Article

Consensus statement on essential patient characteristics in systemic treatment trials for metastatic colorectal cancer: supported by the ARCAD Group

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Funding.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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ABSTRACT

Background.

Patient characteristics and stratification factors are key features influencing trial outcomes. However, there is substantial heterogeneity in reporting of patient characteristics and use of stratification factors in phase 3 trials investigating systemic treatment of metastatic colorectal cancer (mCRC). We aimed to develop a minimum set of essential baseline characteristics and stratification factors to include in such trials.

Methods.

We performed a modified, two-round Delphi survey among international experts with wide experience in the conduct and methodology of phase 3 trials of systemic treatment of mCRC.

Results.

Thirty mCRC experts from 15 different countries completed both consensus rounds. A total of 14 patient characteristics were included in the recommended set: age, performance status, primary tumor location, primary tumor resection, prior chemotherapy, number of metastatic sites, liver-only disease, liver involvement, surgical resection of metastases, synchronous versus metachronous metastases, *(K)RAS* and *BRAF* mutation status, MSI/MMR status, and number of prior treatment lines. A total of 5 patient characteristics were considered the most relevant stratification factors: *RAS*/*BRAF* mutation status, performance status, primary tumor sidedness, and liver-only disease.

Conclusions.

This survey provides a minimum set of essential baseline patient characteristics and stratification factors to include in phase 3 trials of systemic treatment of mCRC. Inclusion of these patient characteristics and strata in study protocols and final study reports will improve interpretation of trial results and facilitate cross-study comparisons.

KEY WORDS

Colorectal cancer, metastatic disease, patient characteristics, prognosis, stratification, clinical trials, Delphi survey

INTRODUCTION

Metastatic colorectal cancer (mCRC) is a heterogeneous disease, with patients experiencing varying prognosis and treatment response. Trials investigating systemic treatment of mCRC often demonstrate heterogeneity in response and survival outcomes, which could partly be explained by differences in prognostic factors. However, there is no consensus on which patient characteristics should be reported as baseline characteristics, and what stratification factors should be used to balance key prognostic factors between treatment arms. This complicates cross-study comparisons and extrapolation of trial results to the general patient population.

Following a proposal made in 2007 on standardization of patient characteristic reporting and stratification in trials investigating systemic treatment of mCRC[1], we performed a systematic review to investigate the implementation of this proposal and reporting of prognostic factors in phase 3 trials of first-line treatment of mCRC published between 2005-2016[2]. This systematic review, including >35,000 mCRC patients from 67 phase 3 trials, showed persistent heterogeneity in the reporting of patient characteristics and use of stratification factors. Apparently, the proposal made in 2007 has not resulted in uniform reporting of patient characteristics and use of stratification over time. Moreover, novel prognostic factors that have become relevant in the light of targeted agents were infrequently reported.

There is an urgent need for an international consensus on reporting of patient characteristics and stratification in mCRC trials. Although standardization of stratification factors in mCRC trials is difficult to establish due to different study designs, reaching consensus on a standardized set of baseline characteristics would improve interpretation of trial results and facilitate future meta-analyses. We used the Delphi method to systematically obtain expert opinions for this purpose[3,4]. In a Delphi survey, experts are asked for their opinion on a specific issue, and repeatedly polled with controlled feedback regarding the polled opinions to encourage consensus between experts[5].

Using a two-round Delphi survey, we aimed to 1) reach consensus on a minimum set of essential patient characteristics to include in study protocols and final reports of phase 3 trials investigating systemic treatment of mCRC, and 2) to present a set of prognostic factors that are currently considered the most important stratification factors in these trials.

METHODS

Participants

We performed a Delphi survey among international experts with experience in the conduct and methodology of phase 3 trials of systemic treatment of mCRC. Eligible experts were identified from the Aide et Recherche en Cancérologie Digestive (ARCAD) Group[6] member list, and received an electronic invitation to participate in the survey.

Patient characteristics

To determine a preliminary list of patient characteristics, we retrieved all baseline characteristics reported in 67 phase 3 mCRC trials published between Jan 2005-June 2016 that were included in our systematic review[2]. Reported baseline characteristics were grouped; overlapping baseline characteristics and variables that were deemed too rare or specific were excluded. Prognostic factors that have potentially become relevant during recent years were added to the list.

