ORIGINAL ARTICLE

Deep learning-based assessment of body composition and liver tumour burden for survival modelling in advanced colorectal cancer

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Abstract

Background   Personalized therapy planning remains a significant challenge in advanced colorectal cancer care, despite extensive research on prognostic and predictive markers. A strong correlation of sarcopenia or overall body composition and survival has been described. Here, we explore whether automated assessment of body composition and liver metastases from standard of care CT images can add to clinical parameters in personalized survival risk prognostication.
Methods   We retrospectively analysed clinical imaging data from 85 patients (50.6% female, mean age 58.9 SD 12.2 years) with colorectal cancer and synchronous liver metastases. Pretrained deep learning models were used to assess body composition and liver metastasis geometry from abdominal CT images before the initiation of systemic treatment. Abdominal muscle-to-bone ratio (MBR) was calculated by dividing abdominal muscle volume by abdominal bone volume. MBR was compared with body mass index (BMI), abdominal muscle volume, and abdominal muscle volume divided by height squared. Differences in overall survival based on body composition and liver metastasis parameters were compared using Kaplan–Meier survival curves. Results were correlated with clinical and biomarker data to develop a machine learning model for survival risk prognostication.
Results   The MBR, unlike abdominal muscle volume or BMI, was significantly associated with overall survival (HR 0.39, 95% CI: 0.19–0.80, $P = 0.009$). The MBR ($P = 0.022$), liver metastasis surface area ($P = 0.01$) and primary tumour sidedness ($P = 0.007$) were independently associated with overall survival in multivariate analysis. Body composition parameters did not correlate with *KRAS* mutational status or primary tumour sidedness. A prediction model based on MBR, liver metastasis surface area and primary tumour sidedness achieved a concordance index of 0.69.
Conclusions   Automated segmentation enables to extract prognostic parameters from routine imaging data for personalized survival modelling in advanced colorectal cancer patients.

Keywords   Body composition; Machine learning; Colorectal cancer; Prognosis; Computed tomography

Background

Colorectal cancer (CRC) is the third most common cancer in Western countries. Up to 50% of patients either are initially diagnosed with synchronous metastases or develop metachronous metastases. The predominant organ of metastases is with 77% the liver with 5 year overall survival of only 15% in these patients.[1,2] Curative resection of liver metastases is well established in colorectal cancer care, but only about 25% of patients qualify for this procedure.[1,3] The personalized identification of colorectal liver metastasis (CRLM) patients with poor prognosis under current treatment standards is of utmost importance. This may prevent futile overtreatment and enable personalized referral for experimental therapies within clinical trials. In this regard, studies have shown that sarcopenia is an independent predictor of prognosis in advanced CRC.[4–7] However, to date, body mass index (BMI) has been used as a standard measure in routine clinical care, although it is not an appropriate prognostic marker in CRC. Because the BMI fails to distinguish between different tissues, it does not accurately reflect the physical condition of patients. In contrast, CT image-based markers of body composition have been shown to be more informative than BMI.[8,9] By assessing the body composition, the individual distribution of fat, muscle and bone of each patient can be examined. Previous studies calculated the body composition by segmentation of CT sectional images at the level of the L3 vertebra, which is only an approximation of the actual body composition. Moreover, this approach depended to varying degrees on manual processing, which is time- and labor-intensive and is not suited for integration in routine care. Consequently, body composition analysis is still largely neglected in survival risk stratification. Due to recent developments in deep learning and image segmentation, fully automated assessment of body composition and tumour characteristics from 3D CT scans has become possible.[10,11] In addition to assessing body compositions, this also enables the accurate geometric analysis of CRLM, which has been shown to be associated with overall survival in advanced CRC patients.[12–15] As regular CT scans are part of routine care in oncology, automated extraction of in-depth information could allow more granular prediction of prognosis.

Against this background, we have taken advantage of current technical capabilities to develop a new prediction model that can be incorporated into routine clinical care to enable personalization.

