

Importance of histological tumor response assessment in predicting the outcome in patients with colorectal liver metastases treated with neo-adjuvant chemotherapy followed by liver surgery

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Background: The purpose of the study was to characterize histological response to chemotherapy of hepatic colorectal metastases (HCRM), evaluate efficacy of different chemotherapies on histological response, and determine whether tumor regression grading (TRG) of HCRM predicts clinical outcome.

Patients and methods: TRG was evaluated on 525 HCRM surgically resected from 181 patients, 112 pretreated with chemotherapy. Disease-free survival (DFS) and overall survival (OS) were correlated to TRG.

Results: Tumor regression was characterized by fibrosis overgrowing on tumor cells, decreased necrosis, and tumor glands (if present) at the periphery of HCRM. With irinotecan/5-fluorouracil (5-FU), major (MjHR), partial (PHR), and no (NHR) histological tumor regression were observed in 17%, 13%, and 70% of patients, respectively. With oxaliplatin/5-FU, MjHR, PHR, and NHR were observed in 37%, 45%, and 18% of patients, respectively. Five patients, treated with oxaliplatin, had complete response in all their metastases. MjHR was associated with an improved 3-year DFS compared with PHR or NHR. MjHR and PHR were associated with an improved 5-year OS compared with NHR.

Conclusion: Histological tumor regression of HCRM to chemotherapy corresponds to fibrosis overgrowth and not to increase of necrosis. TRG should be considered when evaluating efficacy of chemotherapy for HCRM. Histological tumor regression was most common among oxaliplatin-treated patients and associated with better clinical outcome.

Key words: colorectal cancer, irinotecan, oxaliplatin, pathological response to chemotherapy, sinusoidal obstruction syndrome, tumor regression grade

introduction

Approximately 60% of patients with colorectal cancer develop lymph node or distant metastases. The liver is the initial distant metastatic site in ~30% of them. Five-year survival of 30%–60% can be achieved if the metastases are totally removed [1–4]. Unfortunately, most patients are poor candidates for liver surgery, mainly due to the high number of hepatic nodules, their size, or their location.

Over the last decade, combined chemotherapy regimens including irinotecan and oxaliplatin have markedly improved the response rate and the survival. Several groups apply these chemotherapies preoperatively to reduce the size of hepatic colorectal metastases (HCRM) and to render resectable patients who are initially unresectable [5–8]. Moreover, in patients with advanced disease, the neo-adjuvant treatment may allow the

identification of a subgroup who could benefit from a more aggressive approach [9, 10].

The efficacy of preoperative chemotherapy is generally assessed by radiological evaluation. The radiological response according to Response Evaluation Criteria in Solid Tumors [11, 12] corresponds to the reduction in the number and size of metastases—essentially a tumor shrinkage. Preoperative radiology, however, has been shown to overestimate downstaging of the tumor [13, 14], and histology remains the best way of assessing residual tumor viability. Moreover, in tumors such as in breast cancer [14] and osteosarcoma [15], histological response to preoperative chemotherapy is directly correlated with disease-free survival (DFS) and overall survival (OS). In gastrointestinal cancers, the correlation between histological response to preoperative radiotherapy and/or chemotherapy and clinical outcome has been investigated in esophageal [16] and rectal carcinomas [17, 18], but little is known concerning HCRM.

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The objectives of this study were (i) to define histological criteria of response to neo-adjuvant chemotherapy and to establish a histological tumor regression grading (TRG) system for HCRM, (ii) to evaluate the degree of histological response to different types of neo-adjuvant chemotherapy regimens, and (iii) to assess if TRG of HCRM has a clinical prognostic significance in terms of tumor recurrence or OS.

patients and methods

patients

All patients ($n = 196$) with colorectal carcinoma who underwent first hepatic resection for metastases confined to the liver at the University Hospital, Geneva, Switzerland ($n = 99$), and at the Hôpital Cochin, Paris, France ($n = 97$), from 1994 to 2003 were included. The last clinical follow-up was in December 2005. The study was in accordance with the Helsinki Declaration of the World Medical Association. Adequate pathological material was available for 181 patients (Table 1); 15 were excluded because of incomplete surgical resection and/or insufficient tissue for morphological evaluation. The median age of the patients was 66 years (range 35–82). Surgical resection was the only treatment of HCRM in 69 patients (with 120 HCRM). One hundred and twelve patients (with 405 HCRM) received chemotherapy before surgery. Complete clinical follow-up were available for 106 of the 112 patients (94.6%) pretreated with chemotherapy. DFS or OS was calculated from surgery to diagnosis of progressive disease or death, respectively, to the most recent follow-up visit.

