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Heterogeneous radiological response to neoadjuvant therapy is associated with poor prognosis after resection of colorectal liver metastases

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ABSTRACT

Introduction: Surgery combined with perioperative chemotherapy has become standard of care in patients with resectable colorectal liver metastases. However, poor outcome is expected for a significant subgroup. The clinical implications of inter-metastatic heterogeneity remain largely unknown. In a prospective, population-based series of patients undergoing resection of multiple colorectal liver metastases, the aim was to investigate the prevalence and prognostic impact of heterogeneous response to neoadjuvant chemotherapy.

Materials and Methods: Radiological response to treatment was evaluated in a lesion-specific manner in 2–5 metastases per patient. Change of lesion diameter was evaluated and response/progression was classified according to three different size thresholds; 3, 4 and 5 mm. A heterogeneous response was defined as progression and response of different metastases in the same patient.

Results: In total, 142 patients with 585 liver metastases were examined with the same radiological method (MRI or CT) before and after neoadjuvant treatment. Heterogeneous response to treatment was seen in 16 patients (11%) using the 3 mm size change threshold, and this group had a 5-year cancer-specific survival of 19% compared to 49% for patients with response in all lesions ($p = 0.003$). Cut-off values of 4–5 mm were less sensitive for detecting a heterogeneous response, but the survival difference was similar and significant.

Conclusion: A subgroup of patients with multiple colorectal liver metastases had heterogeneous radiological response to neoadjuvant chemotherapy and poor prognosis. The evaluation of response pattern is easy to perform, feasible in clinical practice and, if validated, a promising biomarker for treatment decisions.

Introduction

Hepatic resection is considered to be the only potentially curative treatment of colorectal liver metastases (CRLM) [1]. With the increased use of new oncological, surgical and ablative treatments, the indications for surgery have expanded, and about 25% of CRLM patients are offered liver resection today. A five-year overall survival of about 50% is typical in non-selected series [2], with early

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relapse and death after surgery in about one third of the patients. At present there is no reliable way to identify these patients, and precise markers for patient stratification and treatment selection are highly warranted. Traditional prognostic scores like Nordlinger [3] and Fong [4] are less reliable after the introduction of extensive perioperative treatment.

Perioperative treatment usually includes chemotherapy and in some cases targeted treatment with the aim to improve outcome, although the evidence for this is weak [5,6]. The response to neoadjuvant therapy is evaluated by computed tomography (CT) and/or magnetic resonance imaging (MRI) before and after treatment, but whether there is an association between response and prognosis after resection is debated. Several studies have demonstrated that progression during neoadjuvant therapy is a poor prognostic marker [7–10], and some argue that these patients should not undergo resection.

Cancer progression during chemotherapy is caused by the presence of resistant cancer cells. As the cancer cells of a patient can gain resistance mechanisms at any time during cancer evolution, patients with multiple liver metastases could harbor metastases with varying sensitivity to chemotherapy. In daily routine, the response to neoadjuvant chemotherapy is usually reported based on the overall change in diameter of metastatic lesions and classified as complete or partial response, stable disease, or progression. The recommended method of assessing objective response in clinical trials, mainly used for evaluation of response to palliative oncological treatment, is the Response Evaluation Criteria in Solid Tumours (RECIST) [11]. Here, the total tumor burden is evaluated by selecting up to five target lesions (up to two in each organ) and calculating the average diameter change; a reduction of at least 30% is classified as response, and an increase of at least 20% as progression. These methods only evaluate gross change in tumor burden and do not consider potential subtle differences in response among metastases in a patient. A heterogeneous response pattern has been demonstrated to reflect molecular heterogeneity [12], and a prognostic association has been shown both for unresectable metastatic colorectal cancer [13] and other cancer types [14,15]. Still, little is known about response heterogeneity of colorectal liver metastases to chemotherapy before resection.

In this study, the aim was to explore prevalence and prognostic impact of intra-hepatic inter-metastatic heterogeneity in response to neoadjuvant treatment. We tested a comprehensive new radiological method to classify the response pattern, sensitive to small changes in size of multiple liver lesions in each individual.

Material and methods

Patients and samples

The SMART (Screening, Management, Research, Translation) study is an ongoing project including patients admitted to Oslo University Hospital for resection of CRLM. The present substudy included patients admitted in the period October 2013 to December 2016, who received neoadjuvant treatment before resection of at least two liver metastases, and with either MRI or CT examinations taken both before and after neoadjuvant treatment. Occasionally, liver resection was combined with radiofrequency ablation of non-resectable liver metastases, and also in the presence of extrahepatic metastases, if these were considered resectable. Patients participating in the Oslo COMET study [16] (laparoscopic versus open liver resection) were not included. A comprehensive clinico-pathological dataset was registered prospectively. Approvals were given from the Norwegian Data Protection Authority and the Regional Committee for Medical and Health Research Ethics, South-Eastern Norway (REC: 1.2005.1629; 2010/1805), and all patients provided written informed consent.

Liver metastases were usually detected on CT scans during standard diagnostic work-up after diagnosis of colorectal cancer or during follow-up after surgery. Supplementary MRI of the liver was performed in the majority of patients. Treatment response to neoadjuvant therapy in the liver was evaluated by either MRI or CT depending on the policy of the local hospitals, as the radiological examinations were performed in several hospitals in the South-Eastern Norway health region.

