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ORIGINAL ARTICLE

Prognostic value of different CT measurements in early therapy response evaluation in patients with metastatic colorectal cancer

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Abstract

Objectives: Patients with advanced stage colorectal carcinoma (CRC) display hepatic metastases on initial staging in up to 20% of cases. The effectiveness of chemotherapy is generally evaluated by computed tomography (CT) imaging using standardized criteria (RECIST). However, RECIST is not always optimal, and other criteria have been shown to correlate with pathologic response and overall survival. The aim of this study was to evaluate the prognostic value of different CT measurement for response assessment after initiation of chemotherapy in patients with synchronous colorectal cancer liver metastases. **Methods**: Fifty-five patients with CRC and synchronous hepatic metastases were evaluated retrospectively at 2 academic centers. Different size, volume, ratio and attenuation parameters were determined at baseline and after 3 cycles of chemotherapy. The prognostic value of baseline measurements and of the change between baseline and second measurements was analyzed using Kaplan–Meier estimates. **Results**: Median time to progression was 279 days, median overall survival was 704 days. In this selective patient population, neither a significant prognostic value of initial baseline CT parameters nor a prognostic value of the change between the first and the second CT measurements was found. **Conclusion**: Initial morphological response assessment using different CT measurements has no prognostic value concerning time to progression or overall survival in patients with synchronous colorectal liver metastases.

Keywords: *CT measurement; colorectal cancer; prognosis; therapy response; tumor response.*

Introduction

Cancer of the colon and rectum (CRC) is the third most commonly diagnosed tumor type in men, and the second most common type in women worldwide[1]. It represents the second (in men) and third (in women) most common cause of cancer-related death in developed countries[1,2]. Of all patients diagnosed, up to 20% have liver metastases (CRC stage IV) on initial staging[2]. Only a minority of these patients are eligible for curative resection[3].

Systemic chemotherapy without biological agents offered a mean overall survival of 12–20 months, and 5-year survival rates of less than 5%[4]. The introduction of targeted agents such as bevacizumab and cetuximab in combination with chemotherapy has led to an increase in progression-free and overall survival (OS) rates in several clinical studies[5–8], with median OS exceeding 2 years.

Patients receiving chemotherapy are closely monitored by clinical course, laboratory parameters (e.g. tumor markers), and imaging. The evaluation of treatment response

is usually done by computed tomography (CT) after 2–3 cycles of chemotherapy[9]. The current standard criteria used to evaluate tumor response, the modified Response Evaluation Criteria in Solid Tumors (RECIST 1.1)[10], were developed to assess tumor shrinkage after cytotoxic chemotherapy, and may be limited in assessing response to biological agents, which exhibit a cytostatic mechanism of action[11]. It has been recognized that there is discordance between the World Health Organization (WHO) criteria and RECIST guidelines[12]. RECIST has also been shown to be of limited value, e.g. for therapy response evaluation in gastrointestinal stroma tumors (GIST)[13]. Furthermore, it has been reported that CT-based morphological CT criteria have a significant association with pathologic response and OS in patients with colorectal liver metastases treated with bevacizumab[11]. Functional imaging modalities like positron emission tomography (PET)/CT that focus on metabolic parameters such as glucose consumption, also provide reliable parameters for tumor response assessment[14–17]. However, although PET/CT is helpful in tumor response assessment, standardization is still partly insufficient and there is limited availability in some countries.

The aim of this study was to evaluate the prognostic value of a variety of different morphological CT measurement parameters for response assessment after initiation of chemotherapy in patients with synchronous colorectal cancer liver metastases at initial staging.

Materials and methods

Patients

Fifty-five patients (35 men, 20 women, median age 64 years, range 30–84 years) with colorectal carcinoma and synchronous hepatic metastases on initial staging CT were evaluated retrospectively at 2 academic centers (Lucerne Cantonal Hospital, Switzerland and National University Hospital, Singapore). In all patients, the primary tumor was verified by biopsy and/or surgery. Liver metastases were diagnosed by imaging. In questionable lesions, an additional biopsy was taken to confirm the presence of liver metastases. A total of 150 lesions were analyzed. For inclusion in the study, there had to be at least 1 liver metastasis, and no surgery or additional radiotherapy was allowed until the second CT. All patients received the same groups of chemotherapeutic substances according to the National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology[9]. The chemotherapy schemes applied were FOLFOX/CapeOx (5-fluorouracil, leucovorin, and oxaliplatin), XELOX (capecitabine and oxaliplatin), XELIRI (capecitabine and irinotecan), or FOLFIRI (5-fluorouracil, leucovorin, and irinotecan), partly together with either bevacizumab or cetuximab. The second CT was scheduled after 3 cycles of CapeOx, or after up to 6 cycles of FOLFIRI or XELIRI due to shorter chemotherapy intervals.

This retrospective study was approved by the institutional review boards of both institutions, and by the cantonal ethics committee.

CT

CT scans were performed with a Somatom Definition® scanner, Somatom Definition Flash® scanner, Sensation 16® scanner (Siemens Healthcare, Forchheim, Germany), or LightSpeed VCT® scanner (GE Healthcare, Fairfield, CT, USA). All CT scans were standard abdominal staging CT scans with intravenous application of 80 ml or 100 ml (depending on body weight) of non-ionic iodinated contrast medium (Ultravist® 370 mg/ml, BayerSchering Healthcare, Leverkusen, Germany; Omnipaque® 350 mg/ml, GE Healthcare, Fairfield, CT, USA). The scan delay was 45–60 s. CT scans were performed as monophasic scanning in portal venous phase at a tube current of up to 168 mAs and an effective tube voltage of up to 120 kV. Collimation was between 128×0.6 mm and 16×1.5 mm. Image reconstruction was performed with a 512×512 pixel matrix.

Data analysis

All measurements were done manually on commercial PACS workstations (Merlin Diagnostic Workcenter, Phönix-PACS, Freiburg, Germany; GE Centricity RA1000, GE Healthcare, Fairfield, CT, USA) by 2 radiologists. The reconstructed slice thickness was 3 mm or less for lesion evaluation, and 7 mm or less for liver volumetry. The reconstruction increment was 0.8 to 2.5 mm for lesion evaluation, and 2.5 to 7 mm for liver volumetry. The liver volume was measured by manually drawing a region of interest (ROI) around the contour of the liver on each axial slice that displayed liver tissue. Three types of parameters were determined for each lesion at each time point, i.e. on baseline CT and second CT: size parameters, ratios, and attenuation parameters.

