shorter time interval between the last hepatic resection and ablation. Also, there was a trend ($p=0.065$) for repeated ablation sessions in patients with mutant *RAS*. Other relevant demographic or clinical characteristics did not differ significantly between patients with mutant *RAS* and wild-type *RAS* CLM.

Local outcomes assessment

The overall actuarial 1- and 3-year LTPFS rates for all 218 ablated CLM were 79 % and 62 %, respectively. Treatment characteristics and rates of LTP according to *RAS* mutational

Table 1 Patient, primary tumour and systemic treatment characteristics according to *RAS* mutational status for 136 patients who underwent ablation for colorectal liver metastasis

	Total (n=136)	Wild-type *RAS* (n=82)	Mutant *RAS* (n=54)	*P*§
Age at CLM ablation (years)*	60 (28–92)	61 (33–92)	58 (28–84)	0.361¶
Sex ratio (M: F)	91: 45	58: 24	33: 21	0.243
Primary tumour				0.450
Colon	109 (80)	64 (78)	45 (83)	
Rectum	27 (20)	18 (22)	9 (17)	
Lymph node metastases	95 (70)	54 (66)	41 (76)	0.210
Time from diagnosis of primary to discovery of CLM treated with ablation (months)*	15 (0–295)	17 (0–295)	13 (0–93)	0.166¶
History of hepatic resection before ablation	67 (49)	45 (55)	22 (41)	0.107
Time from last hepatic resection to ablation (months)*	11 (0.4–125)	13 (0.4–125)	8.0 (0.9–28)	0.080¶
Pre-ablation chemotherapy	75 (55)	44 (54)	31 (57)	0.667
≤ 6 cycles	37 (49)	19 (43)	18 (58)	0.204
≥ 2 regimens	15 (20)	11 (25)	4 (13)	0.197
Fluorouracil-based regimen				
Oxaliplatin	45 (60)	23 (52)	22 (71)	0.101
Irinotecan	27 (36)	18 (41)	9 (29)	0.291
Use of bevacizumab	43 (57)	24 (55)	19 (61)	0.561
Interval from CLM discovery to ablation (days)*	126 (4–1397)	127 (5–828)	125 (4–1397)	0.936¶
CEA level at ablation (ng/ml)*	3.7 (0.6–3258)	3.7 (0.7–186)	3.8 (0.6–3258)	0.535¶
Clinical risk score†				0.183
0–1	75 (55)	49 (60)	26 (48)	
≥ 2	61 (45)	33 (40)	28 (52)	
Post-ablation chemotherapy	74 (54)	42 (51)	32 (59)	0.357

CLM colorectal liver metastasis, *CEA* carcinoembryonic antigen

§χ^2 test, except ¶Wilcoxon rank sum test

Values are numbers of patients with percentages in parentheses unless indicated otherwise

*Values are median (range)

†Defined by a disease-free interval from primary to liver metastasis of 12 months or less, more than one liver tumour, largest hepatic metastasis at least 5 cm, CEA level above 200 ng/ml, and presence of extrahepatic disease (Fong et al., Ann Surg, 1999)

status per ablated CLM are shown in Table 2. LTPFS rates of the lesions with mutant *RAS* were significantly lower than those with wild-type *RAS* in both subgroups of ablation margin ≤10 mm (3-year LTPFS, 29 % [mutant *RAS*] vs. 70 % [wild-type *RAS*], $p<0.001$) and ablation margin >10 mm (3-year LTPFS, 48 % [mutant *RAS*] vs. 94 % [wild-type *RAS*], $p=0.006$) (Fig. 1). The LTPFS rates of the lesions with an ablation margin ≤10 mm were significantly worse than those with an ablation margin >10 mm in both subgroups of mutant *RAS* (3-year LTPFS, 29 % [ablation margin ≤10 mm] vs. 48 % [ablation margin >10 mm], $p=0.038$) and wild-type *RAS* (3-year LTPFS, 70 % [ablation margin ≤10 mm] vs. 94 % [ablation margin >10 mm], $p=0.039$) (Fig. 1).

On multivariable analysis, independent predictors of worse LTPFS were minimal ablation margins ≤10 mm (HR: 2.17, 95 % CI: 1.22–4.12, $p=0.007$), CLM size ≥2 cm (HR: 1.80, 95 % CI: 1.11–2.89, $p=0.017$), and mutant *RAS* (HR: 2.85, 95 % CI: 1.74–4.69, $p<0.001$) (Table 3).

