Radiological imaging markers predicting clinical outcome in patients with metastatic colorectal carcinoma treated with regorafenib: post hoc analysis of the CORRECT phase III trial (RadioCORRECT study)

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ABSTRACT

Objective To identify imaging markers predicting clinical outcomes to regorafenib in metastatic colorectal carcinoma (mCRC).

Methods The RadioCORRECT study is a post hoc analysis of a cohort of patients with mCRC treated within the phase III placebo-controlled CORRECT trial of regorafenib. Baseline and week 8 contrast-enhanced CT were used to assess response by RECIST 1.1, changes in the sum of target lesion diameters (ΔSTL), lung metastases cavitation and liver metastases density. Primary and secondary objectives were to develop ex novo univariable and multivariable models to predict overall survival (OS) and progression-free survival (PFS), respectively.

Results 202 patients were enrolled, 134 (66.3%) treated with regorafenib and 68 (33.7%) with placebo. In the univariate analysis, PFS predictors were lung metastases cavitation at baseline (HR 0.50, 95% CI 0.27 to 0.92, p=0.03) and at week 8 (HR 0.58, 95% CI 0.36 to 0.93, p=0.02). Baseline cavitation (HR 0.23, 95% CI 0.08 to 0.66, p=0.007), RECIST 1.1 (HR 0.23, 95% CI 0.14 to 0.4, p <0.0001) and ΔSTL (HR 1.16, 95% CI 1.06 to 1.27, p=0.002) predicted OS. We found an increase of 9% of diameter as the best threshold for discriminating OS (HR 2.64, 95% CI 1.61 to 4.34, p <0.001). In the multivariable analysis, baseline and week 8 cavitation remained significant PFS predictors. Baseline cavitation, RECIST 1.1 and ΔSTL remained predictors of OS in exploratory multivariable models. Assessment of liver metastases density did not predict clinical outcome.

Conclusions RECIST 1.1 and ΔSTL predict favourable outcome to regorafenib. In contrast to liver metastases density that failed to be a predictor, lung metastases...
cavitation represents a novel radiological marker of favourable outcome that deserves consideration.

INTRODUCTION
Regorafenib prolongs progression-free survival (PFS) and overall survival (OS) in patients with pretreated metastatic colorectal carcinoma (mCRC). The multitargeted activity of regorafenib makes it difficult to identify molecular markers of sensitivity or resistance. In the era of targeted therapies, a rapidly growing body of knowledge has generated criticisms regarding timing and parameters for cancer response evaluation. Preliminary studies suggest that radiological assessment of early tumour shrinkage and changes in tumour density are potential predictive markers to targeted agents. Regorafenib induces tumour shrinkage, although commonly not reaching partial response (PR) by RECIST. We also noticed that regorafenib causes reduction in tumour density of liver metastases and cavitation of pulmonary metastases; the latter appears to be associated with a reduced risk of progressive disease (PD).

Based on these observations, we hypothesised that these radiological changes likely mirror a biological effect that parallels clinical outcome. Therefore, we tested whether changes in tumour characteristics detected by contrast-enhanced CT (CECT) would be a radiological imaging marker predicting clinical outcomes.

PATIENTS AND METHODS
RadioCORRECT is an investigator-initiated post hoc analysis of patients from the phase III placebo-controlled CORRECT trial (NCT 01103323), which enrolled 760 patients with refractory mCRC randomly assigned (2:1) to receive regorafenib (n=505) or placebo (n=255). The RadioCORRECT study was approved by the Institutional Review Board at the coordinating centre (Grande Ospedale Metropolitano Niguarda, Milan, Italy) and at participating institutions, and was conducted in accordance with Declaration of Helsinki. Patients were collected from the 13 highest recruiting institutions (four Italy, four France, three Belgium, one Spain, one the USA) and were included whether they had their first post-treatment evaluation by CECT at week 8.

Primary and secondary objectives were to develop univariable and multivariable models for patients treated with regorafenib by testing the following early radiological parameters for prediction of OS and PFS, respectively: response by RECIST 1.1 at week 8; change in the sum of target lesion diameters (ΔSTL) at week 8; cavitation of lung metastases at baseline and at week 8; tumour density of liver metastases at baseline and at week 8.