All patients were discussed in multi-disciplinary team meetings before and after neoadjuvant treatment for evaluation of resectability, surgical strategy and perioperative oncological treatment. Adjuvant treatment was given when recommended. All patients entered a follow-up program with CT of the liver and lungs and CEA measurement every four months for the first year, then every six months for a total of five years.

Radiological evaluation of treatment response

All radiological examinations were reviewed retrospectively by one radiologist (VC) blinded to treatment and outcome. Difficult cases were reviewed by another radiologist (AA) and consensus reached.

Response classification was based on size measurements of the largest liver lesions, up to five if possible, also including new liver lesions appearing during neoadjuvant treatment. Only the response pattern of the liver metastases was used to classify response, disregarding the status of metastases in other sites. The largest diameter of each liver lesion was measured and the target lesions were classified as progressed, unchanged or regressed. We chose a threshold of 3 mm (mm) based on image resolution for sensitive detection of response heterogeneity. Hence, if size after neoadjuvant chemotherapy was within ±2 mm of baseline, the response was classified as no change. In addition the lesions were classified using thresholds of 4 and 5 mm. If one or more lesions responded while one or more lesions progressed, using the same threshold values, the response was classified as heterogeneous. If new liver lesions appeared during treatment and the other lesions were unchanged, the response was classified as progression; however, if new lesions appeared during treatment when one or more lesions responded, a heterogeneous response was recorded.

The response was also classified according to RECIST 1.1 (evaluating liver lesions only).

All CT exams were performed on machines with 16 or more detector rows. MRI exams were performed on machines with 1.5 or 3 T field strength. With CT, size measurements were performed on axial slices with a thickness of 3 mm, obtained in the portal venous phase after intravenous contrast medium injection. With MRI, size measurements were performed on axial, fat-suppressed T1-weighted images obtained in the hepatobiliary phase after intravenous injection of disodium gadotexate (Primovist, Bayer Healthcare, Berlin, Germany). Slice thickness was 3 mm or less. Measurements were performed using EIZO Flexscan MX210 (21.3 inch, resolution 1600x1200, EIZO, Japan) on PACS workstations (Sectra, Linköping, Sweden) using electronic calipers.

Statistics

Five-year overall (5y-OS) and cancer-specific (5y-CSS) survival, and 3-year disease-free and progression-free survival, were calculated according to the Kaplan-Meier method. The time to event or censoring was calculated from start of neoadjuvant treatment. For OS, all deaths were registered as events, and patients surviving >5 years were censored. For CSS, death from colorectal cancer was defined as event and patients were censored 5 years after start of

treatment or when deceased of other causes [17]. Patients with residual disease (intra- and/or extrahepatic) were excluded for calculation of disease-free survival, and recurrence anywhere and death of all causes were registered as events. Progression-free survival included all patients, and recurrence or progression anywhere and death of all causes were registered as events. Patients dying of complications <90 days after surgery were excluded in OS, disease-free and progression-free survival. Comparisons of survival distributions were performed with the log-rank test. Fisher's exact test was used on categorical data and Independent-Samples Kruskal-Wallis test on continuous data. Two-sided *p*-values of less than 0.05 were considered statistically significant.

All statistical analyses were performed with IBM SPSS software version 25.0 (IBM®SPSS® Statistics for Windows, IBM Corporation, New York, USA).

Results

Patient cohort

In the study period, 347 patients were included in the SMART study, of whom 203 underwent resection of two or more metastases after neoadjuvant treatment. Radiological images were not available in 35 patients, and for various other reasons 26 patients were excluded (Fig. 1). Accordingly, 142 patients (70% of those who fulfilled the inclusion criteria) were included in the analyses; 83 (58%) men and 59 women with a median age of 67 (range 21–80) years.

The analyses were based on MRI in 89 and CT scans in 53 patients. Clinico-pathological details are presented in Table 1.

Outcome

In total, 117 (82%) had a R0-R1 resection, whereas 5 (4%) had residual disease (R2) in liver, 17 (12%) had extrahepatic metastases and 3 (2%) had both intra- and extrahepatic residual disease. Eighty-seven (74%) experienced relapse after R0-R1 resection after median 11 months (range 3–44); 40 (46%) in the liver, 32 (37%) extrahepatic and 15 (17%) with both.

Three patients died of complications within 90 days after surgery. During the observation period of median 37 (range 6–60) months, 67 (60%) patients died of colorectal cancer and four patients died of other not cancer-related disease. The estimated overall survival (excluding those dying of complications within 90 days) was median 46 months (95% CI 40–52).

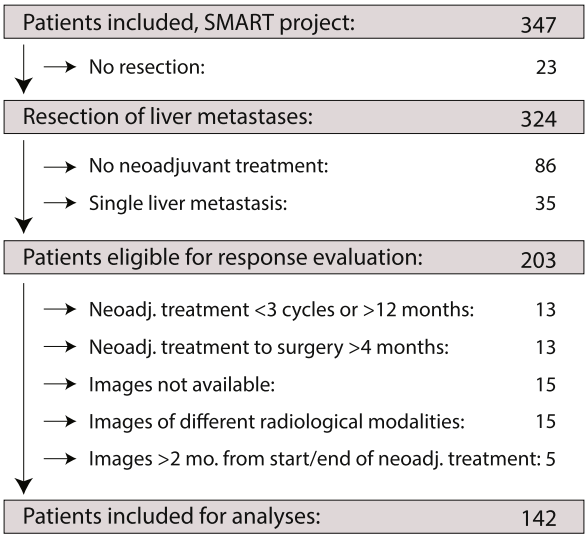

Fig. 1. Flowchart of patient inclusion.