Methods

Study design

We retrospectively evaluated 258 CRC patients treated at the University Hospital Essen and included 85 patients with synchronous CRLM in the final analysis (*Figure* 1). All patients were treated with systemic cancer therapy between 2004 and 2017. Overall survival time was defined as time from the start of systemic treatment to the date of death from
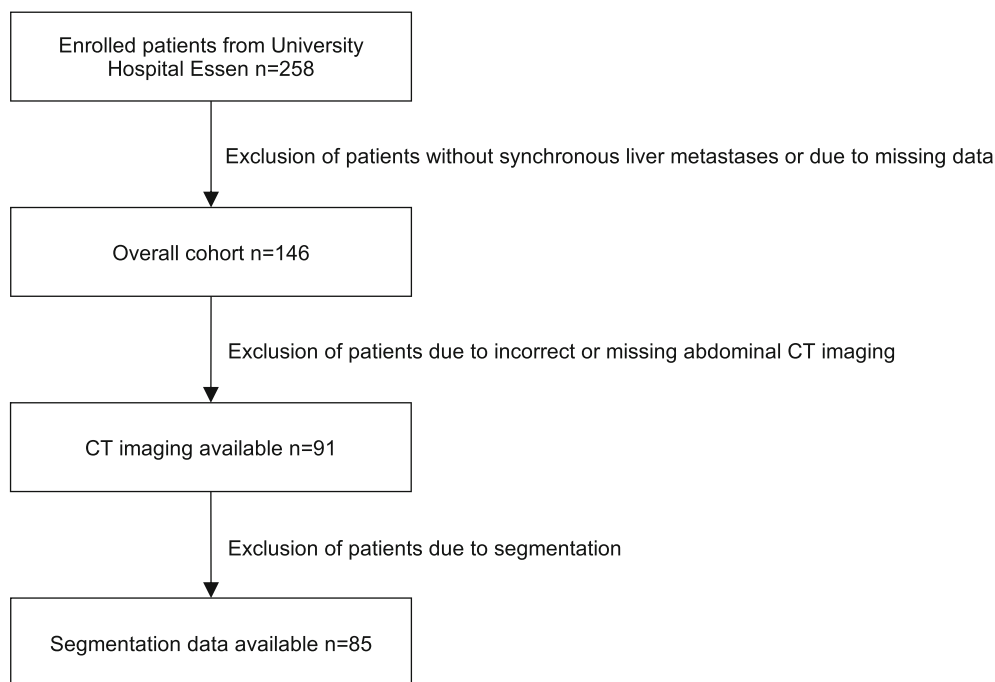

Figure 1 Flowchart depicting the process of patient enrolment.

any cause. We censored patients for whom no date of death was available at the date of the last follow-up. The study was approved by the Ethics Committee of the Medical Faculty of the University Duisburg-Essen (No. 21-10347).

Patient characteristics

All included patients were diagnosed with stage IV CRC with synchronous liver metastases. The median age was 59.0 years and 50.6% were female. 63.5% of patients were diagnosed with a left-sided primary tumour. The median survival time (MST) from start of palliative chemotherapy was 21.2 months (95% CI: 15.6–27.2 months; see *Figure* S1). The patient characteristics are summarized in *Table* 1.

Assessments

Baseline abdominal CT images taken before the initiation of systemic treatment were used to segment body composition and liver metastases. Body composition markers of the abdominal cavity were assessed using a fully automated extraction pipeline.[11] The markers analysed comprised the volumes of muscle, bone, total adipose tissue (TAT), intermuscular adipose tissue (IMAT), subcutaneous adipose tissue (SAT), and visceral adipose tissue (VAT). Prior to extraction of body composition markers, all CT images were resampled to 5 mm slice thickness to meet the requirements of our extraction pipeline. To ensure comparability between patients, the collected markers were divided by the number of CT slices of the automatically detected abdominal cavity for further analysis. Abdominal muscle-to-bone ratio (MBR) and muscle/height^2 were calculated by dividing abdominal muscle volume by abdominal bone volume or by the body height squared (*Figure* S2). Liver metastases were automatically segmented using the pretrained nnU-Net architecture.[10] The volume and surface area of metastases were extracted with a triangle mesh approach using an internal feature extraction pipeline including PyRadiomics 3.0.1 and were normalized to the [0, 1] interval.[16] In four cases, the segmented liver metastases were too small for feature extraction and the respective values were set to zero. Further patient information used in this study, including primary tumour sidedness, was obtained from the patients' electronic health records. Tumours originating from the rectum, sigma, descending colon, and left flexure were defined as left-sided. All tumours located in the transverse colon, right flexure, ascending colon, and caecum were defined as right-sided. BMI was calculated in 80 patients in whom respective data were available at the initiation of therapy. In a subgroup of 71 patients, data from genomic sequencing of macrodissected tissue samples were available.