RADIOLOGICAL METHODS
Participating institutions provided baseline and week 8 CECT images of the chest, abdomen and pelvis. Tumour response by RECIST 1.1, sum of target lesion diameters (STL), PFS and OS were retrieved from the CORRECT database. The cut-off of this data was 21 July 2011 as reported in the final analysis of the CORRECT trial. Cavi
tation of lung metastases and tumour density of liver metastases were analysed at the coordinating centre by two experienced radiologists who were blinded to patient treatment and outcomes. Cavitation was assessed in a consensus reading session. At baseline CECT, cavitation was defined as the presence of an air-filled cavity ≥10% of the maximum diameter in one or more lung metastasis ≥10 mm, while at week 8 CECT as de novo onset or as an increase of a pre-existent cavitation. Tumour density of liver metastases was evaluated in two separate reading sessions and expressed in Hounsfield units (HU) with SD (σ). Measurements were assessed in the portal venous phase by drawing a region of interest (ROI) around the margins of the lesions, excluding necrotic areas. These ROIs were then analysed by week 8 CECT to detect any variation in density. We considered each one of the lesions reported in the CORRECT trial. Tumour density (µ)σ were analysed separately. When two liver metastases were present, µ and σ were summarised by the mean value. The percentage change from baseline at week 8 in µ (Δµ) and σ (Δσ) was calculated as follows: [(week 8 value - baseline value) / baseline value] × 100.

STATISTICAL METHODS
The Cox regression model was the unique statistical tool used for the development of PFS and OS predictive models; the HR was used as the population parameter.

For analysis of continuous parameters, the ratio between week 8 and baseline values (Ra) was computed for each patient; the ratio between Ra for regorafenib and placebo (RR) was estimated by fitting a linear regression model to observed Ra values on a log scale. The t-statistic was used to test H0: log RR=0. For categorical parameters, Fisher’s exact test was used.

Survival functions were estimated using the Kaplan-Meier method. Baseline covariate distributions, radiological parameters and clinical outcomes were summarised using descriptive statistics (median, IQR and range for continuous variables, absolute and percentage frequencies for categorical variables).

Sequential analytical procedures applied for predictive models

Step I: screening predictors
For each predictor, a main effect was mandatory; the Wald test statistic was used to test H0: log HR=0; all statistical tests were two-sided and statistical significance was detected at the 5% probability level; a p-value >0.05 stopped further research on the predictor.

Step II: assessment of model fit and development of univariable PFS predictive models
IIa. In order to test the linearity assumption for a continuous predictor, a restricted cubic spline function was added to each model successfully evaluated in step I;
Cox regression models was performed using the SAS soft-
version 3.2.3. Backward selection for the multivariable
and multivariable Cox regression models was assessed
The discriminatory ability of the identified univariable
model; a backward elimination Cox regression procedure
All identified predictors, time-interaction terms, non-linear
the tree size that minimised the cross-validated error was
chosen; at least one threshold was mandatory.

Step III: developing multivariable predictive models
All identified predictors, time-interaction terms, non-linear
terms and linear interactions were introduced in a full
model; a backward elimination Cox regression procedure
at 0.20 level was run to identify the strongest predictors.

Step IV: performance of predictive models
The discriminatory ability of the identified univariable
and multivariable Cox regression models was assessed
by the Harrell's C-index. Apart from backward selection,
predictive models were developed using the R software,
version 3.2.3. Backward selection for the multivariable
Cox regression models was performed using the SAS soft-
ware (SAS Institute, Cary, NC, USA), version 9.2.