pathological assessment and TRG

All archival slides (from formalin-fixed paraffin-embedded tissue) of HCRM and non-tumor tissue distant from the tumor were reviewed. The hepatectomy specimens were sectioned in 0.5-cm-thick slices. All the HCRM radiologically known before chemotherapy were macroscopically localized and sampled. In patients with multiple metastases, each single lesion was thus included for analysis. Samples from HCRM, whose diameters ranged from 0.2 to 16 cm, were systematically taken for histology from one side to the other of the tumor, with at least one sample per centimeter. Both the center to the periphery of HCRM was thus largely sampled. To avoid discrepancy, all slides were examined together at the multihead microscope by two pathologists (LR-B and BT). Tumor regression was scored for each HCRM according to the scheme from Mandard et al [16] for the assessment of pathologically documented response after preoperative radiotherapy and chemotherapy in esophageal carcinomas, modified for liver metastases. This score identifies five TRGs on the basis of the presence of residual tumor cells and the extent of fibrosis (Figure 1). TRG1 corresponded to absence of tumor cells replaced by abundant fibrosis; TRG2 to rare residual tumor cells scattered throughout abundant fibrosis; TRG3 to more residual tumor cells throughout a predominant fibrosis; TRG4 to large amount of tumor cells predominating over fibrosis; and TRG5 most exclusively to tumor cells without fibrosis. The percentage of HCRM surface interested by necrosis was also graded: grade 0 corresponded to an absence of necrosis, grade 1 to <25% of surface, grade 2 to 25%–50% of surface, grade 3 to 50%–75% of surface, and grade 4 to >75% of surface. Patients with multiple HCRM who showed different TRG or necrosis grade between their metastases were categorized according to the morphological aspect of the worse metastasis (highest TRG). The distribution of viable tumor cells (predominantly located in the center of the tumor, at the periphery, or in equal amounts in the center and in the periphery) and acellular mucin regarded as a form of tumor response (<25%, 25%–50%, and >50% of the HCRM surface) were also recorded. For the non-tumoral liver, histological features, notably the severity of sinusoidal lesions, were

Table 1. Patients and tumor characteristics

Parameter	No. of patients (%) (N = 181)
Occurrence of metastases	
Metachronous	86 (47.5)
Synchronous	95 (52.5)
Sex	
Male	121 (66.9)
Female	60 (33.1)
Type of resection	
Right	87 (48.2)
Left	36 (19.9)
Segmental	47 (25.9)
Wedge	11 (6)
Vascular exclusion ^a during surgery	65 (35.9)
Portal embolization before surgery	11 (6)
Treatment	
Surgery only	69 (38.1)
Neo-adjuvant chemotherapy + surgery	112 (61.9)
No. of metastases, No. of patients (%)	
1	70 (38.7)
2–3	42 (23.2)
≥4	69 (38.1)

^aPringle's maneuver or vascular total exclusion.

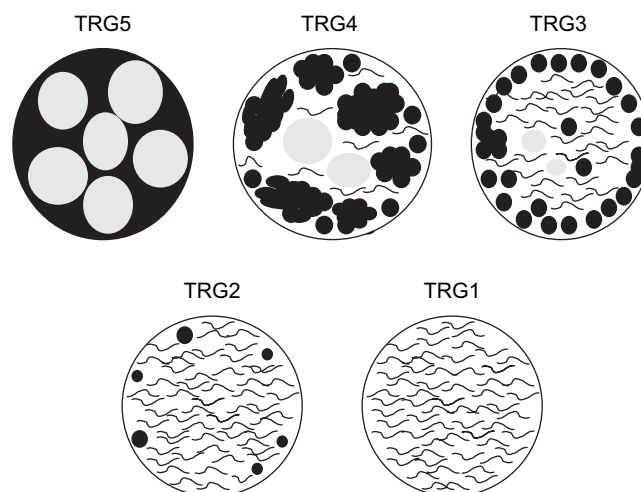


Figure 1. Tumor regression grade (TRG) scoring system. TRG1, absence of residual cancer and large amount of fibrosis; TRG2, rare residual cancer cells scattered throughout the fibrosis; TRG3, more residual tumor cells but fibrosis predominates; TRG4, residual cancer cells predominate over fibrosis; and TRG5, no signs of regression. Black area: tumor cells; gray area: necrotic area; fibrils: fibrosis.