Size parameters were: the maximum diameter of the largest lesion in 1 plane (meaning the longest cross-sectional dimension (max1D)); the product of the 2 maximum diameters of the largest lesion in 2 planes (max2D); the product of the 3 maximum diameters of the largest lesion in 3 planes (max3D); the sum of the longest diameters (SLD) of the 2 largest target lesions (RECIST 1.1 criteria[10]); the volume of the largest lesion, which was determined according to the method used for liver volumetry described above. Volumetric ratio parameters were the tumor-to-liver-ratio (TTLR) of the 3 largest ($TTLR_{three}$) and of all lesions ($TTLR_{all}$). Attenuation parameters as minimum, mean, and maximum Hounsfield units (HU_{min}, HU_{mean}, and HU_{max}) of the 3 largest lesions were measured by manually drawing an ROI around the margin of each lesion in each axial slice that displayed the lesion. Radiodensity
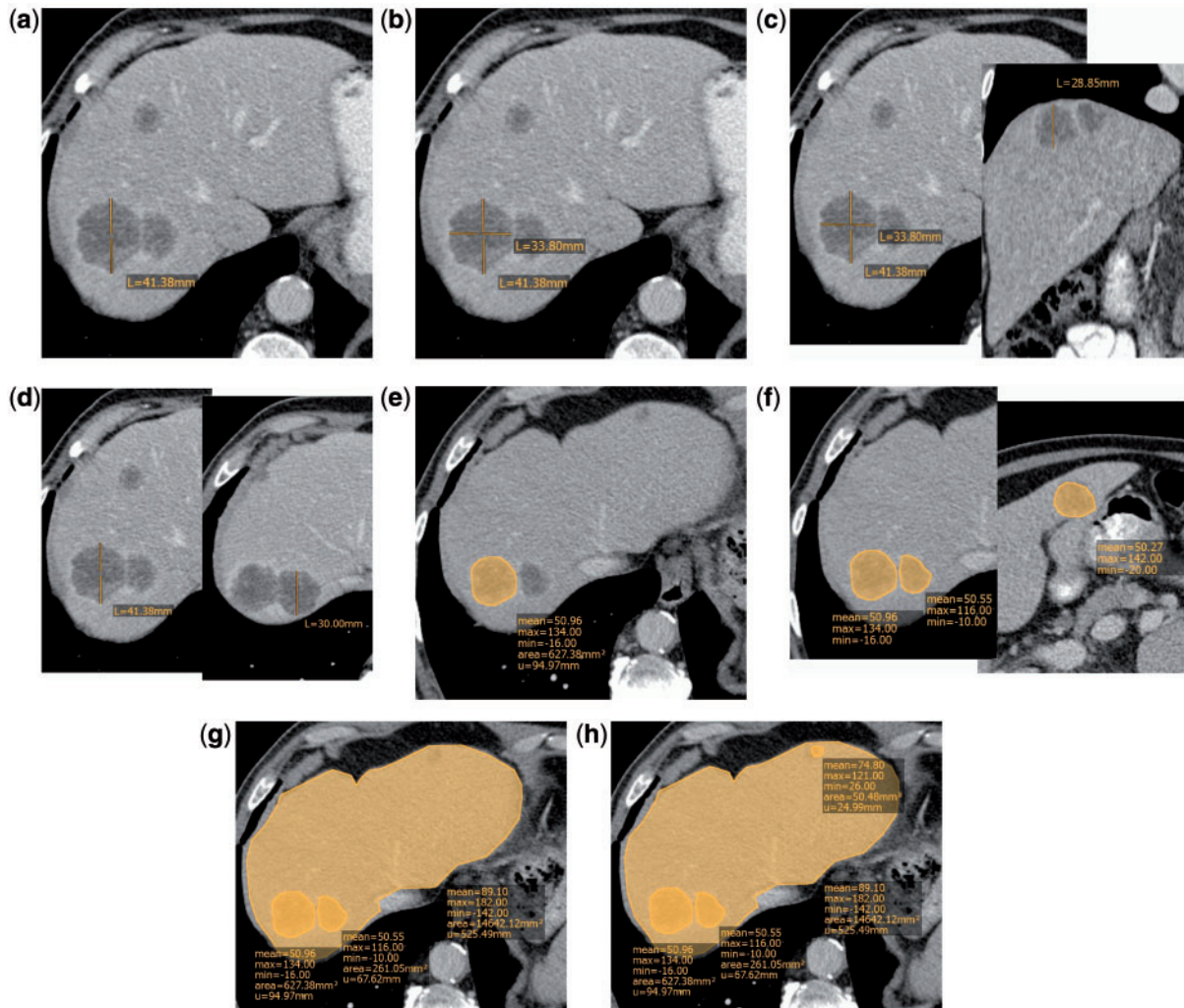
Figure 1 **Parameters determined on baseline CT and second CT. Maximum diameter of the largest lesion in 1 plane (max1D) (mm) (a); product of the 2 maximum diameters of the largest lesion in 2 planes (max2D) (mm^2) (b); product of the 3 maximum diameters of the largest lesion in 3 planes (max3D) (mm^3) (c); sum of the maximum diameters (SLD) of the 2 largest lesions (RECIST 1.1 criteria) (mm) (d); volume of the largest lesion (mm^3) (e); minimum, mean, and maximum Hounsfield units (HU$_{min}$, HU$_{mean}$, and HU$_{max}$) of the 3 largest lesions (f); tumor-to-liver-ratio (TTLR) of the 3 largest (TTLR$_{three}$) and of all lesions (TTLR$_{all}$) (%) (g).**

measurements of every slice were then combined for each lesion. All of those parameter types have already been shown to be useful in different tumor measurement scenarios[11,18–22]. Absolute and percentage changes in all parameters were calculated for each patient. A pictorial overview of the parameters is given in Fig. 1.

For all patients, the OS was identified. Time to progression (TTP), or progression-free survival, as a reflection of only the first treatment schedule, could be identified for 31 patients. A patient's disease was regarded as progressive if there was evidence of clinical progression. This was determined by the treating oncologist, based on a combination of clinical and imaging information. Imaging progression on second CT or subsequent examinations was defined if a radiologist reported a progress of disease according to generally accepted tumor response guidelines such as RECIST, e.g. growth of the primary tumor, growth of known metastases, or formation of new metastases.