RESULTS
Overall, 202 patients were analysed (see online supple-
mentary figure S1). Patient characteristics are reported in
table 1. At baseline, the STL was 91.5 mm (range 10–344)
for regorafenib and 88 mm (range 10–237) for placebo.
At a median follow-up of 8.8 months for regorafenib (IQR
7.2–10.6) and 8.2 months for placebo (IQR 6.3–9.4),
the median PFS was 3.2 months (95% CI 1.9 to 3.5, IQR
1.8–5.5) and 1.7 months (95% CI 1.7 to 1.8, IQR 1.6–1.9),
respectively (HR 0.43, 95% CI 0.31 to 0.59, p <0.001).
Median OS was 9.5 months (95% CI 7.2 to 10.8, IQR 4.9–
NR) and 6.6 months (95% CI 5.4 to 7.8, IQR 3.7–NR) for
regorafenib and placebo (HR 0.67, 95% CI 0.45 to 1.01,
p=0.05). At the time of the analysis, PFS and OS events
were reached in 119/134 (88.8%) and 65/134 (48.5%)
patients in the regorafenib group and in 65/68 (95.6%)
and 39/68 (57.3%) patients in the placebo group.

ASSESSMENT OF RADIOLOGICAL PARAMETERS IN THE
OVERALL POPULATION
REGIST 1.1 and ΔSTL
Among the 199 patients evaluable for dimensional
response, the disease control rate (DCR) was 53.4%
(70/131) and 20.6% (14/68) in patients treated with
regorafenib and placebo (p <0.001). No PR to rego-
rafenib was reported. Median ΔSTL was 4% (IQR –3.8
to 16.4) and 21% (IQR 5.1–40.4%) in the regorafenib
and placebo groups (RR 0.89, 95% CI 0.84 to 0.95, p <0.001),
respectively (see online supplementary figure S2).

Cavitation of lung metastases
At baseline, cavitation was found in 18/88 (20.4%)
and in 3/43 (6.9%) patients treated with regorafenib
and placebo (p=0.07). Some examples of cavitation are
displayed in figure 1. At week 8, cavitation was found
in 36/88 (40.9%) and 0/43 (0%) patients treated with
regorafenib and placebo, respectively (p <0.001). Overall,
24/70 (34.3%) patients had de novo cavitation and 12/18
(66.7%) had an increase of a pre-existing cavitation
(p=0.002). Week 8 cavitation was associated with RECIST
1.1 response. In the regorafenib group, DCR was 69.7%
(23/33) and 42.3% (22/52) in patients with and without
cavitation at week 8 (p=0.01) and 66.7% (12/18) versus
49.2% (33/67) in patients with and without baseline cavi-
tation (p=0.29). In the subgroup with baseline cavitation,
the DCR was 91.7% (11/12) and 16.7% (1/6) in patients
with or without cavitation increase at week 8 (p=0.004).
However, the small number of patients with cavitated
metastases at baseline limits the interpretation of data.
In the subgroup without baseline cavitation, the DCR was
57.1% (12/21) and 45.6% (21/46) in patients with or
without cavitation onset at week 8 (p=0.44).

Density of liver metastases
At baseline, median μ for regorafenib and placebo was 59
HU (range 19–108) and 51 HU (range 26–92) versus 58
HU (range 24–110) and 52 HU (range 22–88) as assessed
by radiologist A and B, respectively. Median σ for rego-
rafenib and placebo was 17 HU (range 9–38) and 18 HU
(range 9–40) versus 18 HU (range 9–30) according to radiologists A and B, respectively. At week 8, the Δμ for regorafenib and placebo was −33% (IQR −44 to −20) and −15% (IQR −21.8 to 0.3) as assessed by radiologist A (RR 0.79, 95% CI 0.71 to 0.88, p <0.001) versus −29% (IQR −41 to −19) and −12% (IQR −19 to −2) as assessed by radiologist B (RR 0.78, 95% CI 0.70 to 0.86, p <0.001). The Δσ for regorafenib and placebo was −11% (IQR −21 to −5) and 7% (IQR −7.1 to 32.3) according to radiologist A (RR 0.81, 95% CI 0.73 to 0.90, p <0.001) versus −11% (IQR −21 to −4) and 6% (IQR −9 to −31) according to radiologist B (RR 0.85, 95% CI 0.79 to 0.92, p <0.001). Bland-Altman plots showed good inter-ob-
er agreement (see online supplementary figure S3).