Classification of response to neoadjuvant treatment

A total of 585 metastatic lesions (2–5 per patient) were evaluated for size changes. The response classification according to cut-off values of 3, 4 or 5 mm is shown in Table 2. The majority of patients had a similar response in all metastatic lesions, predominantly (74–79% depending on cut-off value) response in all lesions. However, a subgroup had a heterogeneous response with progression of some lesions and response in others, and this subgroup varied from 11% to 6% with cut-off values from 3 to 5 mm.

The clinico-pathological details of patients in the different response groups are shown in Table 1. The groups were similar except that those with a heterogeneous response had received more chemotherapy cycles (median 5 vs. 4) and had more liver metastases (median 8.5 vs. 5) than patients with a homogeneous response pattern.

The response classification according to our method and RECIST is shown in Table 2. A large proportion (41%) of those with response in all lesions according to the 3 mm cut-off method had stable disease according to RECIST. Patients with heterogeneous response according to the 3 mm cut-off method had stable disease (62.5%) or progression (37.5%) according to RECIST.

Outcome according to treatment response

The 13 patients with progression according to RECIST had inferior 5-year overall survival compared to patients with partial response, median 33 months (95% CI 19–47) vs. > 60 months ($p = 0.026$). Survival of patients with stable disease was median 47 months (95% CI 39–55) and not significantly different from those with partial response ($p = 0.326$).

Using the new classification method, median 5-year overall survival of patients with heterogeneous response was 23 months (95% CI 15–31) versus 49 months (95% CI not reached) for patients with response in all lesions ($p = 0.008$), using 3 mm as threshold. The median 5-year cancer-specific survival for the same groups were 23 months (95% CI 15–31) versus 50 months (95% CI not reached, $p = 0.003$), see Figs. 2–3a. The results for 5y-CSS for patients with heterogeneous response versus response in all were similar using a threshold of 4 mm ($p = 0.001$) and 5 mm ($p = 0.001$), see Fig. 3b and c.

For patients with stable disease and progression in all lesions, both 5y-OS and 5y-CSS were 32 months (95% CI 13–51) and 34 months (95% CI not reached), respectively, with a 3 mm threshold (Figs. 2–3a). These response groups were too small for meaningful comparisons of survival. However, with a 5 mm threshold, 5y-CSS for patients with stable disease (n = 18) was 48 months (95% CI 34–62) compared to 50 months for patients with response in all lesions (n = 105, 95% CI not reached). Similarly, the survival for patients with progression in all lesions (n = 10) was converging with survival of the heterogeneous response group (n = 9) with a median 5y-CSS of 25 (95% CI 14–36) and 21 months (95% CI 9–33), respectively. With this cut-off, patients with progression in all lesions also had significantly shorter survival than patients with response in all ($p = 0.031$), see Fig. 3c.

Survival was associated with number of metastases. Five-year CSS in patients with 2–4 metastases was >60 months vs. 41 months (95% CI 31–51) for patients with 5–12 metastases ($p = 0.033$), and median 33 months (95% CI 13–53) for patients with >12 metastases.

Table 1
Clinico-pathological characteristics of all patients and according to radiological response pattern of liver lesions, 3 mm cut-off. Homogeneous response: Response in all or stable disease.

Variable	All patients n = 142		Heterogeneous response, n = 16		Progression in all, n = 8		Homogeneous response, n = 118		
	n	(%)	n	(%)	n	(%)	n	(%)	*p*-value
Primary tumor in right colon[a]	**31**	**(22)**	5	(31)	2	(25)	24	(20)	0.540
Positive nodal status primary tumor	**95**	**(70)**	11	(73)	5	(83)	79	(69)	0.851
Previous resection of CRLM	**21**	**(15)**	0		2	(25)	19	(16)	0.125
Synchronous liver metastases[b]	**109**	**(77)**	14	(88)	6	(75)	89	(75)	0.607
Chemotherapy for CRLM									0.143
5-FU	**2**	**(1)**	0		0		2	(2)	
Oxaliplatin/5-FU	**83**	**(58)**	9	(56)	3	(38)	70	(59)	
Irinotecan/5-FU	**44**	**(31)**	3	(19)	3	(38)	38	(32)	
Both oxaliplatin and irinotecan	**14**	**(10)**	4	(25)	2	(25)	8	(7)	
Targeted agents for CRLM	**46**	**(32)**	4	(25)	3	(38)	39	(33)	0.764
Median (range) number of cycles	**4**	**(3–15)**	5	(3–15)	5.5	(4–15)	4	(3–12)	***0.006***
Median (range) number of CRLM[c]	**6**	**(2–21)**	8.5	(4–21)	4.5	(2–8)	5	(2–21)	***0.001***
Median (range) number of measured metastases	**5**	**(2–5)**	5	(4–5)	4	(2–5)	5	(2–5)	***0.008***
Median (range) size CRLM, mm[c]	**33**	**(8–159)**	35	(12–73)	27	(20–61)	34	(8–159)	0.803
Largest metastasis >5 cm	**38**	**(27)**	5	(31)	1	(13)	32	(27)	0.688
Laparoscopic procedure	**27**	**(19)**	1	(6)	2	(25)	24	(20)	0.352
Two-stage hepatectomy	**33**	**(23)**	5	(31)	1	(13)	27	(23)	0.659
Radiofrequency ablation	**28**	**(20)**	0		1	(13)	27	(23)	0.057
R-status liver									0.232
R0-resection	**55**	**(39)**	6	(38)	2	(25)	47	(40)	
R1-resection[d]	**79**	**(56)**	9	(56)	4	(50)	66	(56)	
R2-resection[e]	**8**	**(6)**	1	(6)	2	(25)	5	(4)	
Metastases other locations (%)	**20**	**(14)**	3	(19)	3	(38)	14	(12)	0.077