Statistical analysis

For statistical analysis, certain baseline CT parameters (max1D, max2D, max3D, SLD, and volume) were divided into 3 groups: small, medium and large lesions; medium lesions were defined as being within the range of ±20% of the median value. Baseline attenuation parameters (HU$_{min}$, HU$_{mean}$ and HU$_{max}$) were also split into 3 groups; intermediate attenuation was also defined as being within ±20% of the median value. Baseline ratio parameters TTLR$_{three}$ and TTLR$_{all}$ were grouped logarithmically with intermediate ratios being defined as between

0.05 (5%) and 0.005 (0.5%). These thresholds were found to work best for creating groups as evenly distributed as possible.

All follow-up results were again divided into 3 groups: stable, progressive, and partial response. Size parameters except volume were defined as progression if they increased by 20% or more, and as partial response if they decreased by 30% or more, based on the RECIST guidelines. Volume was defined as stable if change was within −65% to +44%[18,19,21,23]. Follow-up ratio parameters $TTLR_{three}$ and $TTLR_{all}$ were regarded as stable if change was between −25% and +5%. Attenuation parameters were defined as stable if change was between −10% and +10%. This cutoff was derived statistically.

Regarding TTP and OS, the prognostic value of all baseline measurements and the prognostic value of the change between baseline and second CT measurements were determined using hazard ratios with 95% confidence intervals (95% CI) and Kaplan–Meier estimates. Survival curves were compared using the log rank (Mantel–Cox) test. A *P* value of <0.05 was considered statistically significant. The software used was IBM SPSS Statistics™ 19.0.1 (SPSS Inc., Chicago, IL, USA).

Results

Patients

The start of chemotherapy was after a mean period of 38 days (range 1–214 days) after baseline CT. The median CT interval was 101 days (range 42–435 days). The second CT was carried out after a median period of 63 days (range 28–351 days) after the start of chemotherapy. Median clinical follow-up was 727 days (range 98–2123 days). Twenty-nine patients (53%) had died by the end of the follow-up period, all due to progression of their disease. All but 1 patient showed progression of disease. Median TTP was 279 days, median OS was 704 days. Forty-four of 55 patients underwent surgery of their primary tumor confined to the current clinical stage during the course of the disease. The remaining 11 patients were not eligible for major surgery at the time of diagnosis. Median OS and TTP in patients who underwent surgery differed from that of patients without surgery (median OS/TTP with surgery 759/220 days; median OS/TTP without surgery 561/311 days). According to the histopathologic results, 15 of these patients had a T4 tumor, 28 patients had a T3 tumor, and one patient had a T2 tumor. Thirty-nine patients showed regional lymph node metastases (19 patients N2, 20 patients N1). The remaining 5 patients did not show evidence of regional lymph node involvement. The remaining 11 patients had not been treated surgically.

Baseline values

Overall, the values of the parameters determined on baseline and second CT are shown in Table 1. All size measurements decreased considerably from baseline to second CT, but attenuation parameters HU_{max} and HU_{mean} only showed only a marginal reduction. None of the parameters analyzed on the initial staging CT had a significant correlation with OS or TTP, except HU_{min} (Table 2).

Max1D showed a tendency towards a better prognosis for smaller lesions and a worse prognosis for larger lesions (Fig. 2), although all 3 groups were progressive after a similar span of time. However, this was not statistically significant. Parameters max2D and max3D

Table 1 **Results of both CT scans: mean parameters with 95% confidence intervals (CI)**

Parameters	Baseline CT	Second CT
Max1D (mm)	46.3 (36.8–55.7)	36.2 (28.6–43.7)
Max2D (mm^2)	2919 (1420.–4418)	1776 (953–2599)
Max3D (mm^3)	231650 (44582–418716)	101126 (30788–171465)
SLD/RECIST 1.1 (mm)	74.5 (59.6–89.4)	57.6 (45.2–70.0)
Volume (mm^3)	185342 (14458–356223)	78314 (27670–128958)
TTLR$_{three}$ (%)	6.28 (2.96–9.60)	3.77 (1.73–5.81)
TTLR$_{all}$ (%)	9.66 (5.97–13.35)	5.86 (3.30–8.42)
HU$_{max}$	126.5 (116.4–136.6)	113.1 (102.5–123.6)
HU$_{mean}$	68.2 (62.9–73.6)	59.8 (54.8–64.8)
HU$_{min}$	7.9 (-1.4–17.1)	10.4 (2.2–18.5)

Table 2 **Baseline CT parameters: *P* values of log rank test and hazard ratios (HR) with 95% confidence intervals (CI)**

