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Tumor-size responses to first-line is a predictor of overall survival in metastatic colorectal cancer

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Tumor-size responses to first-line is a predictor of overall survival in metastatic colorectal cancer

Abstract (/250)

Objectives Early tumor shrinkage (ETS) has been reported to be associated with survival of metastatic colorectal cancer (mCRC) patients. Our aim was to analyze long-term tumor-size evolution, according to early mCRC best responses during the first-line therapy, to evaluate first best response–survival links.

Methods Sixty-five patients with unresectable mCRCs, treated between 2010 and 2015, were included retrospectively in this descriptive monocenter study, and grouped according to their RECIST 1.1 first-line best responses: progressive disease (PD_{fl}), stable disease with tumor-size evolution between 0 and +19% (SD_{fl+}) or 0 and –29% (SD_{fl-}), and partial responders (PRs), who were classed PR with ETS (ETS_{fl}) or without (PR_{fl}). Tumor-size evolution and best tumor responses to each chemotherapy line were analyzed.

Results Tumor loads of ETS_{fl} or PR_{fl} mCRCs tended to remain inferior to their initial values: 60% of patients died with target-lesion sums below baseline. For first-line SD_{fl+} or PD_{fl} mCRCs, rapid tumor-load increases continued during successive lines: >80% died with target-lesion sums above baseline. ETS_{fl} mCRCs responded better to subsequent lines (37.5% second-line PR), whereas PD_{fl} mCRCs remained refractory to other therapies (0% second- and third-line PR). Overall survival rates were significantly ($p = 0.03$) longer for the ETS_{fl} group (29.9 [95% CI: 12.6–47.1] months); shorter for the PD_{fl} group (17.1 [95% CI: 1.5–37.5] months).

Conclusion Tumors responding to first-line chemotherapy also responded better to subsequent lines, whereas PD_{fl} mCRCs remained refractory, which may explain the better survival associated with ETS_{fl} .

Online electronic supplemental material is available for this article.

Keywords Response Evaluation Criteria in Solid Tumors, Colonic Neoplasms, Survival rate, Tumor Burden.

Key points

- *Early shrinking tumors under first-line chemotherapy responded better to subsequent lines, maintaining low tumor loads, potentially explaining the link between early tumor shrinkage and overall survival of metastatic colorectal cancer (mCRC) patients.*
- *mCRCs progressing under first-line chemotherapy remained refractory to other therapies and their tumor loads increased rapidly.*
- *Even outside a clinical trial, an early first CT-scan reevaluation with RECIST criteria 8 weeks after starting first-line therapy is crucial to determine long-term mCRC evolution.*

Abbreviations:

CT: computed tomography

EGFR: epidermal growth-factor receptor

ETS: early tumor shrinkage

ETS_{fl}: early tumor shrinkage at first line (defined at 8 weeks)

fl: first line

mCRC: metastatic colorectal cancer

OS: overall survival

PFS: progression-free survival

PD: progressive disease

PD_{fl}: progressive disease at first line

PR: partial response

PR_{fl}: partial response at first line (without ETS_{fl}: delayed response)

RECIST: Response Evaluation Criteria In Solid Tumors

SD: stable disease

SD_{fl}: stable disease at first line

Introduction

Metastatic colorectal cancer (mCRC) management now achieves longer overall survival (OS), reaching 30 months in recent phase III trials [1–4]. For fit patients, first-line treatments are based on doublet- or triplet-chemotherapy combined with a targeted agent. Anti-angiogenic bevacizumab is approved for all patients, whereas panitumumab and cetuximab, which target the epidermal growth-factor receptor (EGFR), are limited to the subgroup of patients with *RAS* (a gene mutation predictive of the non-efficacy of anti-EGFR) wild-type mCRC [5]. At present, the choice of first-line regimen is guided by *RAS* status and the aim of obtaining tumor shrinkage for patients with symptomatic disease or potentially resectable metastases [5].

In general, clinical trials evaluate chemotherapy efficacy by OS, progression free-survival (PFS) and tumor objective response rate (ORR). PFS is often used as a surrogate criterion for OS, as an early endpoint. Tumor response is evaluated by ORR, assessed with revised Response Evaluation Criteria in Solid Tumors (RECIST criteria (version 1.1) [6]) that clinicians also use extensively in routine practice to adapt their therapeutic strategies.