SURVIVAL IN PATIENTS TREATED WITH REGORAFENIB
Progression-free survival
Table 2 summarises the results of univariate analysis.
RECIST response and ΔSTL were excluded from this
analysis because they define PFS. Baseline cavitation
(HR 0.50, 95% CI 0.27 to 0.92, p=0.03; Harrell’s C-index, 0.54)
and week 8 cavitation (HR 0.58, 95% CI 0.36 to 0.93,
Table 1  Patient characteristics

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<td>59 (67.8)</td>
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ECOG, Eastern Cooperative Oncology Group.

p=0.02; Harrell's C-index, 0.57) predicted PFS. Median PFS was 3.5 months (95% CI 2.8 to 5.7) and 1.9 months (95% CI 1.8 to 3.4) in patients with and without cavitation at week 8 versus 3.4 months (95% CI 1.9 to 7.8) and 2 months (95% CI 1.8 to 3.5) in those with and without cavitation at baseline, respectively (figure 2).
multivariable model that included all radiological and clinical predictors identified by the univariate analysis, both baseline and week 8 cavitation remained significant predictors of PFS (see online supplementary table S1). An interaction analysis showed that patients with baseline cavitation had a median PFS of 7.4 months (95% CI 2.8 to NR) if they had an increase of cavitation at week 8 versus 1.8 months (95% CI 1.0 to 3.4) if they did not (HR 0.10, 95% CI 0.02 to 0.42, p=0.002; Harrell's C-index, 0.72) (figure 2). Conversely, the PFS of patients without baseline cavitation was not affected by de novo onset of cavitation at week 8 (HR 0.96, 95% CI 0.57 to 1.63, p=0.88; Harrell's C-index 0.52, interaction p=0.001) (figure 2).

Overall survival
At univariate analysis, the radiological variables predicting OS were baseline cavitation (HR 0.23, 95% CI 0.08 to 0.66, p=0.007; Harrell's C-index 0.60), RECIST 1.1 (HR 0.23, 95% CI 0.14 to 0.4, p <0.001; Harrell's C-index 0.70) and ΔSTL (HR 1.16, 95% CI 1.06 to 1.27, p=0.002; Harrell's C-index, 0.63) (table 2). By applying CART methodology, we found an increase of 9% of diameter in tumour size as the best threshold for discriminating OS. Patients with STL increase ≥9% had a median OS of 5.8 months (95% CI 4.7 to 7.3); instead patients with a variation <9% had a median OS of 10.8 months (95% CI 9.0 to NR) (HR 2.64, 95% CI 1.61 to 4.34, p <0.001) (figure 3). Median OS for patients with and without baseline cavitation was 11.8 (95% CI 10.8 to NR) and 8.7 months (95% CI 5.7 to 10.4), respectively (figure 3). The OS of patients with baseline cavitation was not affected by cavitation onset at week 8 (interaction, p=0.74). Patients with DCR and PD had a median OS of 11.5 months (95% CI 9.8 to NR) and 5.5 months (95% CI 4.4 to 6), respectively (figure 3). In an exploratory analysis, multivariable Cox models showed that cavitation at baseline, RECIST 1.1 and ΔSTL were predictors of OS (see online supplementary table S2). We reported the Harrell's C-index for each predictor statistically associated to PFS and OS. Since no comparison between different predictors was planned by study design, we reported this discriminatory measure only with a descriptive purpose.