| Parameters	*P* values of log rank test		Hazard ratios (95% CI)	
	OS	TTP	OS	TTP
Max1D (mm)	0.21	0.74	1.006 (0.996–1.015)	1.013 (0.998–1.029)
Max2D (mm^2)	0.19	0.72	1.000 (1.000–1.000)	1.000 (1.000–1.000)
Max3D (mm^3)	0.21	0.39	1.000 (1.000–1.000)	1.000 (1.000–1.000)
SLD (mm)	0.15	0.35	1.004 (1.000–1.008)	1.007 (0.999–1.014)
Volume (mm^3)	0.84	0.11	1.000 (1.000–1.000)	1.000 (1.000–1.000)
TTLR$_{three}$ (%)	0.34	0.96	2.136 (0.117–39.14)	342.6 (1.466–80032)
TTLR$_{all}$ (%)	0.39	0.19	4.200 (0.337–52.39)	36.51 (0.921–1447)
HU$_{max}$	0.75	0.46	1.008 (0.999–1.017)	0.988 (0.974–1.003)
HU$_{mean}$	0.81	0.13	0.991 (0.973–1.009)	0.978 (0.958–0.998)
HU$_{min}$	0.02	0.5	0.984 (0.972–0.996)	0.993 (0.981–1.006)
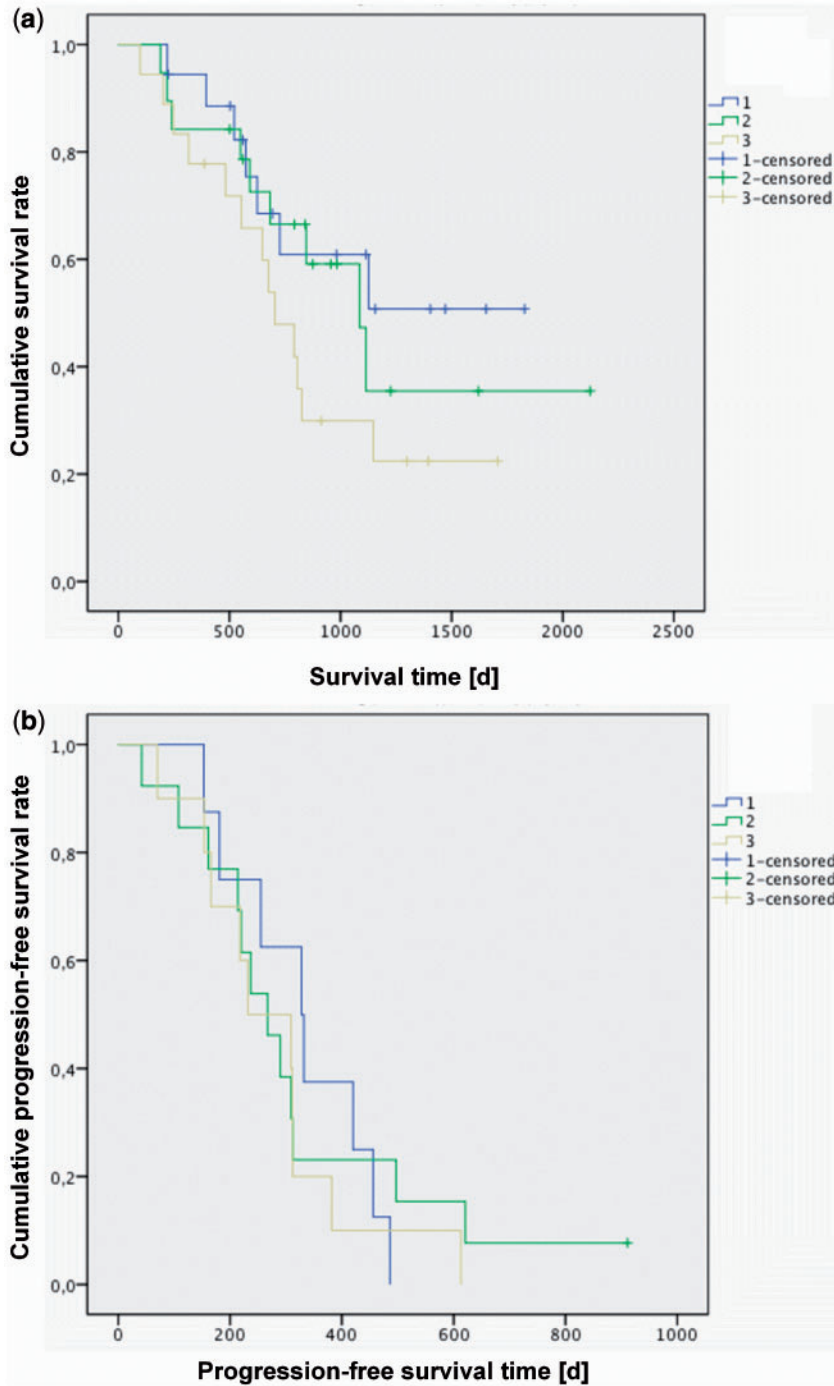
Figure 2 **Survival functions depending on baseline values of max1D (maximum diameter of the largest lesion in 1 plane). (a) OS: group 1/small lesions, *n* = 18; group 2/medium lesions, *n* = 19; group 3/large lesions, *n* = 18. (b) TTP: group 1/small lesions, *n* = 11; group 2/medium lesions, *n* = 10; group 3/large lesions, *n* = 10.**

exhibited similar values (graphs not shown). There was no association between the volume of the largest liver metastasis on the initial staging CT and OS or TTP, although there was again a trend towards better long-term prognosis (OS) for smaller lesions (graph not shown). The RECIST criterion (SLD) also showed a tendency towards better long-term prognosis (OS) for smaller lesions, although without statistical significance.

Progression-free survival for groups evaluated with SLD did not show any tendency (graph not shown). Hazard ratios for all size parameters were close to 1. Despite a slight trend, neither $TTLR_{three}$ (graph not shown) nor $TTLR_{all}$ (Fig. 3) had a significant correlation with OS or TTP. The hazard ratios for these ratio parameters were different from 1, however with very large confidence intervals. Attenuation of lesions at baseline imaging
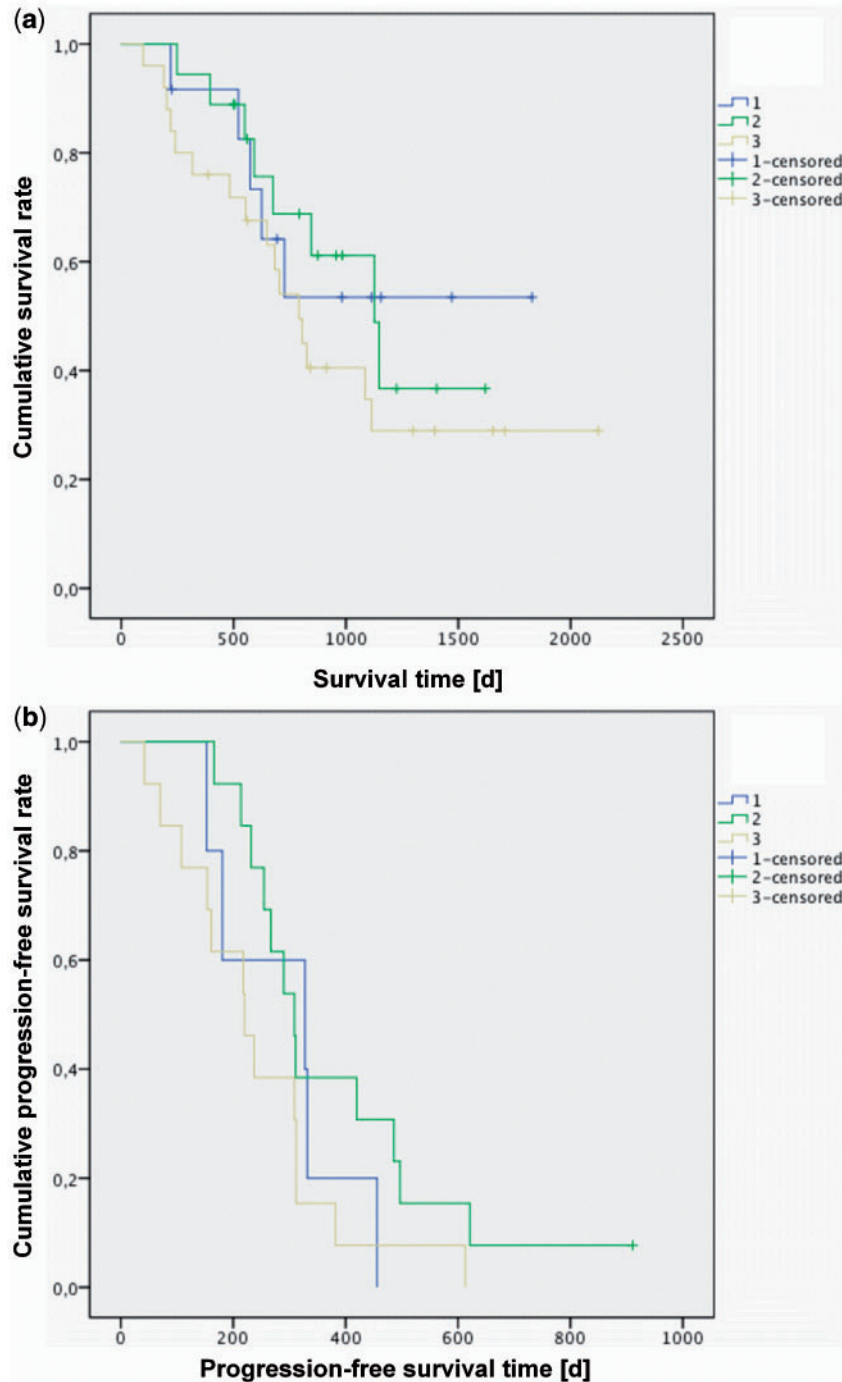
Figure 3   Survival functions depending on baseline values of $TTLR_{all}$ (tumor-to-liver-ratio of all lesions). (a) OS: group 1/low ratio, $n = 12$; group 2/medium intermediate ratio, $n = 18$; group 3/high ratio lesions, $n = 25$. (b) TTP: group 1/ low ratio, $n = 5$; group 2/intermediate ratio, $n = 13$; group 3/high ratio, $n = 13$.