[a] Including the transverse colon.
[b] Detected within 6 months of primary tumor diagnosis.
[c] Visible on radiologic imaging.
[d] < 1 mm margin or RFA treatment.
[e] Not completed second stage hepatectomy due to disease progression in observation period (n = 4), missing lesions after neoadjuvant chemotherapy (n = 3) and new lesions discovered during hepatectomy (n = 1).

Table 2
a) Radiological response in individual metastatic lesions after neoadjuvant treatment, according to cut-off value for change in largest diameter of 3, 4 and 5 mm, n = 142. b) Response pattern, comparison of our classification (3 mm cut-off) and RECIST, n = 142.

	(a) New method			(b) New method vs. RECIST			
	Cut-off value			New method	RECIST 1.1		
	3 mm	4 mm	5 mm	Cut-off 3 mm	Partial response	Stable disease	Progression
Response in all (%)	**112 (79)**	109 (77)	105 (74)	**112**	66	46	0
Stable disease (%)	**6 (4)**	10 (7)	18 (13)	**6**	0	6	0
Progression in all (%)	**8 (6)**	8 (6)	10 (7)	**8**	0	1	7
Heterogeneous response (%)	**16 (11)**	15 (10)	9 (6)	**16**	0	10	6

Patients with heterogeneous response had inferior survival, but also more metastases than those with response in all lesions. We therefore performed analyses only including patients with 5–12 liver metastases in order to match the two response groups with regard to this important prognostic factor. The median number of metastases was then equal in the two groups. Median 5y-CSS was 23 months for patients with heterogeneous response (n = 12) compared to 42 months for those with response in all (n = 61), however not significant ($p = 0.267$).

Disease-free and progression-free survival was short (median 13 months (95% CI 11–15) and 12 months (95% CI 11–13), respectively) and not significantly different between the response groups. The proportion relapsing was 73%, 50% and 92%, respectively, in the groups of homogeneous response, progression in all and heterogeneous response using the 3 mm cut-off.

There was a significant association between response patterns and CEA changes during neoadjuvant treatment, see Table 3. Due to low number of patients, multivariable analyses with adjustment for prognostic variables commonly used in clinical scoring systems were not performed.

Discussion

The important finding of this study was that 11% of the patients had a heterogeneous radiological response to neoadjuvant treatment of CRLM, and this was associated with poor prognosis. Progression during neoadjuvant treatment has been shown to impair survival after resection in previous studies [7–10], also confirmed in this study. Accordingly, these response patterns, present in about 15–20% of those offered neoadjuvant treatment, might be of value when selecting further treatment due to their negative prognostic impact.

The selection of patients for resection of CRLM is based on a number of patient, tumor and anatomical factors [18–20]. There is no broad consensus on the use of neoadjuvant treatment or whether response should be emphasized in treatment selection [5,21]. Radiological response evaluation can be performed with different methods based on size measurements, or morphological and metabolic changes of liver lesions. The standard method for response evaluation based on size, RECIST [11], was developed primarily for evaluation of palliative treatment response. The

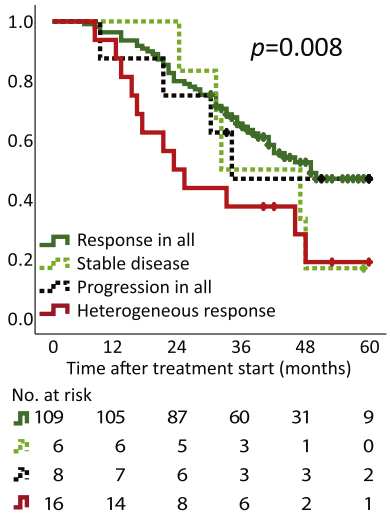

Fig. 2. Five-year overall survival according to response to neoadjuvant treatment, 3 mm cut-off.

method focuses on metastases in all involved organs and is useful for evaluating response of gross tumor burden to cytotoxic agents, but is not a surrogate marker for overall survival [22,23]. These criteria evaluate only two lesions per organ and do not take into consideration the potential difference in response among lesions [24], hence they are not suitable for studying heterogeneous treatment response. Additionally, the required 20–30% change in diameter is not sensitive for small volume changes [25–27], reflected by the substantial fraction of patients classified as having stable disease with large variations in survival [28]. Several studies have also failed to show a prognostic value of RECIST in resectable CRLM [29,30].