The validity of PFS as a surrogate endpoint for OS in mCRC is questioned [7, 8], as median OS now exceeds 30 months, but PFS is still about 10 months. In addition, in a phase III trial that compared doublet-chemotherapy plus anti-EGFR or bevacizumab (FIRE-3) [3], median PFS did not differ between arms, whereas an OS benefit in favor of anti-EGFR was still found. One of the hypotheses to explain this OS–PFS discordance is the efficacy of subsequent chemotherapy lines. Another hypothesis is that other response-related outcome parameters, such as early tumour shrinkage (ETS) and depth-of-response, could have made an OS difference, despite comparable PFS [9]. ETS and depth-of-response are indicators of precociousness and intensity of tumor-size response to therapy, and predictors of OS and PFS [10, 11]. ETS (depending on its definition) is achieved when the tumor load has decreased

10–30% [12], as measured at the time of first imaging control, between 6 to 8 weeks after starting treatment. Depth-of-response is defined as the percentage of tumor shrinkage, based on the sum of the longest diameters, observed at the time of the lowest value (nadir) compared to before starting therapy (baseline). ETS and depth-of-response have since been validated retrospectively by several prospective trials' results [11, 13–17].

The tumor-size evolution in response to first-line therapy (henceforth initial response) has been particularly studied as a predictor of OS and PFS [15, 18], but its impact on responses to subsequent treatment lines has never been investigated. Only radiological data on first-line therapy were available in those retrospective analyses. Hence, evolution under successive lines remains hypothetical [12].

Our aim was to analyze tumor-size evolution over the long-term, according to the early mCRC initial responses, to explore the link between initial tumor-size evolution and OS.

Methods

Patients

Ethics Committee approval was waived for this single-center retrospective study.

All the patients treated in our center for unresectable mCRC, between 01/01/2010 and 30/01/2015, were identified by computer search of the chemotherapy-prescription software. We included only conventional adenocarcinomas (excluding mucinous tumors) treated by cytotoxic and targeted chemotherapies. None of them were treated with immuno therapy. Patients with at least one measurable lesion, according to the RECIST 1.1 criteria [6, 19] were included. Target lesions were defined at baseline and the largest diameter had to be ≥ 10 mm or short axis ≥ 15 mm if the lesion was a lymph node.

We excluded patients: 1) with no available baseline computed-tomography (CT) scan and patients with fewer than five reevaluation CT scans; 2) with no target lesions according to RECIST 1.1 criteria or with target lesions that could not be followed over the long term, especially after secondary metastatic liver resection; and 3) without sufficient clinical follow-up information (on different chemotherapy lines or outcome).

Image analysis and clinical information

All, but 10, baseline scans and all follow-up scans were performed in our institution using two CT systems, with 2x128 detector-rows (ICT 256, Philips healthcare) or with 128 detector-rows (ICT 128, Philips healthcare). The acquisition were done according to the actual standard, without and after an intravenous injection of 2 ml/kg body weight of an iodinated contrast agent (2.5 ml/s) at 350 mg of iodine/ml, during the arterial phase (35 s, slice thickness: 1.5 mm) at the thoracic level, and during the portal phase (70 s; slice thickness: 2 mm) at the abdominal and pelvic levels. Tumor-size evolution was evaluated by CT scan according to RECIST criteria [6], with a first-evaluation at 8 weeks, then every 8–12 weeks. RECIST criteria are based on the largest target-lesion diameters combined with a subjective assessment of non-target lesions. Target lesions are defined on the baseline CT scan. On follow-up images, the target-lesion response is evaluated as the percentage change of the sum of their largest diameters against baseline or subsequent scan with the lowest sum of target disease (nadir). The ORR is defined as the sum of complete (disappearance of all target lesions) and partial responses (PR, $\geq 30\%$ decrease of the sum of target-lesion diameters, compared to baseline). Progressive disease (PD) is $\geq 20\%$ increase of the sum of target-lesion diameters, with the smallest study sum (including baseline) serving as the reference. Stable disease (SD) is neither response nor PD.

The first CT scan analyzed was always the baseline examination just before first-line

therapy. A maximum of five target lesions could be chosen, with a maximum of two per organ. When analyzing a follow-up scan, the same target lesions were measured and their sum was again calculated. Two radiologists (O.L. and A.F., with 25 and 2 years of experience, respectively), blinded to each patient's clinical findings and previous radiology reports, retrospectively analyzed the CT images by consensus. Response-to-therapy was assessed manually using the PACS Carestream (Carestream Health).

Clinical information (patient characteristics, tumor characteristics, chemotherapy lines, responses to chemotherapy and outcome) was collected from each patient's electronic or paper medical chart by the oncologist (L.-J.P.).

Analytical groups

Patients were separated into five groups according to their best responses to first-line (fl) chemotherapy, defined as follows: ETS_{fl} , $\geq 30\%$ tumor reduction at 8 weeks; PR_{fl} , $\geq 30\%$ tumor reduction but without ETS_{fl} (delayed response); SD_{fl+} or SD_{fl-} , respectively, with tumor-size evolution between +1 and +19% or 0 and -29%; and PD_{fl} : $\geq 20\%$ tumor growth and/or appearance of new lesion(s). **Figure 1** is an example of radiological evaluation.