revealed no concordance with prognosis, except for HU_{min} (Fig. 4) which showed statistically significant correlation with OS; prognosis was best for the group with intermediate HU_{min} lesions, and worse for the group with high HU_{min} lesions. HU_{max} and HU_{mean} (graphs not shown) had no prognostic value. Hazard ratios for all attenuation parameters were close to 1.

Trend values

The change in the parameters between baseline CT and second CT had no significant impact on OS or TTP (Table 3). Patients with progressive maximum diameter of the largest lesion (max1D, Fig. 5) had a tendency towards longer OS, but without statistical significance.
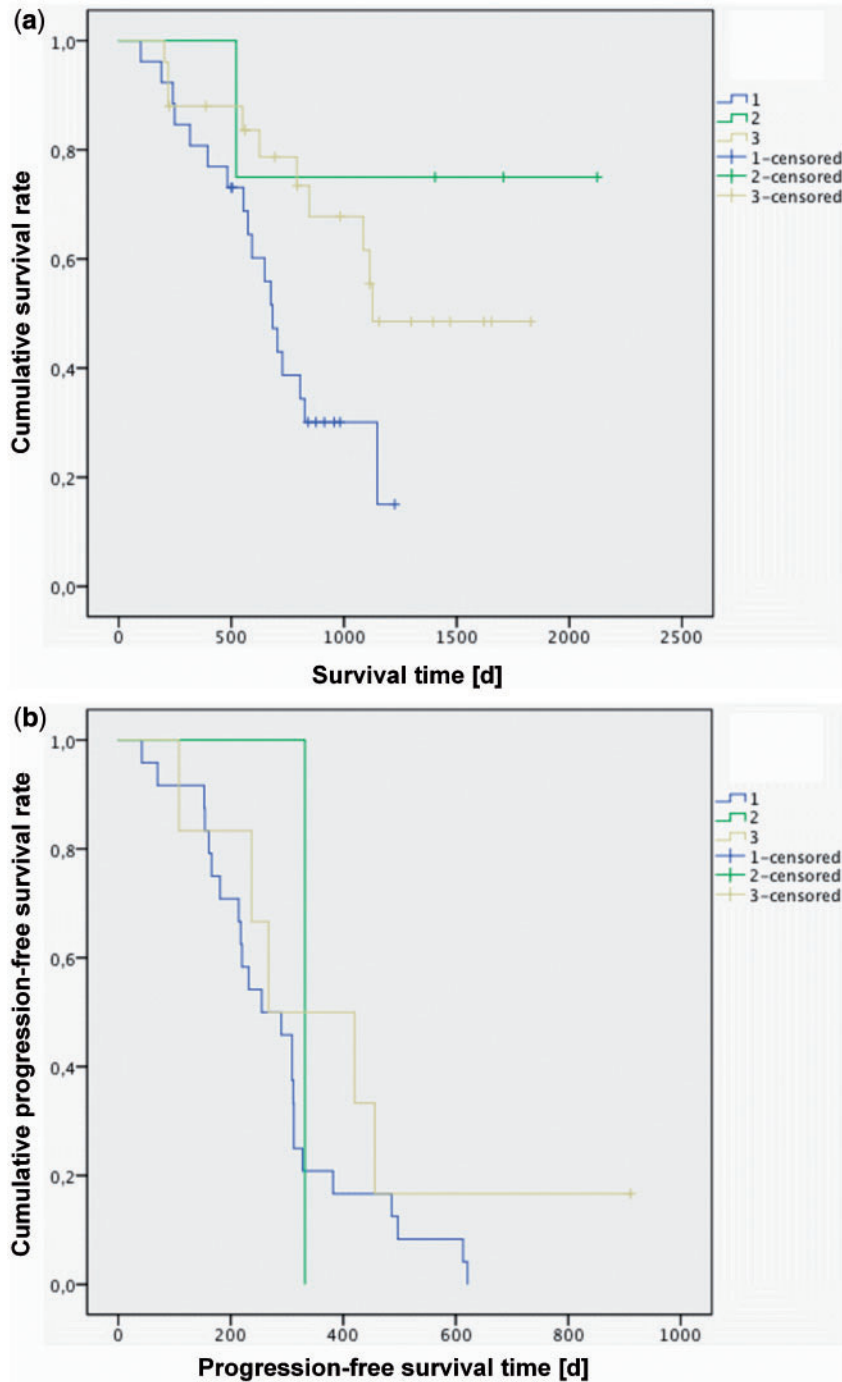
(a)

(b)

Figure 4 **Survival functions depending on the baseline values of HU_{min} (minimum Hounsfield units of the 3 largest lesions). (a) OS: group 1/low HU_{min} lesions, $n = 26$; group 2/intermediate HU_{min} lesions, $n = 4$; group 3/high HU_{min} lesions, $n = 25$. (b) TTP: group 1/low HU_{min} lesions, $n = 24$; group 2/intermediate HU_{min} lesions, $n = 1$; group 3/high HU_{min} lesions, $n = 6$.**

No tendency could be seen concerning TTP. Trend values of parameters max2D and max3D revealed curves without perceptible tendencies concerning OS or TTP (graphs not shown). The change in the volume of the largest liver metastasis was not related to OS or TTP.