evaluated according to the characteristics and score described in our previous publication [19].

statistics

Statistical analysis was performed using the SPSS software (SPSS 10.0; SPSS Inc., Chicago, IL). The chi-square test was used for categorical data distributed between two groups. When there were more than two groups of variables, the correlation was assessed using the non-parametric Kruskal–Wallis test. Survival curves were calculated with the Kaplan–Meier method and the influence of covariates was assessed in a univariate analysis with

the log-rank test. We used a Cox proportional hazards model to test the influence on DFS and OS of all covariates found to be significant in the univariate analysis. A *P* value of <0.05 was considered statistically significant.

results

pathological characteristics of HCRM

Patients and tumoral characteristics are summarized in Table 1. Histologically, some HCRM had a high percentage of viable tumor cells—usually with a high amount of dirty tumor necrosis—occasionally intermingled with minimal fibrosis. Other HCRM were characterized by moderate or major fibrosis, largely or completely replacing both necrosis and tumor glands (Figure 1).

In patients with more than one metastasis (111 of 181), the morphology of the metastases within the same patient was similar, with TRG being equal between HCRM or within one grade range in 99 (90%) patients. The variability of TRG between metastases was in a range of two grades in only 12 (10%) patients. Predominant colloid changes (>50% of the surface) were rarely observed (8%).

Tumor glands, when present, predominated mainly at the periphery in 373 HCRM (71%) and were rarely located at the center in 10 HCRM (2%). Tumor glands were present on the surface of the tumor in 142 HCRM (27%).

HCRM necrosis and TRG and association with preoperative chemotherapy

The percentage of HCRM surface occupied by necrosis was significantly lower in patients treated by preoperative chemotherapy (*n* = 112) compared with HCRM of patients treated with surgery alone (*n* = 69) and was different according to the regimen of neo-adjuvant chemotherapy (Table 2). Necrosis remained high in patients who received 5-fluorouracil (5-FU) monotherapy (*n* = 30) and was not significantly different from HCRM of patients who underwent surgery alone (*n* = 69) (*P* > 0.05). In contrast, patients who received irinotecan/5-FU (*n* = 23), oxaliplatin/5-FU (*n* = 38), or oxaliplatin/irinotecan/5-FU (*n* = 21) had a significantly lower necrosis compared with patients treated with 5-FU or surgery alone (*P* < 0.0001).

The TRG of HCRM in patients treated by neo-adjuvant chemotherapy was significantly lower than TRG of patient treated with surgery alone (*P* < 0.0001). There were, however, significant differences according to the regimen of chemotherapy (Table 3). Three groups could be distinguished. The first group was made of patients with HCRM showing TRG4 or TRG5; this group was categorized as having no histological tumor regressive or response changes (NHR). The patients in this group had been treated with surgery alone without preoperative chemotherapy or with preoperative chemotherapy. A second group was made of patients with HCRM showing TRG3: this group was categorized as having partial histological tumor response (PHR). Finally, a third group was made of patients with HCRM showing TRG2 and TRG1: this group was categorized as having major or complete histological tumor response (MjHR). PHR or MjHR were observed in >80% of the patients treated by oxaliplatin/5-FU

Table 2. Grade of HCRM necrosis in patients treated by surgery alone or by neo-adjuvant chemotherapies and surgery for colorectal liver metastases

Grade of necrosis	Surgery (<i>n</i> = 69)	5-FU (<i>n</i> = 30)	Irinotecan + 5-FU (<i>n</i> = 23)	Oxaliplatin + 5-FU (<i>n</i> = 38)	Oxaliplatin + irinotecan + 5-FU (<i>n</i> = 21)
0–1	9 (13%)	8 (27%)	12 (52%)	25 (66%)	12 (57%)
2	31 (45%)	11 (36%)	9 (39%)	8 (21%)	5 (24%)
3–4	29 (42%)	11 (37%)	2 (9%)	5 (13%)	4 (19%)

0–1, 0–25% of HCRM surface interested by necrosis; 2, 25–50% of surface interested by necrosis; 3–4, >50% of surface interested by necrosis. HCRM, hepatic colorectal metastases; 5-FU, 5-fluorouracil.