Long-term tumor-size evolution

For each patient, we used RECIST criteria customized for this study as follows: first, we focused only on the target lesions, not taking into account the non-target lesions. Second, the largest diameters of the initial target lesions on every reevaluation CT scan, from baseline to death or end of follow-up, were summed. Target lesions were not modified when chemotherapy changed. To display the results, we considered the sum of the first line

baseline CT scan's target lesions to be 100% and the evolution of the sum of the largest diameter(s) at each of the subsequent CT scans, regardless of different chemotherapy lines, was systematically assessed as a percentage of variation from that first line baseline 100%. To avoid, as much as possible, bias induced by the appearance of new lesions, we systematically added 20% to the curve when new lesions were identified. We choose arbitrarily 20% because this increase defines progression according to the Recist criteria as the appearance of new lesion does. Finally, to easily visualize deaths and to distinguish non-survivors from survivors or censored in one readable graph, we arbitrarily represented death visually as top line on the graph reached by each patient's curve. We analyzed the tumor burden (the sum of target lesions) at endpoint, defined as the last reevaluation CT scan.

Response to each new chemotherapy line

In a second analysis, the evolution of the sum of the largest diameters at the time of the best response was systematically assessed as a percentage of variation from the corresponding baseline for each new chemotherapy line. Each baseline was thus considered 100%, independently from the baselines of the previous chemotherapy lines. Hence, graphically, a return to 100% means a treatment-line change. This analytical methodology yielded a “sawtoothed” line for each patient. Each new treatment line was defined as a change of chemotherapy or targeted agents. Unlike the analysis of the tumor-size evolution over the long term, death is not represented on the graph. Maintenance therapies and reintroduction of the first-line cytotoxic agent(s) after progression under maintenance were not considered a new line. We evaluated second- and third-line ORRs, defined as best responses to therapy (sum of complete and PRs) and the disease-control rate (sum of complete responses, PRs and SDs).

Statistical analyses

Quantitative variables are summarized using descriptive statistics: number of patients with available data (n) or mean \pm standard deviation; and compared with ANOVA test. Qualitative variables are expressed by arm as n (%) and compared with χ^2 test with Yates correction for small sample sizes.

Survival rates, estimated with the Kaplan–Meier method, are expressed as median (95% confidence interval (CI)) duration, and compared using the log-rank test. OS lasted from the date of the first administration of the first-line regimen to that of death (all causes). PFS was defined as the time from the date of the first administration of the first-line regimen and to that of progression or death. Survivors without progression were censored on the date of the most recent information up-date. The cut-off date for the final data analysis was November 15, 2016.

Statistical analyses were computed with R software, with statistical significance set at p value < 0.05 .

Results

Population studied

Among the 226 potentially eligible patients (**Figure 2**), 161, whose lesions could not be followed over the long term, were excluded; the final analysis concerned the 65 patients with complete radiological and clinical follow-up information available. According to the radiological review, patients' best responses at first line were scored as follows: 14/65 (22%) ETS_{fl}, 18/65 (28%) PR_{fl}, 19/65 (29%) SD_{fl-}, 8/65 (12%) SD_{fl+} and 6/65 (9%) PD_{fl}.

The global characteristics of the 65 patients and according to their five groups, defined by their initial tumor ORRs, are described in **Table 1**. No significant differences were found between the five groups for sex ratio, age, primary tumor and the metastatic sites, mutational status, tumor differentiation, and the type of first-line therapy. Only the microsatellite instability (MSI) status distribution differed significantly among the five groups ($p = 0.02$), with the ETS_{fl} group having more microsatellite stability (MSS).

Long-term tumor-size evolution and clinical outcomes

Spider plots of individual patient's tumor-size evolution, appearance of new lesions over the long-term, and death as assessed with our customized RECIST criteria, according to initial best response group, are represented in **Figure 3**. Clinical outcomes (Death, OS, PFS) and tumor burdens at endpoint and death are reported in **Table 2**.

Among the patients with PD_{fl} or SD_{fl+}, 12/14 (86%) had target-lesion sums superior to their first baseline assessment at endpoint (dead or alive), as opposed to 18/51 (35%) patients with ETS_{fl} or PR_{fl} or SD_{fl-} ($p < 0.001$). Considering death as the only endpoint, 11/12 (92%) patients with PD_{fl} or SD_{fl+} died with lesion sums superior to their initial baseline, whereas for patients with ETS_{fl}, PR_{fl} or SD_{fl-}, only 15/37 (41%) did ($p < 0.01$).

OS also differed significantly among groups ($p = 0.03$), being longer for the ETS_{fl} group (median OS: 29.9 (95% CI: 12.6–47.1) months) and shorter for the PD_{fl} group (median OS: 17.1 (95% CI: 1.5–37.5) months). Median PFS lasted 15 (95% CI: 9.8–24.2) months for the ETS_{fl} group vs 2.9 (95% CI: 4.9–15.3) months for the PD_{fl} group, however the between-group difference did not reach significance ($p = 0.3$).