Consensus rounds

The consensus procedure consisted of a modified two-round Delphi survey(Figure 1), resulting in a recommended and suggested set of baseline characteristics. The survey was done on a secure survey website. Non-responders received up to three reminders.

In round 1, a preliminary list of patient characteristics was presented. Experts were asked to rate the importance of reporting each variable as a baseline characteristic in final reports of phase 3 trials of systemic treatment of mCRC. They could vote for as many patient characteristics as desired. Experts were asked to give their preferred definition of 'primary tumor location' and 'synchronous versus metachronous metastases' if they considered these variables 'very important'. Furthermore, they could suggest baseline characteristics that were not already mentioned in the list. Finally, experts were asked to provide ≤4 prognostic factors that they considered the most relevant strata in phase 3 trials of systemic treatment of mCRC.

Following round 1, variables rated 'very important' by ≥67% of the experts were included in the recommended set. Variables rated 'not important' by ≥50% of the experts were excluded. Remaining variables were presented in round 2. Additional patient characteristics mentioned during round 1 were evaluated by the study team, grouped if possible, and presented in round 2. Preferred definitions of

‘primary tumor location’ and ‘synchronous versus metachronous mCRC’ were evaluated. Definitions with most votes plus additional definitions suggested by experts were entered in round 2. Prognostic factors that were reported as most relevant stratification factors were summarized.

Second round forms were sent to all responders of the first round, accompanied by feedback on results of round 1. Round 2 consisted of the same list of baseline characteristics as round 1, except those rated as ‘very important’ by ≥67% or ‘not important’ by ≥50% of the experts, plus additional characteristics suggested in round 1. Procedures in round 1 and 2 were comparable. In round 2, all experts were asked for their preferred subdivision of ‘primary tumor location’ and ‘synchronous versus metachronous metastases’. Prognostic factors that were voted the most relevant stratification factors during round 1 were presented. In addition to the three prognostic factors that received the highest number of votes in round 1, experts were asked to choose ≤3 prognostic factors that they considered relevant to include as strata in phase 3 trials of systemic treatment of mCRC.

After round 2, variables rated ‘very important’ by ≥67% of the experts were included in the recommended set. Remaining variables were incorporated in the suggested set, except variables rated ‘not important’ by ≥33% of the experts. Variables not fulfilling the criteria to be included in either set were excluded. Preferred definitions of ‘primary tumor location’ and ‘synchronous versus metachronous metastases’ were compared with results from round 1. Prognostic factors that were reported as most relevant strata were summarized and compared with round 1 results.

Stratification factors

Following both rounds, we assembled an overview of prognostic factors that are currently considered the most important stratification factors in phase 3 trials of systemic treatment of mCRC. Based on these results, we suggested a minimum set of strata to include in systemic treatment trials for mCRC.

Statistical analysis

Data were analyzed using Excel and SPSS version 21.0.

RESULTS

Participants

Sixty-two experts were contacted, of whom 29 medical oncologists and 1 statistician from 15 different countries participated in both rounds. All participants had known expertise in the field of mCRC based upon experience in designing and conducting mCRC trials, publications, and (inter)national committee leadership.

Patient characteristics

In round 1, 33 patient characteristics were presented, subdivided into different categories: demographics; disease characteristics; prior treatment; laboratory testing; biomarkers; and disease symptoms. In round 2, 29 patient characteristics were presented using the same categories as round 1, plus a category concerning specific baseline characteristics for later-line trials. In both rounds, patient characteristics were formulated with examples in parentheses.

Consensus rounds

During round 1, 13 characteristics were rated ‘very important’ by ≥67% of the experts and were directly included in the recommended set (Table 1;Figure 2). One characteristic was rated as ‘not important’ by ≥50% of the experts and was therefore excluded. Remaining characteristics plus eleven additional characteristics suggested by the experts were entered in round 2. After round 2, one additional characteristic was rated as ‘very important’ by ≥67% of the experts and was included in the recommended set (Table 1;Figure 3). Six characteristics were excluded from further analysis, as they were rated ‘not important’ by ≥33% of the experts. The remaining 22 characteristics were added to the suggested set(Table 2).

Consensus statement

Fourteen patient characteristics were included in the essential, recommended set of baseline characteristics to include in study protocols and final reports of phase 3 trials investigating systemic treatment of mCRC(Table 1). Twenty-two patient characteristics were incorporated in the suggested set(Table 2). For both sets, recommendations were made on how to report a specific item.