Table 3. HCRM TRG in patients treated by surgery alone or by neo-adjuvant chemotherapy and surgery for colorectal liver metastases; TRG1, 17 patients; TRG2, 10 patients

TRG	Surgery (<i>n</i> = 69)	5-FU (<i>n</i> = 30)	Irinotecan + 5-FU (<i>n</i> = 23)	Oxaliplatin + 5-FU (<i>n</i> = 38)	Oxaliplatin + Irinotecan + 5-FU (<i>n</i> = 21)
1–2 (MjHR)	0 (0%)	2 (7%)	4 (17%)	14 (37%)	7 (33%)
3 (PHR)	0 (0%)	6 (20%)	3 (13%)	17 (45%)	10 (48%)
4–5 (NHR)	69 (100%)	22 (73%)	16 (70%)	7 (18%)	4 (19%)

HCRM, hepatic colorectal metastases; TRG, tumor regression grade; 5-FU, 5-fluorouracil; MjHR, major histological tumor response; PHR, partial histological tumor response; NHR, no histological tumor response.

or oxaliplatin/irinotecan/5-FU (Table 3). In contrast, only 30.4% of the patients treated with irinotecan/5-FU had PHR or MjHR (*P* < 0.001), and with 5-FU alone, only 26.7% had a PHR or MjHR (*P* < 0.001) (Table 3).

Seventeen of the 112 (15%) patients who received preoperative chemotherapy [representing 44 of 405 (11%) HCRM] had at least one HCRM showing a complete histological response without residual tumor (TRG1). Thirteen of these 17 patients had received oxaliplatin-based treatments: five had a TRG1 in all of their HCRM, while eight had a complete response (TRG1) in some HCRM and residual tumor glands (TRG2) in the remaining HCRM. Two of the 17 patients had been treated with 5-FU alone and the remaining two with irinotecan/5-FU; most of the HCRM in these patients had a TRG2.

TRG and tumor size or sinusoidal obstruction syndrome

There was no significant correlation between the diameter of the HCRM and the TRG (*P* = 0.126) or with the percentage of necrosis (*P* = 0.074). Among 405 HCRM treated with preoperative chemotherapy, 172 measured <1 cm (<0.5 cm, *n* = 58; 0.6–1 cm, *n* = 114); 41 (23.8%) had no residual tumor cells (TRG1); and 131 (76.2%) had persistent viable tumor glands, of which 43 (25%) had a large amount of viable tumor cells (TRG4 or TRG5). Among the 233 HCRM treated with neo-adjuvant chemotherapy measuring >1 cm, three HCRM

(all <2 cm) had no residual tumor cells. All the others had viable tumor cells.

There was no correlation between the degree of tumor regression in HCRM and the severity of sinusoidal obstruction syndrome (SOS) lesions in the liver parenchyma ($P > 0.05$).

TRG as a prognostic factor for DFS and OS in patients treated with preoperative chemotherapy

Results on survival of patients treated with preoperative chemotherapy are illustrated in Figures 2 and 3. In patients with MjHR, the 1-, 3-, and 5-year DFS rates were 78%, 49%, and 38%, respectively. In patients with PHR, the 1-, 3-, and 5-year DFS rates were 58%, 37%, and 37%, respectively. In patients with NHR, the 1-, 3-, and 5-year DFS rates were 53%, 18%, and 15%, respectively. By univariate analysis, the 3-year DFS was significantly higher in patients with MjHR compared with patients with PHR or NHR (log-rank $P = 0.0014$). The 5-year DFS was significantly higher in patients with MjHR and PHR compared with patients with NHR (log-rank $P = 0.008$).

The 5-year OS was 41% in patients with MjHR and 38% in patients with PHR compared with 9% in patients with NHR. The 5-year OS was significantly higher in patients with MjHR or PHR compared with patients with NHR (log-rank $P = 0.0003$ and $P = 0.0019$, respectively).

For multivariate analysis, we included the following factors: patients age, number of metastases, size of the largest metastasis, total size of the metastases, TRG, synchronous versus metachronous HCRM, and chemotherapy. We found that TRG was an independent prognostic factor for 5-year DFS [$P = 0.001$; hazard ratio = 0.713; 95% confidence interval (CI) 0.517–0.982] and OS ($P = 0.004$; hazard ratio = 0.550; 95% CI 0.366–0.829). The size of the largest metastasis was also an independent prognostic factor for 5-year DFS ($P = 0.001$; hazard ratio = 1.123; 95% CI 0.46–1.205) and OS ($P = 0.001$; hazard ratio = 1.149; 95% CI 1.062–1.243).

discussion

This study describes the histological tumor response patterns of HCRM to chemotherapy, establishes a simple five-point scoring system to quantify the response as a TRG, shows that the TRG is related to the type of chemotherapy, and establishes a correlation between the histological response and survival in a large series of patients who underwent neo-adjuvant chemotherapy before liver resection.