The RECIST classification also had no prognostic effect (Fig. 6). Hazard ratios for all size parameters were again close to 1. Neither the trend for $TTLR_{three}$ or $TTLR_{all}$ was related to OS or TTP (graphs not shown). In contrast to the baseline values, hazard ratios for the trend values

Table 3 **Trend CT parameters: *P* values of log rank test and hazard ratios (HR) with 95% confidence intervals (CI)**

Parameters	*P* values of log rank test		Hazard ratios (95% CI)	
	OS	TTP	OS	TTP
Max1D (mm)	0.12	0.91	0.739 (0.275–1.981)	1.414 (0.384–5.207)
Max2D (mm^2)	0.33	0.47	0.848 (0.485–1.482)	1.388 (0.601–3.207)
Max3D (mm^3)	0.67	0.76	0.911 (0.707–1.174)	1.236 (0.620–2.464)
SLD/RECIST 1.1 (mm)	0.78	0.76	0.832 (0.401–1.724)	1.372 (0.395–4.762)
Volume (mm^3)	0.68	0.91	0.910 (0.730–1.136)	1.139 (0.702–1.848)
TTLR$_{three}$ (%)	0.66	0.91	0.946 (0.818–1.094)	1.116 (0.736–1.693)
TTLR$_{all}$ (%)	0.58	0.91	0.974 (0.908–1.045)	1.036 (0.706–1.522)
HU$_{max}$	0.61	0.40	0.983 (0.966–1.001)	1.004 (0.988–1.020)
HU$_{mean}$	0.68	0.79	0.984 (0.963–1.005)	0.993 (0.961–1.025)
HU$_{min}$	0.83	0.16	0.989 (0.970–1.010)	0.986 (0.965–1.008)

were close to 1. Change in HU$_{max}$, HU$_{mean}$ or HU$_{min}$ was again not related to OS or TTP, although there was a statistically non-significant tendency towards longer OS for patients with increasing HU$_{mean}$, and towards longer TTP for patients with increasing HU$_{min}$ (graphs not shown). Hazard ratios for all attenuation parameters were again close to 1.

Discussion

Although several studies have already investigated the possible prognostic value of baseline CT and early second CT in different tumor entities, no study has systematically evaluated all potential measurements in one study in such a specific patient population.

In this selective patient population, neither a significant prognostic value of initial baseline CT parameters (except HU$_{min}$) nor a significant prognostic value of the change between the baseline and the second CT measurement was found.

Unidimensional parameters are readily applicable. The current standard in assessing response of solid tumors to oncologic therapy by CT is still RECIST[10,13]. These criteria have been developed to evaluate decrease in tumor size after cytotoxic chemotherapy, and it has been shown that they are limited in assessing tumor response to biological agents, which exhibit a cytostatic mechanism of action (e.g. bevacizumab), used for the treatment of colorectal liver metastases[11]. In general, targeted therapies with receptor or angiogenesis inhibitory agents may make RECIST inappropriate[13,24–26]. In this study, RECIST 1.1 was again not helpful in predicting the intermediate (TTP) or final outcome (OS) of patients treated with chemotherapy with or without biologicals. Considering only the longest diameter of the largest lesion (max1D) was not useful either. However, it still showed the best *P* value concerning the trend between baseline and second CT when relating to OS, but that is probably related to the small number of patients in certain subgroups.

In recent years, new response criteria with different response parameters have been proposed, which are often tumor specific or modality bound, e.g. Choi criteria for GIST response assessment to imatinib, Cheson criteria or International Working Group (IWG) criteria for malignant lymphoma by PET/CT, MacDonald criteria for malignant glioma by contrast-enhanced CT or magnetic resonance imaging (MRI), and different other criteria for malignant pleural mesothelioma and bone tumors[27–32]. With the increasing use of imaging to evaluate an increasing number of therapeutic options, these various response parameters have contributed to rising concern about the general sensitivity of conventional tumor response criteria[13,16,33].

This is partly in line with our results because the attenuation criteria HU$_{mean}$ showed a trend towards better TTP when measured at baseline, and HU$_{min}$ at baseline was the only parameter found to be statistically significant when relating with OS. Hazard ratios for these parameters at baseline and second CT were close to 1, so any prognostic value is excluded.

Volumetric measurement traditionally played a minor role in tumor response evaluation due to its time-consuming evaluation. With the introduction of digital PACS workstations and automated volume calculation programs, volumetry became more interesting, but still needs additional software resources. Intraindividual comparisons between RECIST and volumetric data revealed differences[21,34,35] regarding tumor response evaluation with partial advantages for volumetric measurements.