Statistical analysis

All statistical analyses were performed using Python 3.8 and the packages lifelines, scikit-survival and SciPy.[17–19] Based on a Cox proportional hazards model, we selected the three parameters MBR, liver metastasis surface area, and primary tumour sidedness for further analysis. We formed subgroups based on median MBR, median CRLM surface area or the primary tumour sidedness and compared overall survival using Kaplan–Meier survival curves and a log-rank test. From these parameters, we then built a prediction model using a component-wise gradient boosting algorithm with partial likelihood loss of a Cox proportional hazards model.[17,20] Predictive performance was assessed calculating the mean concordance index as result of a 5 × 5-fold cross validation. The correlation between parameters was analysed by calculating the Pearson correlation coefficient (r). P-values ≤0.05 were regarded statistically significant. To understand the decision-making of our model, we used SHapley Additive exPlanations (SHAP).[21]

Results

MBR is a predictor of prognosis in advanced CRC patients

Body composition parameters extracted from abdominal CT images were analysed (*Table* 1). Cox proportional hazards analysis adjusted for age and gender revealed that abdominal muscle volume alone did not serve as prognostic parameter (HR 0.98, 95% CI: 0.95–1.00, $P = 0.062$). However, calculating MBR by dividing abdominal muscle volume by abdominal bone volume provided an independent predictor of prognosis (HR 0.39, 95% CI: 0.19–0.80, $P = 0.009$). None of the remaining body composition parameters were significantly associated with overall survival (*Table* S3).

MBR compared with muscle/height^2 and BMI

For 80 patients, data on weight and height at initiation of therapy were available. The median BMI was 24.0 kg/m^2 with a range of 14.5 to 38.4 kg/m^2. In this subgroup, the MBR (HR 0.41, 95% CI: 0.19–0.87, $P = 0.02$) and muscle/height^2 (HR 0.91, 95% CI: 0.84–0.98, $P = 0.013$), unlike the BMI (HR 0.98, 95% CI: 0.93–1.03, $P = 0.507$), were significantly associated with overall survival (*Table* 2). Further analysis using Kaplan–Meier curves showed that based on the median MBR, two subgroups could be defined that had significantly different overall survival ($P = 0.019$, *Figure* 2A). In contrast, subgroups based on median muscle/height^2 ($P = 0.219$, *Figure* 2B), or median BMI ($P = 0.733$, *Figure* 2C) did not show significantly different overall survival. By plotting the rela-

Table 1 Characteristics of the overall cohort

	n = 85
Age, years	
Median	59.0
Range	26–83
Gender, N (%)	
Male	42 (49.4)
Female	43 (50.6)
AJCC Stage, N (%)	
IV	85 (100)
Liver metastasis, N (%)	
Synchronous	85 (100)
First-line chemotherapy, N (%)	
FOLFOX	57 (67.1)
FOLFIRI	18 (21.2)
Other	10 (11.8)
First-line antibody, N (%)	
Bevacizumab	39 (45.9)
Cetuximab	21 (24.7)
***KRAS* status, N (%)**	
Mutant	21 (24.7)
Wild-type	50 (58.8)
Unknown	14 (16.5)
Primary tumour sidedness, N (%)	
Left	54 (63.5)
Right	31 (36.5)
Abdominal body composition, median (range), L	
Muscle	5.77 (3.21–10.10)
Bone	2.43 (1.66–3.84)
TAT	10.57 (1.22–33.09)
SAT	7.08 (0.50–21.33)
VAT	2.59 (0.25–10.60)
IMAT	0.89 (0.24–3.73)
Median survival time, months (95% CI)	21.2 (15.6–27.2)
1 year mortality rate, % (95% CI)	23.5 (15.9–34.1)
Censored, N (%)	6 (7.1)

Table 2 Results of a univariate Cox proportional hazards model adjusted for age and gender in a subgroup where BMI was available

n = 80	HR (95% CI)	P-value
BMI	0.98 (0.93–1.03)	0.507
MBR	0.41 (0.19–0.87)	0.020
Muscle/height^2	0.91 (0.84–0.98)	0.013

tionship between BMI and MBR, we found that a low BMI was related to a lower MBR. With a higher BMI, there was no clear correlation to MBR (*Figure* S4).

Prognostic relevance of CRLM geometry, primary tumour sidedness and KRAS mutational status

Using automated image segmentation, we confirmed the surface area (*P* = 0.006) and volume (*P* = 0.035) of liver metastases being predictors of prognosis (*Table* 3). Furthermore, pri-

mary tumour sidedness significantly associated with overall survival (*P* = 0.034). *KRAS* mutational status was available in 71 of our 85 patients (84%). There was no significant association between the *KRAS* mutational status and overall survival (*P* = 0.274, *Table* 3). In a multivariate analysis together with *KRAS* mutational status, primary tumour sidedness, age, and gender, MBR remained an independent predictor of overall survival (HR 0.32, 95% CI: 0.15–0.69, *P* < 0.005).