Discussion

In this study, we demonstrated that both a minimal ablation margin ≤ 10 mm and mutant *RAS* status are independent predictors for worse LTPFS following CLM ablation. Moreover, we also demonstrated that, despite the worse prognosis associated with mutant *RAS* CLM, achieving minimal ablation margins > 10 mm significantly improves LTPFS rates. Until now, limited attention has been given to the impact of colorectal tumour biology on the outcomes of percutaneous thermal ablation as a means for locoregional control of oligometastatic colorectal cancer. Our study provides pertinent information regarding the interaction of minimal ablation margins and *RAS* mutational status on LTPFS following percutaneous thermal ablation of CLM. Overall, mutant *RAS* CLM represented 37 % (80/218) of our ablated CLM, but contributed to 58 % (22/38) of all the LTP events. Furthermore, when the same minimal ablation margins were achieved for wild-type and mutant *RAS* CLM, the latter demonstrated significantly worse LTPFS. This suggests that *RAS* mutational status is an independent prognosticator for LTPFS regardless of the minimal ablation margins, and emphasizes the criticality of tumour biology on locoregional control outcomes following liver-directed therapies for CLM.

Although the mutant *RAS* CLM group demonstrated worse LTPFS, improved outcomes were achieved with statistical significance when minimal ablation margins >10 mm were achieved (3-year LTPFS, 48 % [mutant *RAS* with ablation

Table 2 Tumour and treatment characteristics according to *RAS* mutational status for the 218 ablated colorectal liver metastases (CLM)

	Total (n=218)	Wild-type *RAS* (n=138)	Mutant *RAS* (n=80)	*p*-value§
Ablation modality				0.406
Radiofrequency	73 (33)	49 (36)	24 (30)	
Others	145 (67)	89 (64)	56 (70)	
No. of ablation sessions				0.065
1	124 (57)	85 (62)	39 (49)	
≥ 2	94 (43)	53 (38)	41 (51)	
Minimal ablation margins (mm)				0.637
0 - 10	158 (72)	103 (75)	55 (69)	
> 10	60 (28)	35 (25)	25 (31)	
Ablated lesion adjacent to major vessel(s)‡	51 (23)	35 (25)	16 (20)	0.367
Liver metastases				
Timing of occurrence				0.101
Synchronous	104 (48)	60 (43)	44 (55)	
Metachronous	114 (52)	78 (57)	36 (45)	
Tumour size at ablation (cm)*	1.6 (0.5–5.2)	1.6 (0.5–5.2)	1.6 (0.6–4.2)	0.571¶
No. of tumours				0.357
1	92 (42)	55 (40)	37 (46)	
≥ 2	126 (58)	83 (60)	43 (54)	
Subcapsular lesion	117 (54)	76 (55)	41 (51)	0.585
Concomitant extrahepatic metastases	43 (20)	22 (16)	21 (26)	0.065
Post-ablation chemotherapy	125 (57)	76 (55)	49 (61)	0.374
Local tumour progression	38 (17)	16 (12)	22 (28)	0.003

Values in parentheses are percentages unless indicated otherwise

*Values are median (range)

‡Major vessel was defined as a vessel more than 3 mm in diameter

§χ^2 test, except ¶Wilcoxon rank sum test

margins >10 mm] vs. 29 % [mutant *RAS* with ablation margins ≤10 mm], p=0.038). Relevantly, there was no significant difference in LTPFS between mutant *RAS* CLM with >10 mm margins and wild-type *RAS* CLM with ≤10 mm margins. These findings support the hypothesis of a more infiltrative behaviour of mutant *RAS* CLM, as demonstrated at the molecular level [13], and by the present surgical literature with respect to the association between mutant *RAS* and positive surgical resection margins (11.4 % [mutant *RAS*] vs. 5.4 % [wild-type *RAS*], p=0.007) [14].