Preoperative chemotherapy has gained an important place in the management of HCRM this last decade [1–3]. It improves the survival of patients with resectable lesions and helps to convert a proportion of patients with initially unresectable disease to a resectable status [5–7, 10]. Response to chemotherapy in HCRM, however, has been mainly reported as a variation in the radiological size of the tumor, which evaluates mostly tumor shrinkage [11] and little is known on the underlying histological changes, unlike other cancers, where a TRG has been defined and evaluated clinically [16–18, 20]. The present investigation is to our knowledge the first one to address the question of the histological response to chemotherapy in a large series of patients, and has clarified several points.

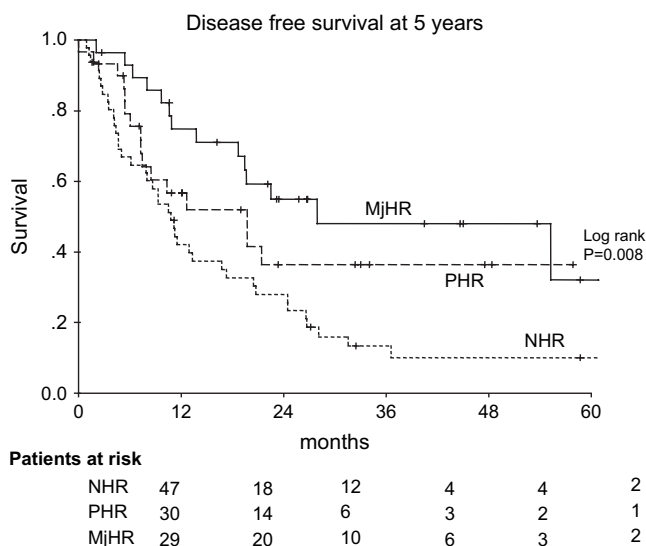


Figure 2. Disease-free survival of 106 patients with complete clinical follow-up and with major (MjHR), partial (PHR), or no (NHR) histological tumor response in liver colorectal metastasis after neo-adjuvant chemotherapy.

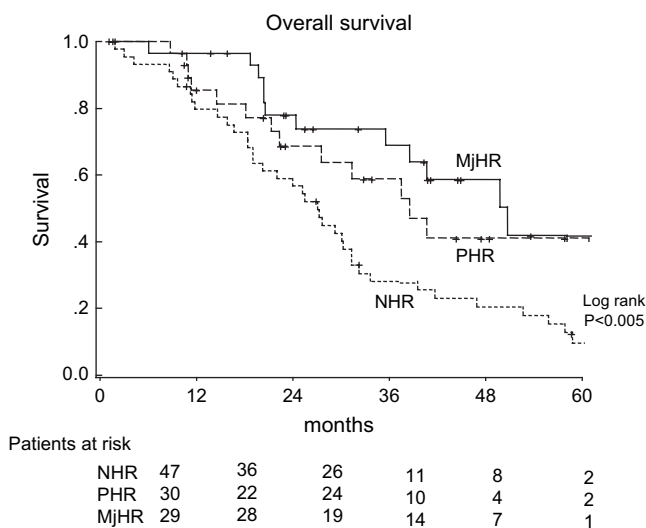


Figure 3. Overall survival of 106 patients with complete clinical follow-up and major (MjHR), partial (PHR), or no (NHR) histological tumor response in liver colorectal metastasis treated by neo-adjuvant chemotherapy and surgery. $P < 0.005$.

First, we observed that the dominant morphological feature of untreated HCRM was the presence of large areas of viable tumor glands intermingled with zones of dirty necrosis, with absent or minor regions of fibrosis, always outgrown by tumor glands. In contrast, response to chemotherapy corresponded to a fibrotic involution of the HCRM characterized by a decrease in the number or complete disappearance of tumor glands, a reduction of the amount of necrosis, and the appearance or an increase of fibrosis. This supports the concept that necrosis in HCRM is more likely related to spontaneous phenomena involving insufficient vascular supply of the tumor, while the cytotoxic effects of chemotherapy are mediated by other mechanisms such as apoptosis [21].