DISCUSSION
The RadioCORRECT study showed that an early radiological evaluation of tumour response is helpful to predict clinical outcome to regorafenib in mCRC. We found that RECIST 1.1 and ΔSTL are predictors of OS. Moreover, our findings suggest that slowing tumour progression down by limiting the increase in STL to 9%, even without tumour shrinkage, was sufficient to predict a prolongation of OS. Since response to multikinase inhibitors may not be adequately described by dimensional criteria, we evaluated if other radiological markers could be identified, such as cavitation of lung metastases and density of liver metastases. Literature data indicate that cavitation in lung metastases may occur spontaneously or, more frequently, may be induced by cancer therapy, especially by anti-angiogenetic agents. It has been postulated that the appearance of an air-filled cavity is a consequence of central necrosis due to an insufficient blood supply after inhibition of angiogenesis or caused by arterial thrombosis. In 2013, we described for the first time the onset of cavitation of lung metastases in a small cohort of patients with mCRC treated with regorafenib and subsequently found an association with DCR. The present study confirms our preliminary observations. We hypothesise that cavitation induced by regorafenib might depend on its broad multikinase inhibitory activity on tumour microenvironment, angiogenesis and tumour growth. The absence of onset of cavitation in patients receiving placebo corroborate this remark. In patients treated with regorafenib, we found that the presence of cavitation in lung metastases at week-8 was associated with DCR and PFS. More than 20% of patients treated with regorafenib showed cavitation at baseline CECT. These patients are more likely to develop an increase of cavitation at week-8 and they achieved greater PFS and OS when compared with those without baseline cavitation. These findings have significant implications and might be helpful for therapeutic choice before treatment begins. Our data appear in agreement with the proposal of other authors to consider tumour cavitation as a new radiological biomarker. Recently, Lim et al evaluated lung metastases cavitation in 53 mCRC patients treated with regorafenib. Although 32.1% of these patients developed cavitation, no significant association with clinical outcome was reported. These results are in contrast with those of the present study, but the small number of patients may have underpowered the statistical analysis. Indeed, patients with cavitory changes showed a non-significant prolongation of PFS and a greater DCR (82.4% vs 63.9%). Furthermore, these authors analysed...
Table 2  Univariate analysis of progression-free survival (PFS) and overall survival (OS) in patients receiving regorafenib

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<th>Category</th>
<th>PFS</th>
<th>OS</th>
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<td>Cavitation</td>
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<td>Yes</td>
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Density of liver metastases

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<tr>
<th>Radiologist A</th>
<th>µ (unit:10 HU)</th>
<th>1.02 0.89–1.16</th>
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<td>σ (unit:10 HU)</td>
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<td>0.76 0.51–1.13</td>
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<td>σ (unit:10 HU)</td>
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<td>0.92 0.62–1.38</td>
<td>0.151 0.70</td>
<td>1.84 1.10–3.06</td>
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Sum of target lesions (unit: 1 cm)

| | - | 0.99 0.96–1.02 | 0.394 0.53 | 1.05 1.02–1.09 | 9.964 0.02 |

Radiological predictors at baseline CECT

Radiological predictors at week 8 CECT

Other predictors

Age (years) at random (unit: 10 years)

| | - | 1.01 0.83–1.22 | 0.003 0.96 | 0.87 0.66–1.14 | 0.975 0.32 |

Sex

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ECOG

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KRAS mutation

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More than three lines before regorafenib

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<td>0.62–1.30</td>
<td>0.97</td>
<td>0.60–1.59</td>
<td></td>
</tr>
</tbody>
</table>

Time from M1 diagnosis to randomisation (years)

| | - | 0.90 0.78–1.03 | 2.552 0.11 | 0.92 0.76–1.10 | 0.873 0.35 |

Continued
all metastatic lesions, including non-target metastases (<1 cm), and only 66% of patients had measurable lesions, making it difficult to compare data from these two different studies. Since the occurrence of cavitation of lung metastases can be of clinical concern in terms of risk of pulmonary haemorrhage,21 25 we reviewed the occurrence of grade 3 and 4 pulmonary adverse events in our cohort based on matched reporting from the CORRECT Trial. In our study, among the 36 patients who had cavitation of lung metastases, we found only one respiratory grade 4 adverse event (pulmonary embolism) that has been judged as not related to regorafenib.