Development of a machine learning model for survival risk prognostication

In a multivariate Cox proportional hazards model together with MBR and primary tumour sidedness, CRLM surface area was an independent predictor (HR 4.52, 95% CI: 1.43–14.3, *P* = 0.01, see *Table* S5), whereas CRLM volume showed only borderline significance (HR 3.00, 95% CI: 1.00–9.05, *P* = 0.051). All three independent parameters could significantly separate the overall cohort in Kaplan–Meier analyses (*Figure* 3). Using the three predictors MBR, CRLM surface area and primary tumour sidedness, a prediction model was developed. After 5x5 cross validation our model achieved a mean concordance index of 0.69 (95% CI: 0.65–0.72). Our model was able to identify risk groups that showed significantly different overall survival (*P* < 0.005, *Figure* S6). Through SHAP, we could confirm that our model uses the three parameters in a reasonable way and in accordance with the hazard ratios calculated by the Cox proportional hazards model (*Figure* 4). Interestingly, primary tumour sidedness had the highest impact on the model output, followed by CRLM surface area and MBR.

Correlation analysis of the selected parameters and KRAS mutational status

In the overall cohort there was a weak negative correlation between both MBR and CRLM volume (*r* = −0.28, *P* = 0.009) and between MBR and CRLM surface area (*r* = −0.27, *P* = 0.014). We found no significant correlation between MBR and the primary tumour sidedness (*P* = 0.82) as well as between primary tumour sidedness and CRLM surface area (*P* = 0.15). In a subgroup with available data (*n* = 71), there was no significant correlation between *KRAS* mutational status and MBR (*P* = 0.57), CRLM surface area (*P* = 0.37), or primary tumour sidedness (*P* = 0.87).

Discussion

Multiple effective treatment options and strategies are available for patients with CRC. In clinical practice, patients are characterized by clinical and laboratory examination, imaging
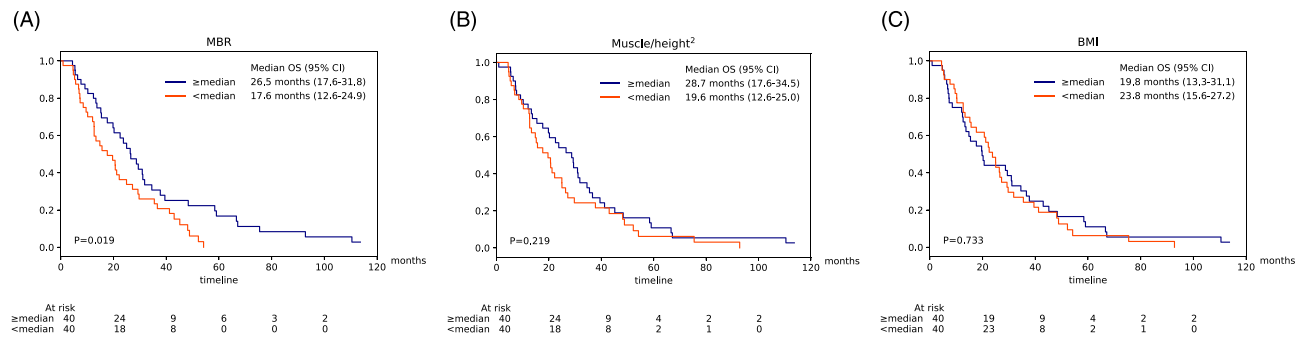
Figure 2 Kaplan–Meier survival curves showing the overall survival according to MBR (A), muscle/height^2 (B), or BMI (C) in a subgroup (*n* = 80) where data on weight and height were available.

Table 3 Results of a univariate Cox proportional hazards model adjusted for age and gender

	HR (95% CI)	*P*-value
CRLM volume (*n* = 85)	2.96 (1.08–8.16)	0.035
CRLM surface area (*n* = 85)	4.49 (1.55–13.02)	0.006
Left-sided primary tumour (*n* = 85)	0.61 (0.38–0.96)	0.034
KRAS mutation (*n* = 71)	1.37 (0.78–2.41)	0.274

studies, tumour histology and molecular pathology. Nevertheless, the selection of the best strategy for an individual patient is still based on very few parameters, and thus does not make sufficient use of all available clinical information. Against this background we have demonstrated that it is possible to exploit body composition and liver tumour burden by automated extraction from staging CT images. In contrast to previous studies, we have assessed the body composition of the entire abdomen and not only at the level of the L3 vertebra. We have identified MBR and CRLM surface area in addition to primary tumour sidedness as independent predictors of overall survival. These parameters enabled us to develop a prediction model that can be easily implemented in routine clinical care.