In most HCRM, necrosis or fibrosis predominated at the center while viable tumor glands were mainly located at the periphery. This pattern was more prominent after chemotherapy, often with a spiculated configuration at the borders of the lesion, where viable tumor cells intermingled with non-tumoral liver tissue. A scattered distribution of the response throughout the metastasis or a concentric pattern with viable cells at the center of the mass was never observed in our series. The presence of viable tumor cells at the periphery of the HCRM could be explained by the effect of high hydrostatic intratumoral pressure on the efficacy of drug diffusion [22]. On a practical side, the finding of viable cells at the periphery even in cases of MjHR should be taken into account in deciding the surgical safety margin around a lesion, and may explain the limits of single-needle radio frequency tumor ablation for HCRM [23].

We observed no significant correlation between the diameter of metastases and the TRG or with the percentage of necrosis. For HCRM <1 cm in patients treated with chemotherapy, 76.2% had persistent viable tumor glands, and 25% had major amount of tumor cells (TRG4 or TRG5). In addition, despite the relative frequency of MjHR with oxaliplatin, complete sterilization of the tumors was rare (4.5% of patients). The above-mentioned findings argue for surgical removal of all known lesions even if they have disappeared or appear extinct on morphological or functional imaging as recently published [24]. The persistence of viable tumor cells in such minute lesions may require chemotherapy to be stopped before the metastases can no longer be localized, and argues against the practice of some centers of not pursuing such small foci of disease [25].

The TRG was mostly equivalent in the different HCRM of the same patient, suggesting that the factors that influence response to chemotherapy are homogeneously represented in all lesions. Discrepancies in the histological pattern of response were rare (10%), a finding that renders classification of the tumor regression meaningful and that allows clinicopathological correlation.

The TRG grading system used in the present investigation is based on the Mandard scheme elaborated for esophageal carcinoma [16] and applied to rectal tumors [17, 18]. The correlation of the TRG with survival suggests its validity as a prognostic marker and we propose to implement it in pathological reports.

A second objective of our study was to evaluate the degree of histological response in relation to different chemotherapy regimens. We observed histological tumor regression in 56% of patients treated by chemotherapy in contrast to preoperative untreated patients (0%), but results varied widely according to the regimens. With oxaliplatin, >80% of patients had a histological tumor regression in their HCRM. Complete response with no residual tumor cells in all the metastases within a same patient was rare and only observed after oxaliplatin-based chemotherapy. In patients treated with irinotecan/5-FU, there was no significant increase in the proportion of patients with histological regression compared with 5-FU-treated patient, but there was a significant decrease in the amount of intratumoral necrosis. This observation suggests that radiological tumor shrinkage observed with irinotecan could be in part related to a decrease in necrotic areas, more

than to disappearance of tumor cells. In these cases, the favorable prognostic significance of decrease in tumor size could be due to having rendered resection possible.

Tumor downstaging has been regarded as a marker of radio- or chemosensitivity and as an important prognostic factor [17, 18, 20, 26–28]. More precisely, our study indicates that MjHR has a better 5-year DFS and OS than NHR. Multivariate analysis confirmed TRG as an independent prognostic factor for DFS and OS, independently from the type of chemotherapy used.

Finally, we reported recently a high prevalence of sinusoidal obstruction syndrome, related in particular to the use of oxaliplatin [19]. We found no correlation between the degree of tumor regression in HCRM and the severity of SOS lesions.

In conclusion, the histological tumor regression of HCRM to chemotherapy corresponds to fibrosis overgrowth and not to an increase of necrosis. Oxaliplatin adds substantial efficacy to 5-FU and irinotecan regimens in terms of histological tumoral regression. MjHR appears to be associated with DFS and MjHR or PHR to OS. The small number of patients achieving a complete tumor response supports the use of surgery for all patients with HCRM including those who have responded to neo-adjuvant chemotherapy with no apparent disease on medical imaging. Although radiological assessment of tumor response to neo-adjuvant chemotherapy is essential for evaluating the surgical resectability of HCRM, we suggest that the TRG grading described in the present study should be integrated in studies evaluating chemotherapy regimens for colorectal metastases and be validated in prospective investigations.

acknowledgements

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