A combination of changes in tumor size and morphology on CT has proven better for evaluation of treatment response to biological agents with a cytostatic mechanism of action [31,32], also demonstrated in metastatic colorectal cancer [33]. These morphological criteria are promising markers of pathological response and survival after neoadjuvant treatment in resectable CRLM [34,35]. One-third of our patients received EGFR and/or VEGF inhibitors, but the number of patients with CT before and after treatment was too low to perform meaningful analyses of morphological response. Chemotherapy-induced metabolic changes of metastases can be demonstrated with PET/CT [36], and most studies show a correlation with pathological response and survival [37–41], also for heterogeneous response [42], but the method is not in routine use in resectable CRLM.

In this study, we performed a detailed measurement of lesion diameter in up to five metastases, which can be performed with either CT or MRI. This is easy to perform and feasible for implementation in the routine radiology report, and it is sensitive for detection of a heterogeneous size response, which in our series had a negative prognostic impact. The present study is to our knowledge the first to evaluate the prognostic impact of a heterogeneous

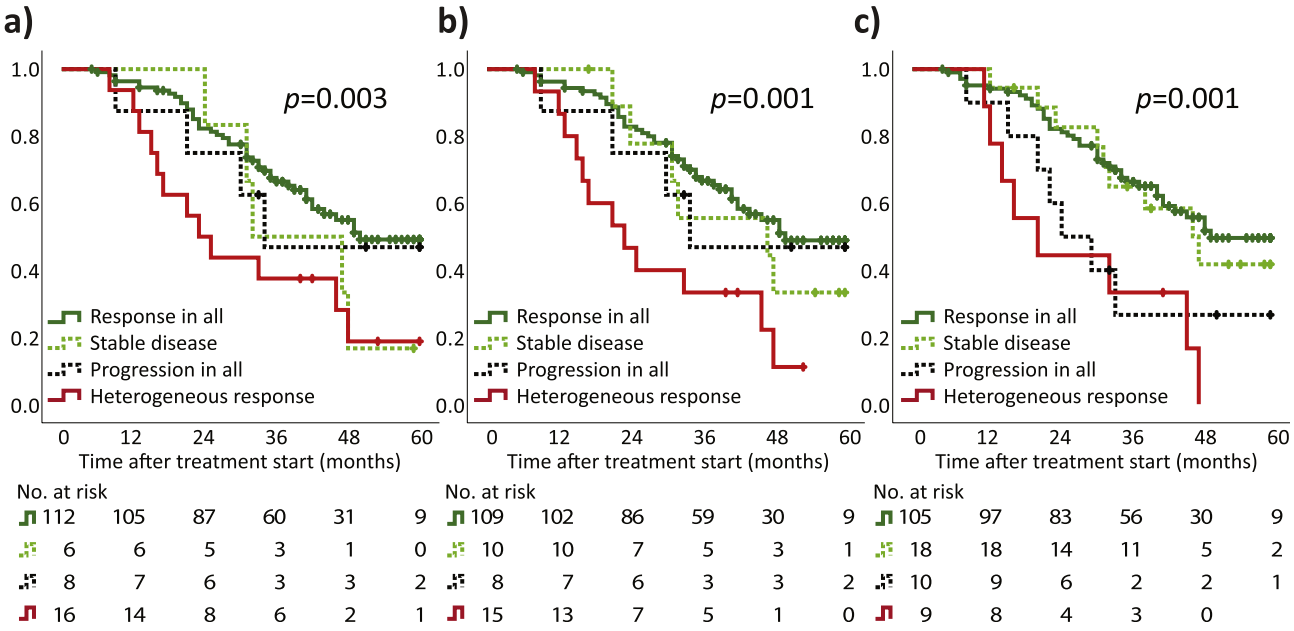

Fig. 3. Five-year cancer-specific survival according to response to neoadjuvant treatment, with (a) 3 mm, (b) 4 mm, and (c) 5 mm as cut-off value for change in diameter. P-value for response in all vs. heterogeneous response indicated in figure.

Table 3
CEA change after neoadjuvant treatment according to response group, 3 mm cut-off. CEA change is based on percentage change from initial value. Unchanged: CEA ≤5 ng/ml both before and after treatment or <20% change; reduced: CEA reduced with ≥20%, increased: CEA increased with ≥20%.

	CEA known, n (%)	CEA reduced,%	CEA unchanged, %	CEA increased,%	*p*
Response in all	*88 (79)*	77%	15%	8%	<0.001
Stable disease	*3 (50)*	0	33%	67%	
Progression	*8 (100)*	25%	50%	25%	
Heterogeneous response	*13 (81)*	62%	8%	31%	

response to neoadjuvant chemotherapy before attempted curative resection of CRLM. A high proportion of patients experience disease recurrence after liver resection for CRLM, within one year for the majority. The time to disease progression or recurrence was similar in all the response groups in the present series. However, both overall and cancer-specific survival was significantly shorter in the heterogeneous response group compared to patients with response in all lesions, which is an important finding. Of note, a negative prognostic effect of a heterogeneous response has previously been shown in the palliative setting, using RECIST in combination with a new response model [13].

The group with progression seemed to have slightly better prognosis than the heterogeneous response group using 3 mm cut-off, but the numbers were small. Using 5 mm as cut-off, the progression group was larger and had survival similar to the group with heterogeneous response.