There are conflicting studies on the importance of body mass index in the prognosis of advanced CRC.[22–24] In many other solid tumours, however, a favourable effect of a higher BMI on overall survival has been found, which is referred to as the obesity paradox.[25] In early stage CRC, the negative correlation between BMI and sarcopenia was found to be an underlying factor of this effect.[26] In advanced CRC, sarcopenia was thus demonstrated to be an independent negative predictor of overall survival.[4–7] Because BMI does not distinguish between fat and muscle tissue, CT image-derived body composition analyses proved to be a superior approach to assess prognostic parameters such as sarcopenia.[8,9] In those studies, body composition was measured from CT sectional images at the level of the L3 vertebra, which due to the limited data source may be prone to imprecision or confounders. In contrast, our study is the first to automatically assess body composition from the entire abdominal cavity and compare resulting markers with BMI. By segmenting the entire abdominal cavity instead of single sectional images, our study seeks to describe body composition more accurately and thus does not rely on approximation. Moreover, previous studies have used the skeletal muscle index, which normalizes muscle area with the square of height, whereas we have normalized muscle volume with bone volume by calculating the MBR. This is based on the assumption that bone volume allows an inference of the general body structure and remains relatively constant regardless of other changing body composition parameters. Our finding that MBR, as well as abdominal muscle volume divided by height squared, are predictors of overall survival in CRC patients independent of age and gender supports this hypothesis. Because only MBR could form subgroups that showed significantly different overall survival and can be automatically extracted from CT images without additional patient information, we propose MBR as a new prognostic marker in this cancer entity.

Treatment decisions in advanced CRC are highly dependent on the tumour genotype. In particular, the presence of *RAS* mutations in association with the primary tumour sidedness is of major importance for the selection of antibody therapies. In our study, we saw no correlation between the *KRAS* mutational status and body composition parameters, which is in line with previous studies.[27] Because MBR was a predictor of overall survival independent of *KRAS* mutational status and the primary tumour sidedness, this suggests high generalizability. In a subgroup with available information at baseline, we could demonstrate that BMI, unlike MBR, did not serve as predictor of overall survival. This finding is consistent with the study by Dell'Aquila et al., which also found no association between BMI and overall survival in metastatic CRC.[22] This underscores the need for a more differentiated analysis of body composition than by using the traditional body mass index, which is still part of routine clinical care.

To obtain additional assessment of individual patients beyond body composition, we performed automated image segmentation to measure liver tumour burden. Previous studies investigating CRLM from CT images have often placed a strong focus on complex radiomic signatures in-
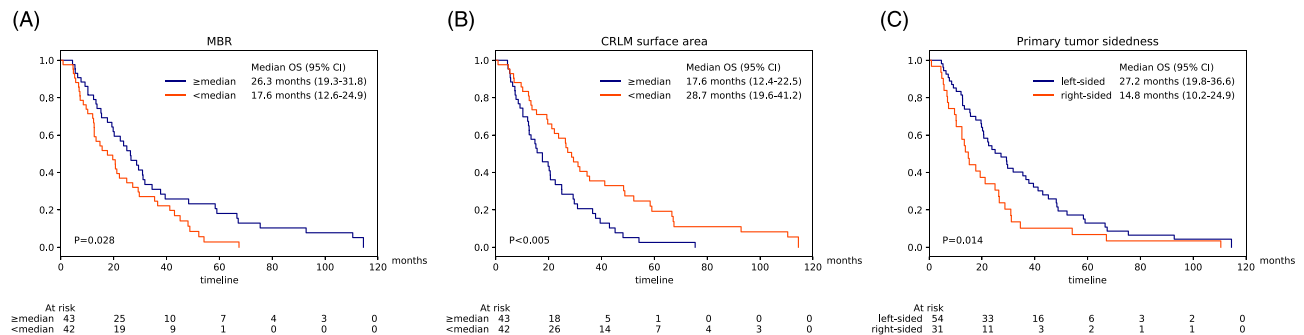
Figure 3 Kaplan–Meier survival curves showing the overall survival according to MBR (A), CRLM surface area (B), or primary tumour sidedness (C) in the overall cohort.
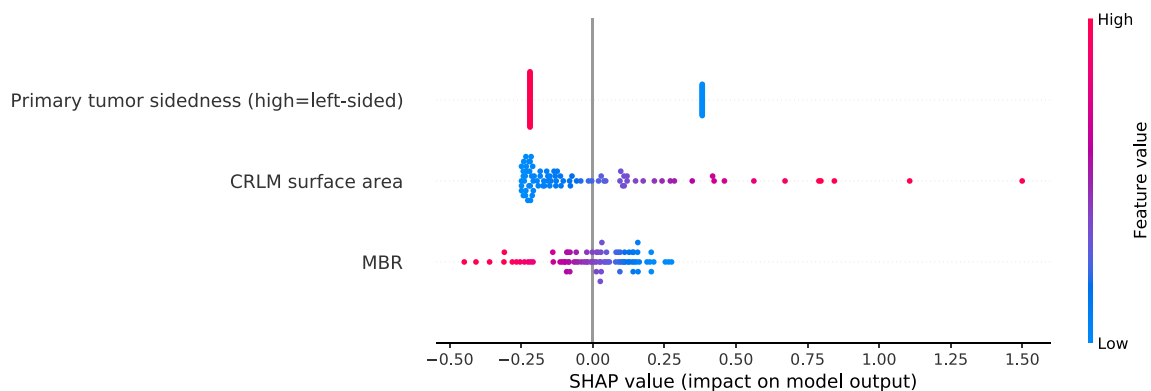