Response to each new chemotherapy line

Individual patient's best responses to each chemotherapy line, according to his/her initial response, are represented in **Figure 4**. Response and disease-control rates to second- and third-line therapies are detailed for each initial response group in **Table 3**. Visually, tumor responses to successive lines differed substantially, depending on the initial response.

Patients with ETS_{fl} had more negative peaks below baseline 100% and SD_{fl+} or PD_{fl} patients had more positive peaks above that baseline for successive treatments. In other words, patients with an initial response to first-line chemotherapy tended to have a response to the following lines of chemotherapy, whereas patients who progressed initially tended to also not respond to following lines. This tendency was not statistically significant due to the small number of patients in each group.

Discussion

Assessing tumor responses with ETS and depth-of-response was recently shown to be associated with better OS and PFS outcomes [12], but only responses to first-line therapy were reported. Herein, we focused on the impact of the initial responses on long-term outcomes. Two mCRC-evolution types were distinguished. First, mCRCs with ETS_{fl}, PR_{fl} or SD_{fl-}, which maintained low tumor loads (only 41% patients died with tumor sizes superior to baseline), had better responses to subsequent therapy lines. Their initial tumor ORR was significantly associated with longer OS. Indeed, that beneficial response to first-line chemotherapy seemed to be prolonged over time, under successive lines. Second, mCRCs with PD_{fl} or SD_{fl+}, whose tumor loads rose (91% died with a target-lesion sums superior to their baseline assessment), continued to be mostly refractory to later therapy lines.

Our results are in accordance with those of the analysis of the role of tumor-size reduction in response to first-line therapy as a predictor of mCRC patients' long-term outcomes [12, 14]. ETS, defined a $\geq 20\%$ or 30% response, was proved to be associated with better PFS and

OS after doublet-chemotherapy with an anti-EGFR [9, 13, 15, 17, 20, 21], and after bevacizumab with triplet- or double-chemotherapy [14]. In the literature, patients with ETS, compared to those without, had maximum Δ PFS of 7.6 months and maximum Δ OS of 33.8 months. Those findings are summarized in Table E1 (online). We also described tumor-size evolution after this early response to chemotherapy, which had not been studied previously. Even outside a clinical trial, an early first CT-scan reevaluation with RECIST criteria between 6 and 8 weeks seems crucial to determine long-term mCRC evolution. Notably, we found that the initial response might be suggestive of future responses to later lines of therapy and, hence, longer OS and PFS.

Explanations that can be put forward are: on the one hand, initial intrinsic tumor aggressiveness remains constant or worsens, regardless of the chemotherapy prescribed. Indeed, changing the chemotherapy did not visibly impact the factors responsible for that aggressiveness. On the other hand, less aggressive tumors maintain a favorable profile in response to different types of chemotherapy, even after resistant-clone selection by the previous lines. This observation suggests that some aggressiveness factors are independent, or unaffected, by the different chemotherapy lines currently being used. This hypothesis raises the question of whether or not to pursue chemotherapy for mCRCs with initial progression at the first CT reevaluation at 8 weeks. Indeed, these tumors with immediate progression, which represent 10% of mCRCs, do not seem respond to the successive chemotherapies and have very little chance of later disease control. This issue should be evaluated prospectively, comparing best supportive care alone to best supportive care plus chemotherapy, but conducting such a study is complicated, for ethical reasons.

Our study has some limitations. First, our single-center study included a relatively small number of patients, only 65, but all had fully documented clinical and radiological (at least five reevaluation scans) follow-up. Indeed, we excluded many potential subjects because CT

scans were not available to analyze the evolution from first scan to death. Our study population was, however, quite representative of mCRCs with, at the first reevaluation: 49.2% ETS_{fl} or PR_{fl} responders, 41.5% SD_{fl} and 9.2% PD_{fl}, rates similar to those published previously [2, 3]. Also, the five groups' characteristics were quite similar. Second, the representation of new lesions is another potential limitation. Indeed, we chose to represent new lesions by systematically adding 20% to each patient's curve, which could be too much or too little. In addition, we did not consider non-target lesions, even though we know that the tumor burden sometimes increases due to the non-target lesions and not because of preexisting target lesions that can become necrotic or fibrotic. Hence, following the same lesion through the different chemotherapy lines may underestimate the true tumor-burden evolution. However, that bias would be similar for all groups, and does not explain the differences we found. Third, we did not analyze tumor-size responses according to treatment regimen for the different groups, because heterogeneous chemotherapies were used and more patients would be required to obtain meaningful information. Fourth, we decided arbitrarily to split into two parts the RECIST "stable disease" group. Our aim was to consider separately the outcome of all the patients with an initial positive slope for their lesion size evolution (ie, PD_{fl} and SD_{fl}⁺) and those with a negative slope (ie, SD_{fl}⁻, PR_{fl} and ETS_{fl}). However even if our results suggest that the SD group gather patients with different evolutive profiles, this is based on a small cohort and further studies are needed to confirm this point. Fifth tumor response assessment was done by two radiologists by consensus, consequently no interobserver agreement can be known, however we did not study or use non-validated methods to assess the tumor responses.