A three-dimensional quantification of lesion volume or organ-based tumor load leads to less abstractions than a simplified evaluation according to RECIST or WHO[18,21,36]. In our study, the baseline volume of the largest lesion showed a (partial) correlation with TTP. More simplified two- (max2D) and three-dimensional data (max3D) were also not helpful. But with hazard ratios close to 1 for both baseline and second CT values, these size parameters have to be omitted. Even complex volumetry of the 3 largest (TTLR$_{three}$) and of all lesions (TTLR$_{all}$) related to the liver volume was of no significance, although it has been shown to be useful in patients with hepatocellular carcinoma[22]. Thus, even the most summarizing morphological parameter,
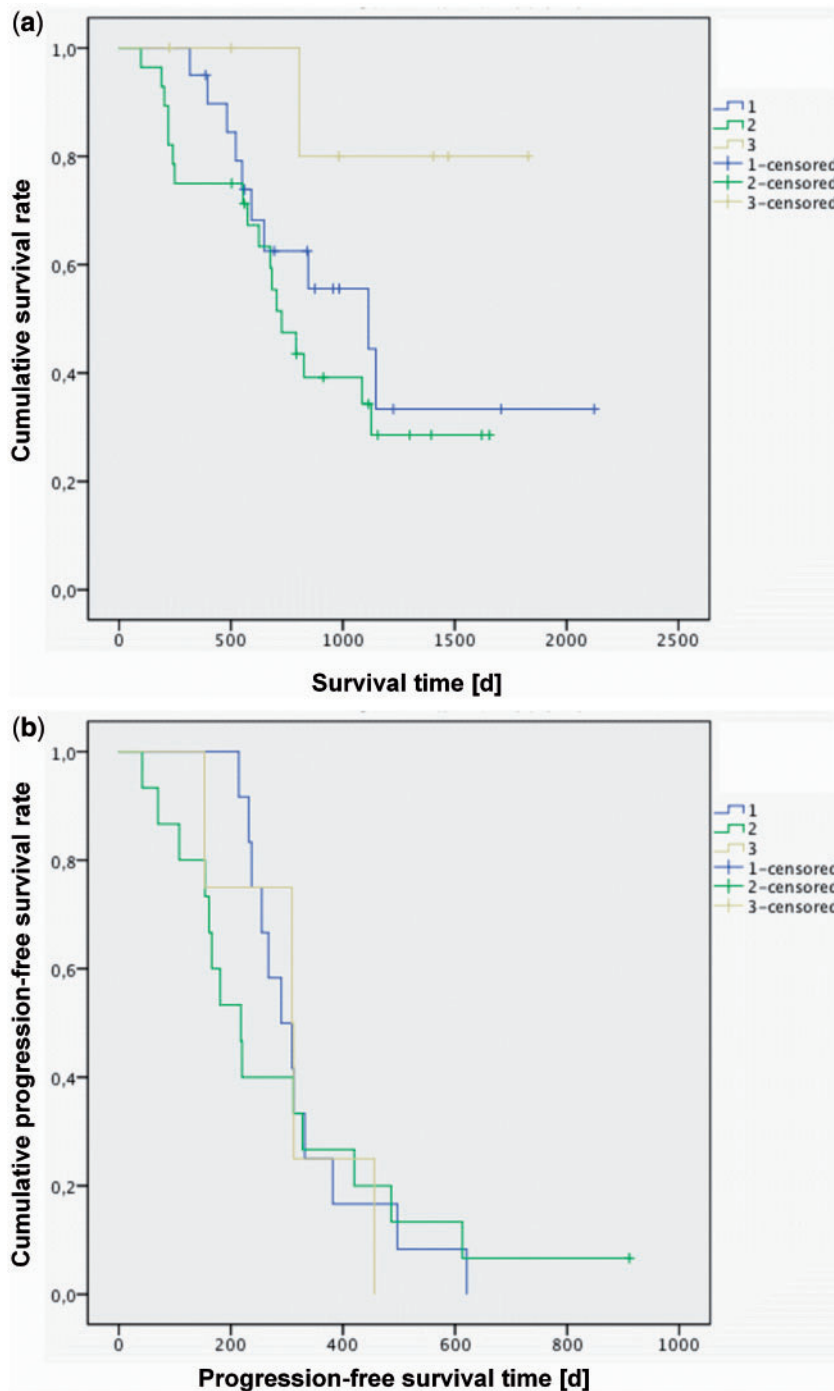
Figure 5 Survival functions depending on trend values of max1D (maximum diameter of the largest lesion in 1 plane). (a) OS: group 1/regressive lesions, $n = 20$; group 2/stable lesions, $n = 28$; group 3/progressive lesions, $n = 7$. (b) TTP: group 1/regressive lesions, $n = 12$; group 2/stable lesions, $n = 15$; group 3/progressive lesions, $n = 4$.

i.e. relative tumor load shrinkage, was not associated with prolonged OS or progression-free survival rates. It is obvious that the dimensions of a tumor may not accurately reflect its intrinsic biological activity, as has been shown for GIST treated with imatinib[13].

Recently, other morphology-based CT criteria have been proposed for tumor response assessment[11,13,37].

Among them are the definition of lesion margins, homogeneity of lesions, and total and relative attenuation of lesions. Tumor radiodensity parameters do not play a role in traditional tumor response assessment. Like size measurements, they are readily applicable and, other than margins or homogeneity, can be quantified objectively and may be measured on images in clinical routine[13]. It is believed that a decrease in
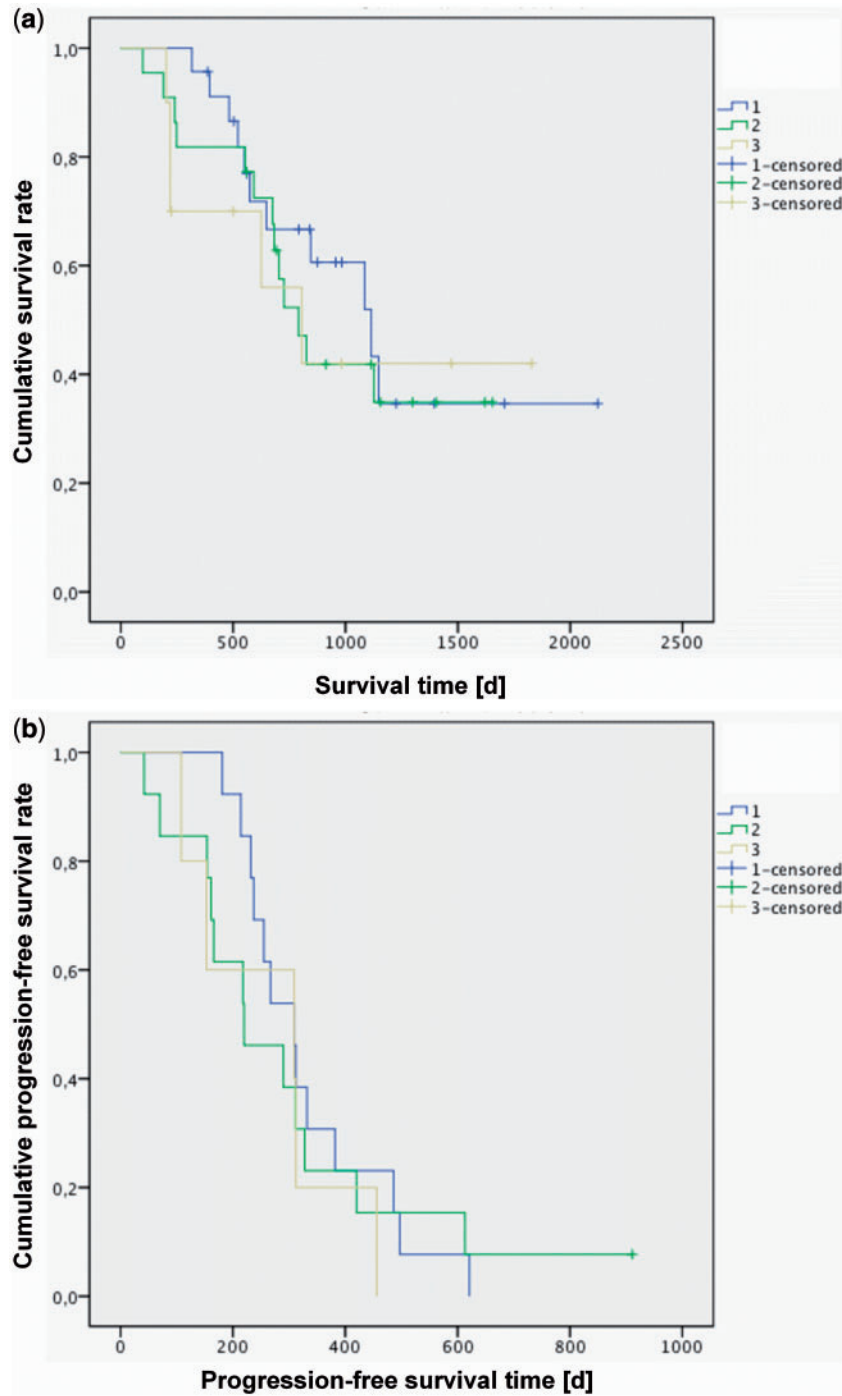
Figure 6 **Survival functions depending on trend values of SLD (sum of the longest diameters) of the 2 largest lesions (RECIST 1.1). (a) OS: group 1/partial response (PR), $n = 23$; group 2/stable disease (SD), $n = 22$; group 3/progressive disease (PD), $n = 10$. (b) TTP: group 1/partial response (PR), $n = 13$; group 2/stable disease (SD), $n = 13$; group 3/progressive disease (PD), $n = 5$.**