Preferred definitions

In round 1, 29 (97%) experts gave their preferred definition of ‘primary tumor location’. All experts gave their preferred subdivision of primary tumor location in round 2. Following both rounds, the definition with the highest number of votes was: right colon (cecum up to and including transverse colon) versus left colon (splenic flexure up to and including sigmoid) versus rectum (rectosigmoid and rectum)(Supplementary Figure 1).

In round 1, twenty-two (73%) experts gave their preferred definition of ‘synchronous versus metachronous metastases’. All experts gave their preferred subdivision of ‘synchronous versus metachronous metastases’ in round 2. Definitions with the highest number of votes were: synchronous versus metachronous (diagnosed ≤6 versus >6 months following CRC diagnosis); and synchronous versus early metachronous versus late metachronous (diagnosed before or at time of CRC diagnosis versus ≤0-12 months versus >12 months following CRC diagnosis)(Supplementary Figure 2).

Stratification factors

In round 1, prognostic factors that were considered the most important strata in phase 3 trials on systemic treatment of mCRC were: *RAS/BRAF* mutation status, performance status and primary tumor sidedness. Liver-only disease received the highest number of votes in round 2(Figure 4).

DISCUSSION

This study provides a recommended and suggested set of patient characteristics to include in the study protocol and baseline table of final reports of phase 3 trials investigating systemic treatment of mCRC. We performed a two-round Delphi survey to develop a consensus recommendation based on opinions of 30 international mCRC experts. Furthermore, we present a set of prognostic factors that are currently considered the most important stratification factors in phase 3 trials on systemic treatment of mCRC.

The recommended set includes 14 patient characteristics (Table 1) that should be regarded as a minimum set of essential characteristics to include in the study protocol and baseline table of final reports of phase 3 mCRC trials. The suggested set consists of 22 patient characteristics, of which a selection may be considered to collect and report in phase 3 mCRC trials(Table 2). Clearly, the recommended and suggested set will evolve over time. Therefore, plans are being made to update the consensus recommendation every 2-3 years in a continuing subprogram of ARCAD, a worldwide collaboration of clinicians, statisticians and scientists specializing in gastrointestinal cancer, whose ultimate goal is to develop more efficient clinical trials [6]. Evidently, the final set of patient characteristics will depend on each trial's study objectives, eligibility criteria, treatment line, and drugs evaluated.

Based on a literature review, Sorbye et al. made a proposal in 2007 on standardization of patient characteristic reporting and stratification in systemic treatment trials for mCRC[1]. Overall, there was high concordance between patient characteristics included in our recommended set and their proposal[1]. However, none of the laboratory values suggested by Sorbye et al. fulfilled the criteria for inclusion in our recommended set. Laboratory values were also infrequently reported in mCRC trials studied in our systematic review[2]. Although several studies have reported the importance of abnormal laboratory values as prognostic factors in mCRC[7,8], our findings show that general acceptance of their prognostic value has not been reached.

Molecular and genetic testing has become increasingly important to define different subtypes of mCRC[10]. Since the prognostic value of *RAS*/*BRAF* mutation status and MSI/MMR status has only been established in recent years[11-14], it seems logical that these prognostic factors were not yet incorporated in the proposal made in 2007[1], but will now be included. It is likely that in upcoming years, the established prognostic factors will be better incorporated in routine clinical practice, and

other (bio)markers will be identified to complement these factors. Nonetheless, 'classic' clinical and pathological characteristics currently cannot be disregarded, since biomarkers or gene expression profiles with high predictive specificity are not yet available.

There is increasing evidence that in mCRC, tumors arising from different sides of the colon (left versus right) have different prognosis and response to anti-EGFR therapy[15,16]. Almost all experts acknowledged the importance of using primary tumor location or sidedness as a baseline characteristic and/or stratification factor in mCRC trials. We recommend to use the preferred subdivision of primary tumor location (right colon [cecum up to and including transverse colon] versus left colon [splenic flexure up to and including sigmoid] versus rectum [rectosigmoid and rectum]) in the baseline table of mCRC trials. It has been hypothesized that differences between right-sided and left-sided tumors arise from a non-random distribution of molecular characteristics that change gradually along the length of the colorectum[17]. Until underlying mechanisms have been clarified, we advise to specify the exact anatomical segment of the colorectum in Case Report Forms (CRFs) of mCRC trials to facilitate meta-analyses.