Analyses of long-term tumor-size evolutions according to early response to first-line chemotherapy could be applied to larger populations in multiple centers with mathematical modeling of those evolutions. In addition, in the near future, we should be able to assess

tumor evolution reliably and even earlier with circulating tumor DNA. Indeed, an early change of the latter's concentration could be marker of therapeutic efficacy in mCRC patients, as recently assessed in two prospective studies [22, 23].

In conclusion, a response to first-line chemotherapy was associated with the selection of chemosensitive mCRCs, future responses to subsequent treatment lines and longer OS. An initial lack of response or PD_{fl} was associated with tumors refractory to successive therapy lines with rising tumor loads. Tumor-size evolution according to initial response to first line chemotherapy may thus predict survival. These findings reinforce the interest of an early tumor reevaluation, 8 weeks after baseline CT assessment, to predict long-term mCRC evolution.

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Legends

Table 1. Patient characteristics and treatments received according to first-line chemotherapy-response group.

Table 2. Overall survival (OS), progression-free survival (FPS) and tumor burdens at endpoint and death.

Table 3. Response and disease-control rates after second- and third-line treatments, according to initial tumor-response group.

Figure 1. A 68-year-old patient with pT4N1M+ rectal adenocarcinoma and synchronous bilobar liver metastases and peritoneal carcinomatosis **a)** Baseline CT scan before first-line therapy (Folfox + Bevacizumab): example of a target lesion across the upper part of the 2nd, 4th and 8th segments of the liver . **b)** CT scan before the second-line therapy (LV5FU2 + Bevacizumab): Progressive disease with tumor increasing of 30%. **c)** CT scan before the third-line therapy (Folfiri + Bevacizumab): Progressive disease due to appearance of new lesions in the peritoneum (arrow). **d)** CT scan before the fourth-line therapy (Folfiri + Aflibercept): Progressive disease with tumor increasing of 31% compared to c).

Figure 2. Flow chart. *LICI*, line 1 cycle 1, *ETS* early tumor shrinkage, *PR* partial response, *SD* stable disease tumor-size evolution 8 weeks after starting first-line (_{fl}) chemotherapy between 0 and +19% (*SD*_{fl+}) or 0 and -29% (*SD*_{fl-}), or *PD* progressive disease.

Figure 3. Individual patient's global tumor-size evolution over the long-term, as assessed with RECIST 1.1 criteria, including new lesions, represented by systematically adding 20% to the curve, according to the initial first-line (_{fl}) chemotherapy-response group: *ETS* early tumor shrinkage, *PR* partial response, *SD* stable disease tumor-size evolution between 0 and +19% (*SD*_{fl+}) or 0 and -29% (*SD*_{fl-}), or *PD* progressive disease, expressed as the percentage variation from the baseline 100% with return to that visual level.

Figure 4. Responses expressed as the percentage of variation from the baseline of each new chemotherapy line. Each baseline was thus considered 100%, independently from the baselines of the previous chemotherapy lines. On the graph, a return to 100% means a treatment-line change. Each graph provides the responses to each new chemotherapy line for each initial first-line (f_1) best response group: ETS_{f_1} early tumor shrinkage, PR_{f_1} partial response, SD_{f_1} stable disease tumor-size evolution between 0 and +19% (SD_{f_1+}) or 0 and – 29% (SD_{f_1-}), or PD_{f_1} progressive disease.

Table 1 Patient characteristics and treatments received according to first-line chemotherapy-response group