Measurement of pretreatment and on-treatment tumour density of liver metastases has been widely investigated in solid tumour assessments.5 26 In xenograft models, regorafenib led to an early reduction of tumour perfusion and vascularity, assessable by radiological imaging.27–29 In our study, regorafenib induced a decrease in tumour density in most of the patients. However, neither a reduction of tumour density at week 8 nor baseline values were useful for predicting outcomes. This finding is supported by a recent study in patients with gastrointestinal stromal tumours treated with regorafenib, in which CHOI criteria, which include tumour

<table>
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<th>Category</th>
<th>HR</th>
<th>95% CI</th>
<th>Chi²</th>
<th>p Value</th>
<th>HR</th>
<th>95% CI</th>
<th>Chi²</th>
<th>p Value</th>
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</thead>
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<td>1</td>
<td>-</td>
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<tr>
<td></td>
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<td>1.55</td>
<td>1.03–2.33</td>
<td>3.06</td>
<td>1.56–6.00</td>
<td>0.915</td>
<td>0.34</td>
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<tr>
<td>Lung target lesions</td>
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<td>-</td>
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<td>0.55</td>
<td>1</td>
<td>-</td>
<td>0.78</td>
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<tr>
<td></td>
<td>Yes</td>
<td>0.89</td>
<td>0.61–1.30</td>
<td>-</td>
<td>-</td>
<td>0.78</td>
<td>0.46–1.30</td>
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CECT, contrast-enhanced computed tomography; ECOG, Eastern Cooperative Oncology Group; HU, Hounsfield unit; RECIST, Response Evaluation Criteria in Solid Tumors; μ = tumour density in HU; σ = standard deviation; ΔSTL = change in the sum of the target lesion diameters.

**Table 2** Continued

![Figure 2](http://esmoopen.bmj.com/)  
**Figure 2** Kaplan-Meier estimates of progression-free survival (PFS) in patients treated with regorafenib. (A) PFS according to the presence of cavitation at week 8. (B) PFS according to the presence of baseline cavitation. (C) Subgroup analysis of PFS in patients with baseline cavitation, according to its increase at week 8. (D) Subgroup analysis of PFS in patients without baseline cavitation, according to its onset at week 8.
density variation besides dimensional changes, had a less favourable concordance between PFS and OS prediction when compared with RECIST 1.1 or WHO criteria. In mCRC patients treated with regorafenib, Lim et al found a tumour density decrease in most of cases, but the magnitude of change was not associated with clinical outcomes.

Our study has several limitations. First, it is a post hoc analysis of patients enrolled in a prospective, placebo-controlled phase III trial. A priori power statistical analysis was not performed and the number of patients evaluated limits the interpretation of the results.

Second, we found both baseline and week-8 cavitation are associated with a favourable outcome to regorafenib. Unfortunately, the imbalance of baseline cavitation between regorafenib and placebo group did not allow to evaluate clinical outcomes in patients treated with placebo. This hamper to clarify whether baseline cavitation affects the natural history of disease regardless of treatment received. For this reason, the role of cavitation as predictive rather than prognostic marker should be further investigated in larger series and across other studies. Third, density was assessed in the same liver metastases identified in the CORRECT study. Morphological features such as the presence of necrotic area may have affected the analysis of density. Finally, since we included only patients that underwent the first post-treatment CECT, planned at week 8, we cannot rule out a selection bias by excluding patients with more aggressive or primary resistant tumours. It remains to be assessed how fast cavitation occurs and if an earlier evaluation by CECT would be capable of capturing the same radiological signals of efficacy.

CONCLUSIONS

Our findings showed that an early radiological assessment of tumoural response to regorafenib is useful for driving clinical decisions. RECIST 1.1 remains an adequate method to assess therapeutic response, being associated with OS. The evaluation of tumour size as a continuous variable, expressed as ΔSTL, supports continuation of treatment in those patients achieving stable disease without any tumour shrinkage. Our data also indicate that the evaluation of liver metastases density does not provide complementary information to traditional dimensional-based criteria. Conversely, we identify lung metastases cavitation as a novel imaging predictor of
favourable clinical outcome to regorafenib that deserves consideration.

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Competing interests
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Radiological imaging markers predicting clinical outcome in patients with metastatic colorectal carcinoma treated with regorafenib: post hoc analysis of the CORRECT phase III trial (RadioCORRECT study)


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