Interestingly, other factors traditionally reported to be associated with the oncological outcome, such as nodal status of the primary colorectal cancer, pre-ablation carcinoembryonic antigen level and metachronous/synchronous CLM seemed to

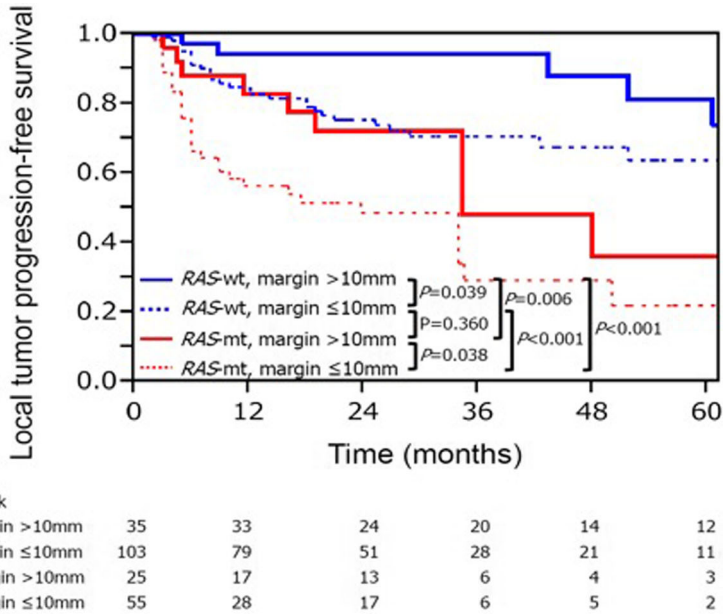

Fig. 1 Kaplan-Meier curves for local tumour progression-free survival (LTPFS) according to *RAS* and minimal ablation margin. *wt* wild-type, *mt* mutated

Table 3 Univariable and multivariable analyses of local tumour progression-free survival for the 218 ablated colorectal liver metastases (CLM)

	No. of tumours (n = 218)	Local tumour progression-free survival (%)*		Univariable p-value†	Multivariable	
		1 year	3 years		Hazard ratio (95 % CI)	p-value‡
Age (years)						
< 60	99	73	54	0.054	1.27 (0.77–2.09)	0.343
≥ 60	119	84	69			
Sex						
M	144	80	68	0.278		
F	74	78	53			
Primary tumour						
Colon	169	76	64	0.805		
Rectum	49	90	52			
Positive metastatic node of primary tumour						
Yes	153	80	66	0.529		
No	65	76	56			
Timing of CLM						
Synchronous	104	82	61	0.232		
Metachronous	114	76	62			
Pre-ablation chemotherapy						
Yes	124	80	56	0.384		
No	94	78	72			
No. of pre-ablation chemotherapy cycles						
> 6	57	75	59	0.179		
≤ 6	161	81	64			
Fluorouracil-based chemotherapy regimen						
Oxaliplatin						
Yes	72	78	46	0.053	1.18 (0.69–2.01)	0.556
No	146	79	74			
Irinotecan						
Yes	43	74	57	0.190		
No	175	80	63			
Use of bevacizumab						
Yes	68	75	46	0.033	1.21 (0.70–2.05)	0.490
No	150	81	72			
Use of anti-EGFR agents						
Yes	19	89	84	0.117		
No	199	78	61			
Time from discovery of CLM to ablation (days)						
> 120	113	78	61	0.149		
≤ 120	105	81	64			
Ablation type						
Others	73	69	59	0.219		
Radiofrequency	145	84	64			
Minimum ablation margin (mm)						
≤ 10	158	75	56	0.012	2.17 (1.22–4.12)	0.007
> 10	60	90	79			
Location of lesion						
Subcapsular	117	75	61	0.570		
Non-subcapsular	101	83	65			
CEA level at ablation (ng/ml)						
≥ 5	78	77	59	0.676		
< 5	140	80	65			
Maximum CLM diameter at ablation (cm)						
≥ 2	78	74	57	0.026	1.80 (1.11–2.89)	0.017
< 2	140	82	66			
Ablated lesion adjacent to major vessel(s)						
Yes	51	81	56	0.370		
No	167	78	65			
No. of liver metastases						
1	92	82	65	0.785		
≥ 2	126	77	60			
Concomitant extrahepatic metastases						
Yes	43	85	53	0.557		
No	175	77	66			
RAS status						
Mutant	80	65	35	<0.001	2.85 (1.74–4.69)	<0.001