Although most experts acknowledged the importance of reporting synchronous versus metachronous metastases as baseline characteristics, there was no consensus on the preferred definition. This is in line with a systematic review which showed that many different definitions of synchronous disease were used in mCRC studies[18]. Following our survey, two definitions received the highest number of votes(Supplementary Figure 2). We recommend to use one of these definitions in future mCRC trials to gain insight into differences in clinical outcome in patients with synchronous and metachronous mCRC. Until consensus is reached, collecting the dates of initial CRC diagnosis and first distant metastasis in CRFs of mCRC trials will help in deriving synchronous versus metachronous disease with different definitions.

Following our survey, prognostic factors that are currently considered the most relevant strata in mCRC trials are performance status, *RAS/BRAF* mutation status, primary tumor sidedness, and liver-only disease. Performance status was the only prognostic factor that was also suggested in 2007[1]; the prognostic value of *RAS/BRAF* mutation status and primary tumor sidedness has only recently been established[11-13,15,16], and more local ablative treatment options have become available for patients with liver-only disease[19]. We recommend to consider these stratification factors

in future mCRC trials investigating systemic treatment. Since the number and type of strata is dependent on multiple factors, including treatment line, drugs evaluated and eligibility criteria, this set can be adjusted and/or supplemented with one or more trial-specific strata.

This study has some limitations. The systematic review used to compile a list of patient characteristics to present in round 1 included first-line mCRC trials published between 2005- 2016[2]. Therefore, recently identified prognostic factors could have been missed. However, novel prognostic factors were added to the list by the study team, and experts' suggestions were presented in round 2. Furthermore, our Delphi survey consisted of two rounds. Characteristics almost fulfilling the criteria to be included in the recommended set after two rounds could have made it after a third round. However, there are no guidelines for Delphi surveys regarding the number of rounds to be performed. Likewise, consensus criteria for the recommended and suggested set were not based on validated guidelines, since these are non-existent, but on considerations of the study team to create manageable sets of baseline characteristics. Due to the heterogeneity in study reporting in current mCRC trials, we were not able to assess the level of evidence of the prognostic value of all recommended characteristics. Our recommendation may facilitate standardization of data collection and reporting of mCRC trials across all treatment lines. This will provide better evidence as to how the actual prognostication works out in each treatment setting. Implementation of our recommendation in future mCRC trials will enable evaluation of whether this minimum set of recommended patient characteristics fulfils its intended purpose.

A strength of our consensus procedure is that it is based on both literature evidence and expert opinions. Thirty international experts with experience in conducting phase 3 mCRC trials participated in this survey, all of which were ARCAD members. Another strength is that each expert voted independently, which encourages an honest opinion based on their clinical expertise in conducting mCRC trials.

CONCLUSION

This is the first consensus recommendation among international mCRC experts on essential patient characteristics and stratification factors in phase 3 trials investigating systemic treatment of mCRC. In future mCRC trials, inclusion of this minimum set of essential baseline characteristics and strata in

study protocols and final study reports will improve trial reporting, interpretation, and cross-study comparisons.

ROLE OF THE FUNDING SOURCE

This research project did not receive financial support for the conduct of the research and/or preparation of the article.

CONTRIBUTORS

KG, MK, MvO and CJAP designed the study. KG collected the data. KG, MK, MvO and CJAP analyzed and interpreted data. KG prepared the manuscript. All authors (except KG and MvO) participated in the Delphi survey. All authors reviewed the manuscript and gave final approval for submission of the manuscript.