Determination of changes in tumor size can be performed with relative (as in RECIST) or absolute size measurements. In our study, the latter was preferred since we sought to identify subtle changes irrespective of tumor size before treatment and tested cut-off values of 3-5 mm change in diameter. The accuracy of the size measurements is limited by resolution of the imaging modality, which is especially important in small tumors. Hence, the optimal cut-off will be a compromise between the need for information on true size changes versus the geometrical accuracy of the imaging modality. As expected, we found that a 3 mm cut-off value was most sensitive in order to detect heterogeneity, but it also seemed robust to misinterpretation of size changes (false positive heterogeneity) and impact on survival when compared to 4 and 5 mm.

Thirty percent of patients fulfilling the inclusion criteria were excluded, mainly because radiological examinations were missing, and thus the final patient cohort with the resulting subgroups were too small for multivariable analyses. The patient population was heterogeneous for a variety of prognostic clinical variables which could not be adjusted for, but most of them were evenly distributed in univariate analyses. The number of metastases is a well-known prognostic factor, and patients with heterogeneous response had a higher number of liver metastases than the other response groups, which may partially explain why heterogeneous responders had poorer prognosis. Still, when matching a subgroup of patients who had 5-12 metastases, survival was shorter for heterogeneous responders, but not significant in this small study. Larger studies may determine whether a heterogeneous response in itself has a negative impact on survival. We are further focusing on possible associations between radiological response heterogeneity and heterogeneity on the molecular level.

In conclusion, a detailed radiological examination identified a heterogeneous response to neoadjuvant chemotherapy in about 10% of the patients, and our findings indicate that this patient group has poor prognosis. If these findings are validated in larger studies, a heterogeneous response pattern detected by this simple radiological method could be a useful negative prognostic biomarker. Such biomarkers might identify patients who will benefit from more intensified perioperative oncological treatment, or who might have comparable outcome without surgery. Future trials are necessary to clarify the best options for these patients.

Author contributions

Study concepts: AN, RAL, BAB.
Study design: AN, RAL, BAB.
Data acquisition: All authors.
Quality control of data and algorithms: THB, MGG, RAL, AA, AN.
Data analysis and interpretation: THB, VC, AS, RAL, AN.
Statistical analysis: THB, AS, AN.
Manuscript preparation: THB, VC, AS, RAL, AN.
Manuscript editing: All authors.
Manuscript review: All authors.

Conflicts of interest

The authors have no conflicts of interest to declare.

Role of the funding source

The funding sources had no role in the study design; collection, analysis or interpretation of data; in the writing of the report or in the decision to submit the article for publication.

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References

[1] de Ridder JAM, van der Stok EP, Mekenkamp LJ, Wiering B, Koopman M, Punt CJA, et al. Management of liver metastases in colorectal cancer patients: a retrospective case-control study of systemic therapy versus liver resection. Eur J Cancer 2016;59:13–21. https://doi.org/10.1016/j.ejca.2016.02.003.

[2] Brudvik KW, Bains SJ, Seeberg LT, Labori KJ, Waage A, Tasken K, et al. Aggressive treatment of patients with metastatic colorectal cancer increases survival: a scandinavian single-center experience. HPB Surg 2013;2013:727095. https://doi.org/10.1155/2013/727095.

[3] Nordlinger B, Guiguet M, Vaillant J-C, Balladur P, Boudjema K, Bachellier P, et al. Surgical resection of colorectal carcinoma metastases to the liver: a prognostic scoring system to improve case selection, based on 1568 patients. Cancer 1996;77(7):1254–62. https://doi.org/10.1002/(SICI)1097-0142(19960401)77:7%3C1254::AID-CNCR5%3E3.0.CO;2-I.

[4] Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. Ann Surg 1999;230(3):309–18. discussion 318-21.

[5] Van Cutsem E, Cervantes A, Adam R, Sobrero A, Van Krieken JH, Aderka D, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol 2016;27(8):1386–422. https://doi.org/10.1093/annonc/mdw235.

[6] Nordlinger B, Sorbye H, Glimelius B, Poston GJ, Schlag PM, Rougier P, et al. Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial. Lancet Oncol 2013;14(12):1208–15. https://doi.org/10.1016/S1470-2045(13)70447-9.

[7] Adam R, Pascal G, Castaing D, Azoulay D, Delvart V, Paule B, et al. Tumor progression while on chemotherapy: a contraindication to liver resection for multiple colorectal metastases? Ann Surg 2004;240(6):1052–61. discussion 1061-4, https://doi.org/10.1097/01.sla.0000145964.08365.01.

[8] Chiappa A, Bertani E, Makuuchi M, Zbar AP, Contino G, Viale G, et al. Neoadjuvant chemotherapy followed by hepatectomy for primarily resectable colorectal cancer liver metastases. Hepato-Gastroenterology 2009;56(91–92):829–34.

[9] Vigano L, Capussotti L, Barroso E, Nuzzo G, Laurent C, Ijzermans JN, et al. Progression while receiving preoperative chemotherapy should not be an absolute contraindication to liver resection for colorectal metastases. Ann Surg Oncol 2012;19(9):2786–96. https://doi.org/10.1245/s10434-012-2382-7.