Figure 4 Decision-making of the prediction model based on SHAP. The parameters are ranked from top to bottom by their responsibility on the model output. Feature values are represented by the colour gradient. Higher SHAP values indicate the responsibility of parameters for higher predicted survival risk.

cluding texture features.[15,28,29] However, it was previously shown that radiomic parameters are often only a surrogate for tumour volume and are not prognostic on their own.[30] Furthermore, the use of different CT scanners and protocols poses significant difficulties for the analysis of many radiomic features. To overcome this issue, we focused on shape features such as the surface area and tumour volume, which are reproducible across different CT scanners and have shown a plausible association with survival independent of the CT settings.[12,31,32] We could confirm the surface area and volume of CRLM as predictors of prognosis in advanced CRC patients. Because CRLM surface area, unlike CRLM volume, was shown to be prognostically independent of MBR and primary tumour sidedness, we included it in our prediction model.

Tumour sidedness was previously shown to associate with overall survival in advanced CRC.[33,34] As studies have indicated remarkable differences between right- and left-sided tumours and also suggested an impact on the body composition of patients, we included primary tumour sidedness as parameter in our model.[7,35] Using SHAP we identified pri-

mary tumour sidedness as most relevant parameter for the decision-making of our model, emphasizing its importance in patient prognostication and treatment planning.

The three parameters included in our model were all independently correlated with overall survival in our study. In contrast to other prognostic tools, our model is based on non-invasive parameters that do not depend on additional laboratory testing or tumour morphology as determined by histopathology.[36] Furthermore, the included parameters are relatively robust to acute events such as inflammation, which can temporarily affect blood values. This distinguishes our model from established prognostic tools such as the Glasgow prognostic score and allows for future integration of additional parameters.[37] We see great potential of our model in identifying patients who are suitable for curative resection of CRLM or who should be enrolled in clinical trials. Further research is needed to investigate the prognostic value of MBR in patients with earlier stages of CRC and in other cancer types.

Our study has limitations, which are particularly due to its retrospective design and the lack of external validation using

an independent patient cohort. As we had to exclude patients for whom no suitable CT image was available or segmentation was not possible, our cohort is only of medium size. We investigated the association of our results with *KRAS* mutational status but were unable to analyse the influence of mutations or additional proto-oncogenes such as *NRAS* or *BRAF* due to their overall rarity and representation in our cohort. Most patients were treated at a time, when *NRAS* and *BRAF* testing were not part of routine diagnostics. Although we performed extensive cross validation to prevent overfitting on our data, external validation will be necessary to confirm the results.

In conclusion, we propose a new pragmatic model for personalized survival risk prognostication in patients with advanced CRC that is based entirely on parameters that can be automatically extracted from routine clinical data. We have demonstrated that the inclusion of body composition and exact metastasis geometry hold great promise in refining current routine decision-making.

Acknowledgement

Conflict of interest

Funding

Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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