Table 3 (continued)

	No. of tumours (n = 218)	Local tumour progression-free survival (%)*		Univariable p-value†	Multivariable	
		1 year	3 years		Hazard ratio (95 % CI)	p-value‡
Wild-type	138	87	77			
Clinical risk score§						
0–1	93	79	62	0.733		
≥ 2	125	79	63			
Post-ablation chemotherapy						
Yes	125	79	62	0.979		
No	93	80	63			

CI confidence interval, *CLM* colorectal liver metastasis, *EGFR* epidermal growth factor receptor, *CEA* carcinoembryonic antigen

§Defined by a disease-free interval from primary to liver metastasis of 12 months or less, more than one liver tumour, largest hepatic metastasis at least 5 cm, CEA level above 200 ng/ml, and presence of extrahepatic disease (Fong et al., Ann Surg, 1999)

*Kaplan-Meier analysis

†log rank test

‡Cox regression model

be of less significance for predicting LTPFS when compared to *RAS* mutational status and minimal ablation margins.

The impact of *RAS* mutational status on LTPFS in our retrospective cohort appears to be independent of study design and different procedural techniques between the two institutions, which are in keeping with the current literature. Critique on the variability in ablated CLM size and minimal ablation margin dimensions should be addressed, as both elements are known local factors associated with worse local tumour control following percutaneous ablation [1, 3, 8, 9]. In our study, lesion size was confirmed as a strong predictor of LTP in both univariable and multivariable analyses, but did not affect comparative analysis of *RAS* mutation variants as demonstrated on the uni- and multivariate analyses. As for ablation margins, there was no consensus regarding acceptable minimum ablation margins among the practitioners within our two Institutions during the span of our 11-year study accrual (2005–2016). Recently, a panel of experts evaluated adequate ablation margins for CLM and recommended with strong consensus ablation margins of at least 1 cm in order to maximize local tumour control [18]. Although the percentage of treated CLM with minimal ablation margin >10 mm in our cohort may appear modest (28 % [60/218]), this is in line with the literature [1], and also displayed no statistical significance in the uni- and multivariate analyses between the *RAS* mutation variants. Furthermore, despite the apparent technical unconformity for minimal ablation margins to the current recommendations, our overall incidence of LTP, 17 % (38/218), and the median LTPFS period of 21.7 months are within historical ranges for CLM ablation, with LTP incidence reported between 2.8 % and 37 % in similar mean follow-up periods of 16–26 months [19–21].

Our present study has some limitations. First, its retrospective design may have predisposed for selection bias of patients in whom *RAS* mutational status had been determined; however, percutaneous ablation and imaging assessment for ablation margins and LTP were performed blinded to the *RAS* mutational status. Second, the variable pre-ablation chemotherapeutic regimens administered for 55 % of our patient cohort might have affected local tumour control; however, no statistically significant differences were identified between wild-type and mutant *RAS* patients with regard to use, type and frequency of chemotherapy. Finally, the correlation of *RAS* mutational status and frequency of residual unablated tumours was not evaluated since our study design intentionally excluded patients with residual unablated tumours in order to focus on the interaction of RAS mutational status and minimal ablation margins on LTPFS rates.

In conclusion, the present study supports *RAS* mutational status as an independent prognosticator for LTPFS following ablation of CLM as demonstrated by worse LTPFS rates among mutant *RAS* CLM when compared to wild-type RAS CLM with similar minimal ablation margins. Moreover, achieving minimal ablation margins >10 mm provide significantly improved LTPFS among mutant RAS CLM. Therefore, while a minimal ablation margin >10 mm remains the optimal goal for CLM ablation in general, this becomes especially critical when treating mutant *RAS* CLM. Taken together, our findings support the criticality of *RAS* mutational status profiling for planning the best treatment strategy for patients with CLM.

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Bruno Odisio.

Conflict of interest The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article.

Statistics and biometry One of the authors has significant statistical expertise.

Informed consent Written informed consent was obtained from all subjects (patients) in this study.

Ethical approval Institutional Review Board approval was obtained.

Study subjects or cohorts overlap Some study subjects have been partially previously reported in one paper: Odisio BC, Yamashita S, Huang SY, et al (2017) Br J Surg 104:760–768

Methodology
- retrospective
- observational
- multicentre study

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