[10] Mao R, Zhao JJ, Zhao H, Zhang YF, Bi XY, Li ZY, et al. Non-response to preoperative chemotherapy is a contraindication to hepatectomy plus radiofrequency ablation in patients with colorectal liver metastases. Oncotarget 2017;8(43):75151–61. https://doi.org/10.18632/oncotarget.20647.

[11] Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228–47. https://doi.org/10.1016/j.ejca.2008.10.026.

[12] Russo M, Siravegna G, Blaszkowsky LS, Corti G, Crisafulli G, Ahronian LG, et al. Tumor heterogeneity and Lesion-Specific response to targeted therapy in

colorectal cancer. Cancer Discov 2016;6(2):147–53. https://doi.org/10.1158/2159-8290.CD-15-1283.
[13] van Kessel CS, Samim M, Koopman M, van den Bosch MAAJ, Borel Rinkes IHM, Punt CJA, et al. Radiological heterogeneity in response to chemotherapy is associated with poor survival in patients with colorectal liver metastases. Eur J Cancer 2013;49(11):2486–93. https://doi.org/10.1016/j.ejca.2013.03.027.
[14] Menzies AM, Haydu LE, Carlino MS, Azer MW, Carr PJ, Kefford RF, et al. Inter- and intra-patient heterogeneity of response and progression to targeted therapy in metastatic melanoma. PLoS One 2014;9(1):e85004. https://doi.org/10.1371/journal.pone.0085004.
[15] Dong ZY, Zhai HR, Hou QY, Su J, Liu SY, Yan HH, et al. Mixed responses to systemic therapy revealed potential genetic heterogeneity and poor survival in patients with non-small cell lung cancer. The Oncologist 2017;22:61–9. https://doi.org/10.1634/theoncologist.2016-0150.
[16] Fretland AA, Dagenborg VJ, Bjornelv GMW, Kazaryan AM, Kristiansen R, Fagerland MW, et al. Laparoscopic versus open resection for colorectal liver metastases: the OSLO-COMET randomized controlled trial. Ann Surg 2018;267(2):199–207. https://doi.org/10.1097/sla.0000000000002353.
[17] Punt CJA, Buyse M, Köhne C-H, Hohenberger P, Labianca R, Schmoll HJ, et al. Endpoints in adjuvant treatment trials: a systematic review of the literature in colon cancer and proposed definitions for future trials. J Natl Cancer Inst 2007;99(13):998–1003. https://doi.org/10.1093/jnci/djm024.
[18] Fiorentini G, Sarti D, Aliberti C, Carandina R, Mambrini A, Guadagni S. Multidisciplinary approach of colorectal cancer liver metastases. World J Clin Oncol 2017;8(3):190–202. https://doi.org/10.5306/wjco.v8.i3.190.
[19] Adam R, de Gramont A, Figueras J, Kokudo N, Kunstlinger F, Loyer E, et al. Managing synchronous liver metastases from colorectal cancer: a multidisciplinary international consensus. Cancer Treat Rev 2015;41(9):729–41. https://doi.org/10.1016/j.ctrv.2015.06.006.
[20] Elias D, Viganò L, Orsi F, Scorsetti M, Comito T, Lerut J, et al. New perspectives in the treatment of colorectal metastases. Liver Cancer 2016;6(1):90–8. https://doi.org/10.1159/000449492.
[21] Khoo E, O'Neill S, Brown E, Wigmore SJ, Harrison EM. Systematic review of systemic adjuvant, neoadjuvant and perioperative chemotherapy for resectable colorectal-liver metastases. HPB 2016;18(6):485–93. https://doi.org/10.1016/j.hpb.2016.03.001.
[22] Wilkerson J, Fojo T. Progression-free survival is simply a measure of a drug's effect while administered and is not a surrogate for overall survival. Cancer J 2009;15(5):379–85. https://doi.org/10.1097/PPO.0b013e3181bef8cd.
[23] Grothey A, Hedrick EE, Mass RD, Sarkar S, Suzuki S, Ramanathan RK, et al. Response-independent survival benefit in metastatic colorectal cancer: a comparative analysis of N9741 and AVF2107. J Clin Oncol 2008;26(2):183–9. https://doi.org/10.1200/jco.2007.13.8099.
[24] Russo M, Siravegna G, Blaszkowsky LS, Corti G, Crisafulli G, Ahronian LG, et al. Tumor heterogeneity and lesion-specific response to targeted therapy in colorectal cancer. Cancer Discov 2016;6(2):147–53. https://doi.org/10.1158/2159-8290.cd-15-1283.
[25] Jaffe CC. Measures of response: RECIST, WHO, and new alternatives. J Clin Oncol 2006;24(20):3245–51. https://doi.org/10.1200/jco.2006.06.5599.
[26] Winter KS, Hofmann FO, Thierfelder KM, Holch JW, Hesse N, Baumann AB, et al. Towards volumetric thresholds in RECIST 1.1: therapeutic response assessment in hepatic metastases. Eur Radiol 2018;28(11):4839–48. https://doi.org/10.1007/s00330-018-5424-0.
[27] Zhao B, Lee SM, Lee HJ, Tan Y, Qi J, Persigehl T, et al. Variability in assessing treatment response: metastatic colorectal cancer as a paradigm. Clin Cancer Res 2014;20(13):3560–8. https://doi.org/10.1158/1078-0432.ccr-14-0245.