Characteristic	Total	ETS _{fl}	PR _{fl}	SD _{fl} -	SD _{fl} +	PD _{fl}
Number of patients	65 (100%)	14 (21.5%)	18 (27.7%)	19 (29.2%)	8 (12.3%)	6 (9.2%)
Sex						
Women	22 (33.8%)	5 (35.7%)	8 (44.4%)	6 (31.6%)	3 (37.5%)	–
Men	43 (66.2%)	9 (64.3%)	10 (55.6%)	13 (68.4%)	5 (62.5%)	6 (100%)
Age (years)						
<65	29 (44.6%)	5 (35.7%)	6 (33.3%)	10 (52.6%)	3 (37.5%)	5 (83.3%)
≥65 and ≤70	15 (23.1%)	4 (28.6%)	5 (27.8%)	5 (26.3%)	–	1 (16.7%)
>70	21 (32.3%)	5 (35.7%)	7 (38.9%)	4 (21.1%)	5 (62.5%)	–
Laboratory values						
Serum albumin (g/L)	34.86 ± 5.3	35.5 ± 5.3	35.6 ± 4.1	33.8 ± 5.3	35.5 ± 9.2	33.4% ± 4.7
Lactate dehydrogenase (IU/L)	571.8 ± 399.4	460.8 ± 191.7	703.7 ± 420.1	684.4 ± 540.7	326.2 ± 142.2	465.5 ± 178.9
Serum alkaline phosphate (IU/L)	217.4 ± 313.9	210.9 ± 400.1	207.4 ± 231.8	294.4 ± 411.5	154.1 ± 178.3	98.8 ± 8.1
Primary tumor site						
Right colon	18 (27.7%)	2 (14.3%)	6 (33.3%)	7 (36.8%)	3 (37.5%)	–
Left colon	31 (47.7%)	8 (57.1%)	12 (66.7%)	7 (36.8%)	–	4 (66.7%)
Rectum	16 (24.6%)	4 (28.6%)	–	5 (26.3%)	5 (62.5%)	2 (33.3%)
Mutational status						
WT <i>RAS/BRAF</i>	18 (27.7%)	5 (35.7%)	6 (33.3%)	2 (10.5%)	3 (37.5%)	2 (33.3%)
Mutated <i>RAS</i>	31 (47.7%)	5 (35.7%)	8 (44.4%)	11 (57.9%)	3 (37.5%)	4 (66.7%)
Mutated <i>BRAF</i>	2 (3.1%)	–	1 (5.5%)	–	1 (12.5%)	–
Unknown	14 (21.5%)	4 (28.6%)	3 (16.7%)	6 (31.6%)	1 (12.5%)	–
MSI status						
MSS	39 (60%)	12 (85.7%)	10 (55.6%)	7 (36.8%)	4 (50%)	6 (100%)
MSI	7 (10.8%)	–	1 (5.6%)	2 (10.5%)	4 (50%)	–
Unknown	19 (29.2%)	2 (14.3%)	3 (16.7%)	10 (52.6%)	–	–
Tumor differentiation						
Poorly differentiated	4 (6.2%)	2 (14.3%)	–	1 (5.2%)	–	1 (16.7%)
Moderately differentiated	34 (52.3%)	10 (71.4%)	10 (55.6%)	7 (36.8%)	5 (62.5%)	2 (33.3%)
Well-differentiated	16 (24.6%)	2 (14.3%)	5 (27.8%)	6 (31.6%)	2 (25%)	1 (16.7%)
Unknown	11 (16.9%)	–	3 (16.7%)	5 (26.3%)	1 (12.5%)	2 (33.3%)
Type of metastases						
Synchronous	40 (61.5%)	10 (71.4%)	14 (77.8%)	12 (63.2%)	1 (12.5%)	3 (50%)
Metachronous	25 (38.5%)	4 (28.6%)	4 (22.2%)	7 (36.8%)	7 (87.5%)	–