density of responding lesions reflects necrosis, cystic or myxoid degeneration, or decreased perfusion[13,38]. That might be a possible explanation why Hounsfield units at least partly seem to have correlations with outcome. However, it is still controversial if the extent of necrosis in liver metastases in relation to the surrounding tumor tissue increases or decreases after the initiation of chemotherapy[39,40]. In addition, morphological changes to hepatic tissue caused by chemotherapeutic agents, such as steatosis or sinusoid obstruction, may lead to an underestimation of metastases[37,41].

Although baseline HU_{min} was of statistical significance concerning OS, we cannot exclude that this is due to the small number of individuals in some of the subgroups analyzed. With a more homogeneous distribution of individuals, no statistical significance has been observed for HU_{min} trend. Another study focusing on neoadjuvant treatment of colorectal liver metastases also found no differences in density before and after chemotherapy[37].

The reason why we did not observe any impact of the parameters analyzed on clinically relevant end points such as OS and TTP is probably a change in therapy respecting the results of the second CT scans. CT reports state if there is progressive, stable or remittent disease, according to established response assessment criteria such as RECIST. These measurements support therapeutic decisions and therapy is adapted accordingly. For colorectal liver metastases, there are several chemotherapeutic options available, which are given as palliative second and third line treatments. Hence, if therapy is changed, the statistical impact of the baseline measurements and of the follow-up trends on OS might be lost. Thus, baseline CT and second CT data may not deliver sufficient prognostic information, at least not for OS since TTP represents only a single treatment schedule.

Other clinical studies evaluating liver metastases from GIST might not have been subjected to such course of therapy because no appropriate second-line therapy was available at that time[13]. While the introduction of imatinib, and later sutinib, as second-line treatment had a highly positive impact on GIST therapy[42], such developments are still to come for colorectal liver metastases. On the other hand, there are promising combined chemotherapeutic options for these lesions. New treatment strategies for colorectal liver metastases, comprising targeted drugs with biological mechanisms, may furthermore accentuate the need for new response criteria[43].

Besides CT-based morphological criteria, quantifiable metabolic criteria from PET/CT imaging (standardized uptake value $(SUV)_{max}$) are reliable parameters for tumor response assessment[14–17]. Morphological changes of tumors may occur late in the course of treatment, while metabolic changes happen within a few hours[43,44], which already may give an indication of prognosis. However, PET/CT scanners are not as widely available as CT scanners, and patients with newly diagnosed colorectal cancer usually are not evaluated primarily by PET/CT.

Limitations

Our study has several limitations. The study design was retrospective and the study cohort was relatively small, although highly specific. Partly different treatment schedules were applied within the range of international guidelines for advanced CRC. While none of the 55 patients was lost to follow-up, the exact date of progression was available only from 31 patients. Hence, survival curves for all parameters were similar concerning TTP

and OS, with the exception of the inequality of HU_{min} levels on baseline CT.

Since the inclusion criterion was synchronous hepatic colorectal metastasis, lesions were partly heterogeneous in shape, size and number, ranging from a few well-defined small metastases to many large metastases with ill-defined borders. The time when patients are initially diagnosed with hepatic metastases is often not related to the course of these lesions themselves, but to the size and local effects of the primary tumor, e.g. large bowel obstruction, or might be completely coincidental. Furthermore, a few patients also had lung metastases and/or advanced nodal stage. The relevance of the different OS and TTP in surgical versus non-surgical patients remains unclear, as the patient count in the non-surgical group was too small.

Another limitation was the partly unequal distribution of the groups for the statistical analysis. However, generally accepted limits of grouping for volumetry and uni- and bidimensional measurements have been used, if available. Furthermore, the time until the start of chemotherapy was variable, because some patients had to undergo emergency surgery of the primary tumor, and post-operative worsening of their clinical condition made a prompt initiation of chemotherapy impossible. But these delays are common problems in clinical routine, and the second CT was performed after 3 cycles of chemotherapy anyway.

Outlook

Novel targeted therapy regimens with receptor inhibitory drugs or antiangiogenic agents may lead to more effectiveness, and to additional inappropriateness of the traditional RECIST-based decision making. For example, it has been shown that epidermal growth factor receptor (EGFR) as well as k-ras mutations are negative predictive factors for treatment response, and BRAF mutations are negative predictive factors for survival in patients with colorectal cancer[45–48]. Thus, future chemotherapeutic regimens may obviate traditional response assessment criteria and emphasize the need for new predictive and probably combined morphological and metabolic imaging criteria.

Conclusion

Initial morphological response assessment using different CT measurements and the assessment of the incipient change in these parameters had (almost) no statistically significant prognostic value concerning TTP and OS in patients with synchronous colorectal liver metastases. The possible reason might be that several consecutive therapy lines with different chemotherapy classes are used. Complex morphological imaging criteria do not perform better than standard criteria used in daily routine. Hence, morphological imaging criteria might be

used for evaluation of the current disease status but not for predicting the final outcome in this selective patient population. The conclusion of this study is partly limited by the somewhat diverse patient group. Further studies might be needed to determine if there is a predictive morphological and measurable parameter in a larger group of patients.

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