[28] Jain RK, Lee JJ, Ng C, Hong D, Gong J, Naing A, et al. Change in tumor size by RECIST correlates linearly with overall survival in phase I oncology studies. J Clin Oncol 2012;30(21):2684–90. https://doi.org/10.1200/jco.2011.36.4752.
[29] Gallagher DJ, Zheng J, Capanu M, Haviland D, Paty P, Dematteo RP, et al. Response to neoadjuvant chemotherapy does not predict overall survival for patients with synchronous colorectal hepatic metastases. Ann Surg Oncol 2009;16(7):1844–51. https://doi.org/10.1245/s10434-009-0348-1.
[30] Neumann UP, Thelen A, Röcken C, Seehofer D, Bahra M, Riess H, et al. Nonresponse to pre-operative chemotherapy does not preclude long-term survival after liver resection in patients with colorectal liver metastases. Surgery 2009;146(1):52–9. https://doi.org/10.1016/j.surg.2009.02.004.
[31] Choi H, Charnsangavej C, Faria SC, Macapinlac HA, Burgess MA, Patel SR, et al. Correlation of computed tomography and positron emission tomography in patients with metastatic gastrointestinal stromal tumor treated at a single institution with imatinib mesylate: proposal of new computed tomography response criteria. J Clin Oncol 2007;25(13):1753–9. https://doi.org/10.1200/jco.2006.07.3049.
[32] Benjamin RS, Choi H, Macapinlac HA, Burgess MA, Patel SR, Chen LL, et al. We should desist using RECIST, at least in GIST. J Clin Oncol 2007;25(13):1760–4. https://doi.org/10.1200/jco.2006.07.3411.
[33] Chung WS, Park MS, Shin SJ, Baek SE, Kim YE, Choi JY, et al. Response evaluation in patients with colorectal liver metastases: RECIST version 1.1 versus modified CT criteria. AJR Am J Roentgenol 2012;199(4):809–15. https://doi.org/10.2214/ajr.11.7910.
[34] Chun Y, Vauthey J, Boonsirikamchai P, Maru D, Kopetz S, Palavecino M, et al. Association of computed tomography morphologic criteria with pathologic response and survival in patients treated with bevacizumab for colorectal liver metastases. J Am Med Assoc 2009;302(21):2338–44. https://doi.org/10.1001/jama.2009.1755.
[35] Shindoh J, Loyer EM, Kopetz S, Boonsirikamchai P, Maru DM, Chun YS, et al. Optimal morphologic response to preoperative chemotherapy: an alternate outcome end point before resection of hepatic colorectal metastases. J Clin Oncol 2012;30(36):4566–72. https://doi.org/10.1200/jco.2012.45.2854.
[36] Wahl RL, Jacene H, Kasamon Y, Lodge MA. From RECIST to PERCIST: evolving Considerations for PET response criteria in solid tumors. J Nucl Med 2009;50(Suppl 1). 122s-50s, https://doi.org/10.2967/jnumed.108.057307.
[37] Ma B, King AD, Leung L, Wang K, Poon A, Ho WM, et al. Identifying an early indicator of drug efficacy in patients with metastatic colorectal cancer-a prospective evaluation of circulating tumor cells, 18F-fluorodeoxyglucose positron-emission tomography and the RECIST criteria. Ann Oncol 2017;28(7):1576–81. https://doi.org/10.1093/annonc/mdx149.
[38] Woff E, Hendlisz A, Garcia C, Deleporte A, Delaunoit T, Marechal R, et al. Monitoring metabolic response using FDG PET-CT during targeted therapy for metastatic colorectal cancer. Eur J Nucl Med Mol Imaging 2016;43(10):1792–801. https://doi.org/10.1007/s00259-016-3365-x.
[39] Formiga MN, Fanelli MF, Dettino AL, Nicolau UR, Cavicchioli M, Lima EN, et al. Is early response by (18)F-2-fluoro-2-deoxy-D-glucose positron emission tomography-computed tomography a predictor of long-term outcome in patients with metastatic colorectal cancer? J Gastrointest Oncol 2016;7(3):365–72. https://doi.org/10.21037/jgo.2016.02.04.
[40] de Geus-Oei LF, Vriens D, van Laarhoven HW, van der Graaf WT, Oyen WJ. Monitoring and predicting response to therapy with 18F-FDG PET in colorectal cancer: a systematic review. J Nucl Med 2009;50(Suppl 1):43s–54s. https://doi.org/10.2967/jnumed.108.057224.
[41] Chiu KWH, Lam KO, An H, Cheung GTC, Lau JKS, Choy TS, et al. Long-term outcomes and recurrence pattern of 18F-FDG PET-CT complete metabolic response in the first-line treatment of metastatic colorectal cancer: a lesion-based and patient-based analysis. BMC Canc 2018;18(1):776. https://doi.org/10.1186/s12885-018-4687-9.
[42] Hendlisz A, Deleporte A, Delaunoit T, Marechal R, Peeters M, Holbrechts S, et al. The prognostic significance of metabolic response heterogeneity in metastatic colorectal cancer. PLoS One 2015;10(9):e0138341. https://doi.org/10.1371/journal.pone.0138341.