Resection of primary tumor						
Yes (before metastatic chemotherap	42 (64.6%)	12 (85.7%)	8 (44.4%)	10 (52.6%)	7 (87.5%)	5 (83.3%)
Yes (during metastatic chemotherap	11 (16.9%)	1 (7.1%)	5 (27.8%)	3 (15.8%)	1 (12.5%)	1 (16.7%)
No	12 (18.5%)	1 (7.1%)	5 (27.8%)	6 (31.6%)	–	–
Metastatic sites						
Liver not affected	9 (13.8%)	4 (28.6%)	–	3 (15.8%)	2 (25%)	–
Liver only	24 (36.9%)	3 (21.4%)	8 (44.4%)	7 (36.8%)	1 (12.5%)	5 (83.3%)
Liver and others	32 (49.2%)	7 (50%)	10 (55.6%)	9 (47.4%)	5 (62.5%)	1 (16.7%)
Number of metastatic sites						
1	32 (49.2%)	7 (50%)	8 (44.4%)	9 (47.4%)	3 (37.5%)	5 (83.3%)
2	23 (35.4%)	4 (28.6%)	6 (33.3%)	7 (36.8%)	5 (62.5%)	1 (16.7%)
3	6 (9.2%)	3 (21.4%)	1 (5.6%)	2 (10.5%)	–	–
>3	4 (6.2%)	–	3 (16.7%)	1 (5.2%)	–	–
First-line therapy						
Single agent	3 (4.6%)	–	–	1 (5.2%)	1 (12.5%)	1 (16.7%)
Doublet chemotherapy	58 (89.2%)	13 (92.9%)	15 (83.3%)	18 (94.7%)	7 (87.5%)	5 (83.3%)
Triplet chemotherapy	3 (4.6%)	1 (7.1%)	2 (11.1%)	–	–	–
Anti-angiogenic agent	36 (55.4%)	7 (50%)	12 (66.7%)	10 (52.6%)	5 (62.5%)	2 (33.3%)
Anti-EGFR	10 (15.4%)	3 (21.4%)	3 (16.7%)	4 (21.1%)	–	–
Therapies received						
5-fluorouracile	65 (100%)	14 (100%)	18 (100%)	19 (100%)	8 (100%)	6 (100%)
Oxaliplatin	56 (86.2%)	12 (85.7%)	18 (100%)	16 (84.2%)	7 (87.5%)	3 (50%)
Irinotecan	53 (81.5%)	9 (64.3%)	15 (83.3%)	17 (89.5%)	8 (100%)	4 (66.7%)
Bevacizumab	49 (75.4%)	9 (64.3%)	15 (83.3%)	16 (84.2%)	5 (62.5%)	4 (66.7%)
Aflibercept	15 (23.1%)	3 (21.4%)	3 (16.7%)	5 (26.3%)	2 (25%)	2 (33.3%)
Cetuximab	18 (27.7%)	5 (35.7%)	6 (33.3%)	3 (15.8%)	3 (37.5%)	1 (16.7%)
Panitumumab	11 (16.9%)	1 (7.1%)	3 (16.7%)	4 (21.1%)	2 (25%)	1 (16.7%)
Intra-arterial therapy	9 (13.8%)	1 (7.1%)	6 (33.3%)	1 (5.2%)	–	1 (16.7%)
Regorafenib	10 (15.4%)	–	6 (33.3%)	3 (15.8%)	1 (12.5%)	–
Number of lines						
1	9 (13.8%)	3 (21.4%)	2 (11.1%)	2 (10.5%)	–	2 (33.3%)
2	25 (38.5%)	8 (57.1%)	5 (27.8%)	9 (47.4%)	2 (25%)	1 (16.7%)
3	16 (24.6%)	2 (14.3%)	4 (22.2%)	3 (15.8%)	5 (62.5%)	2 (33.3%)
4	8 (12.3%)	1 (7.1%)	3 (16.7%)	3 (15.8%)	–	1 (16.7%)
5	6 (9.2%)	–	3 (16.7%)	2 (10.5%)	1 (12.5%)	–

6	1 (1.5%)	-	1 (5.6%)	-	-	-
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Values are expressed as *n* (%) or means ± standard deviation.

ETS early tumor shrinkage, *PR* partial response, *SD* stable disease tumor-size evolution 8 weeks after starting first-line chemotherapy (*n*) between 0 and +19% (*SD_{n+}*) or 0 and -29% (*SD_{n-}*), *PD* progressive disease, *MSS* microsatellite stability, *MSI* microsatellite instability, *EGFR* epidermal growth-factor receptor.

Table 2 Overall survival (OS), progression-free survival (PFS) and tumor burdens at endpoint and death

Characteristic	Total	ETS _{fl}	PR _{fl}	SD _{fl-}	SD _{fl+}	PD _{fl}
Number of patients	65	14	18	19	8	6
Death	49 (75.4%)	6 (42.9%)	13 (72.2%)	18 (94.7%)	8 (100%)	4 (66.7%)
Target lesions >100% at						
Endpoint	30 (46.2%)	2 (14.3%)	6 (33.3%)	10 (52.6%)	7 (87.5%)	5 (83.3%)
Death	26 (53.1%)	1 (16.7%)	5 (38.5%)	9 (50%)	7 (87.5%)	4 (100%)
OS, months	22.7 (20.6–27.0)	33.3 (12.6–47.2)	24.3 (18.6–32.6)	20.8 (17.2–24.7)	22.7 (15.7–37.7)	14.1 (1.5–35.7)
PFS, months	8.6 (9.2–14.3)	15 (9.8–24.2)	9.1 (7.6–16.5)	7.2 (5.9–14.0)	4.7 (1.2–19.5)	2.9 (4.9–15.3)

Results are expressed as *n* (%) or survival median (95% confidence interval). Between-group differences were significant for OS ($p = 0.03$), but not for PFS ($p = 0.3$).

ETS_{fl} early tumor shrinkage, fl first-line chemotherapy, PR_{fl} partial response, SD stable disease tumor-size evolution between 0 and +19% (SD_{fl+}) or 0 and -29% (SD_{fl-}), PD_{fl} progressive disease, expressed as the percentage variation from the baseline 100% with return to that visual level.

Table 3 Response and disease control rates after second- and third-line treatments, according to initial tumor-response group

Parameter	ETS _{fl}	PR _{fl}	SD _{fl-}	SD _{fl+}	PD _{fl}
Second line, <i>n</i>	8	13	18	7	3
Response rate	3 (37.5%)	1 (7.7%)	1 (5.6%)	0 (0%)	0 (0%)
Disease control rate	8 (100%)	12 (92.3%)	14 (77.8%)	6 (85.7%)	1 (33.3%)
Third line, <i>n</i>	3	11	12	4	2
Response rate	0 (0%)	2 (18.2%)	2 (16.7%)	0 (0%)	0 (0%)
Disease control rate	3 (100%)	8 (72.7%)	11 (91.7%)	3 (75%)	2 (100%)

ETS early tumor shrinkage, *fl* to first-line chemotherapy, *PR* partial response, *SD* stable disease tumor-size evolution between 0 and +19% (*SD_{fl+}*) or 0 and -29% (*SD_{fl-}*), or *PD* progressive disease, expressed as the percentage variation from the baseline 100% with return to that visual level.

ESM Table E1. PFS and OS, according to ETS status and reported ETS thresholds

Study	Chemotherapy regimen	ETS definition	Patients with ETS (%)	PFS with ETS (months)	PFS without ETS (months)	Δ PFS	OS with ETS (months)	OS without ETS (months)	Δ OS
BOND, 2009 ^a	Irinotecan + cetuximab	10%	NR	7.1	1.6	5.5	12	7.4	4.6
	Cetuximab		NR	5.1	1.4	3.7	NR	NR	NR
ACCORD 13, 2011	FOLFIRI + bevacizumab	$\geq 20\%$	NR	10	9	1	33	22	11
	XELIRI + bevacizumab		NR	NR	NR	NR	NR	NR	NR
FIRE-1, 2013 ^b	FUFIRI + mIROX	$\geq 20\%$	47%	9.9	6.1	3.8	27.5	17.8	9.7
CRYSTAL, 2013 ^c	FOLFIRI + cetuximab	$\geq 20\%$	62%	14.1	7.3	6.8	30	18.6	11.4
	FOLFIRI		51%	9.7	7.4	2.3	24.1	18.6	5.5
OPUS, 2013 ^c	FOLFOX + cetuximab	$\geq 20\%$	69%	11.9	5.7	6.2	26	15.7	10.3
	FOLFOX		46%	7.2	7.2	0	21.6	17.8	3.8
CIOX, 2013 ^{c,d}	CAPIRI/CAPOX + cetuximab	$\geq 20\%$	59%	8.9	4.7	4.2	31.6	15.8	15.8
	FOLFIRI/mFOLFOX6 + cetuximab	$\geq 20\%$	NR	11.8	4.8	7	38	18.7	19.3
Ye, 2015	FOLFIRI/mFOLFOX6		NR	8	4.6	3.4	30.6	17.7	12.9
	FOLFOX4 + panitumumab	$\geq 20\%$	72%	13.6	6.7	6.9	32.5	12.6	19.9
PRIME, 2015 ^c	FOLFOX		59%	14.9	9.3	5.6	34.5	18.2	16.3
	FOLFOXIRI + bevacizumab	$\geq 20\%$	64%	8.8	7.2	1.6	31.9	21.9	10
TRIBE, 2015	FOLFIRI + bevacizumab		NR	NR	NR	NR	NR	NR	NR
	FOLFOX + cetuximab	$\geq 20\%$	80%	11.3	3.7	7.6	42.8	9	33.8
JACCRO-CC05, 2016	FOLFIRI + cetuximab	$\geq 20\%$	68%	9.7	5.8	3.9	38.3	20.5	17.8
	FOLFIRI + bevacizumab		49%	11.7	8.3	3.4	31.9	21.2	10.7
FIRE-3, 2016	FOLFOX6 + bevacizumab	$\geq 20\%$	62%	11.3	9.5	1.8	32.5	21.8	10.7
	FOLFOX6 + panitumumab	$\geq 30\%$	45%	11.1	9.7	1.4	35.1	23.9	11.2
PEAK, 2017	FOLFOX6 + panitumumab		75%	13.1	9.8	3.3	43.4	21.2	22.2

ETS early tumor shrinkage, *PFS* progression-free survival, Δ change, *OS* overall survival, *CAPIRI* capecitabine + irinotecan, *CAPOX* capecitabine + oxaliplatin, *FOLFIRI* 5-fluorouracil + irinotecan + leucovorin, *FOLFOX* folinic acid + 5-fluorouracil + oxaliplatin, *FOLFOX-4* 5-fluorouracil + leucovorin + oxaliplatin, *FUFIRI* 5-fluorouracil + folinic acid + irinotecan; *mFOLFOX6* modified FOLFOX, *mIROX* modified irinotecan plus oxaliplatin, *XELIRI* capecitabine + irinotecan, *NR* not reported.

^aTime-to-progression used.

^b ETS was assessed at 7 weeks.

^c Evaluation of patients with *KRAS* wild-type tumors.

^d ETS was assessed at 6 weeks.