CONFLICT OF INTEREST STATEMENT

CJAP acted in an advisory role for Nordic-Pharma and Servier. HS reports grants from Novartis, Ipsen, Amgen, and personal fees from Novartis, Celgene, Roche, Ipsen, Amgen, Shire and Merck. RA reports grants from Cancer Research UK, EME MRC, Astra Zeneca, and personal fees and non-financial support from Amgen, Merck Serono, BMS and Servier. TA reports grants from Bayer, BMS, and personal fees from Amgen, Bayer, BMS, Eli-Lilly, MSD Oncology, Servier, Xbiotech and Yaccult. EDR reports grants from Merck and Amgen, and personal fees from Merck, Amgen, MSD, Bayer, Genomica, Sanofi and Roche. CE reports grants from Keryx and Daiichi, consulting fees from Bayer, Sirtex, and other support (speaker's bureau) from Genentech. AF reports grants and personal fees from Amgen, Bayer, Merck, Roche, Servier, Bristol, MSD and Lilly. VH reports grants from Merck, Amgen, Roche, Sanofi, Servier, Boehringer Ingelheim and Pfizer, personal fees from Merck, Roche, Sanofi, Sirtex, Bristol Mayer Squibb, MSD, Novartis and Boehringer Ingelheim, and non-financial support from Merck, Roche, Sirtex and Bayer. HH reports consultancy fees from Bristol Meyers Squibb, Bayer, Merck and Genentech. SK reports personal fees (consultancy fees) from Amgen, Array, Bayer, Genentech, MolecularMatch and Taiho. NM reports grants from Genomic Health (research support) and is an employee of Flatiron Health. TP reports personal fees from Amgen. JS reports grants from Amgen, Roche and Sanofi, personal fees from Amgen, Merck, Roche, Sanofi and

Servier, and non-financial support from Amgen, Merck, Roche and Sanofi The other authors declare no competing interests.

ACKNOWLEDGEMENTS

We would like to acknowledge the ARCAD foundation (non-profit organization) for their support in conducting this research. We would like to acknowledge E. ter Veer and L.B. van Rijssen for their advisory role in designing the Delphi survey. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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TABLES AND FIGURES

TABLES

Table 1. Recommended set of baseline characteristics to report in phase 3 trials on systemic treatment of mCRC

Table 2. Suggested set of baseline characteristics to report in phase 3 trials on systemic treatment of mCRC

FIGURES (only titles and legends; figures are uploaded as separate files)

Figure 1. Flow chart of consensus procedure

Legend: -

Figure 2. Baseline characteristics – Consensus round 1.

Legend: The bars represent the percentage of participants rating each characteristic as ‘very important’ (green), ‘moderately important’ (yellow) or ‘not important’ (orange).

Figure 3. Baseline characteristics – Consensus round 2.

Legend: The bars represent the percentage of participants rating each characteristic as ‘very important’ (green), ‘moderately important’ (yellow) or ‘not important’ (orange).

Figure 4. Stratification factors – Consensus round 1 (blue) and 2 (green).

Legend: N.s. = not specified.

Table 1. Recommended set of baseline characteristics to report in phase 3 trials on systemic treatment of mCRC

Recommended set	
Age	Median (range); <70 vs ≥70 years
Performance status	ECOG / WHO, 0 vs 1-2
Location primary tumor	Right colon vs Left colon vs Rectum*
Surgery primary tumor	Yes or No
Prior chemotherapy	Yes or No
Number of metastatic sites	1 vs >1 (primary tumor excluded)
Liver-only disease	Yes or No
Liver involvement	No vs <25% vs ≥25%
Surgery metastases	Yes or No
Synchronous versus metachronous metastases	**
(K)RAS mutation status	Wild-type or Mutant
BRAF mutation status	Wild-type or Mutant
MSI / MMR status	MSI or MSS; dMMR or pMMR
For later line trials	
Number of prior treatment lines	1, 2, >2

The recommended set should be regarded as a minimum set of essential characteristics to include in the study protocol and baseline table of final reports of phase 3 mCRC trials. * Preferred definitions of primary tumor location: right colon (cecum up to and including transverse colon), left colon (splenic flexure up to and including sigmoid), rectum (rectosigmoid to rectum). ** Preferred definitions of synchronous vs metachronous metastases are depicted in Supplementary Figure 2. MSI = microsatellite instability. MSS = microsatellite stable. MMR = mismatch repair. dMMR = deficient MMR. pMMR = proficient MMR

Table 2. Suggested set of baseline characteristics to report in phase 3 trials on systemic treatment of mCRC

Suggested set	
Gender	Male or Female
Race / Ethnicity	Race: e.g. White, Black, Asian, Other; Ethnicity: e.g. Hispanic, Not Hispanic
Prior radiotherapy	Yes or No
Stage at first diagnosis	I-III vs IV
Tumor differentiation	Well vs Moderate vs Poor vs Undifferentiated
Lactate dehydrogenase (LDH)	Normal vs > UNL
Alkaline phosphatase (ALP)	Normal vs > UNL
Carcinoembryonic antigen (CEA)	Normal vs > UNL
Albumin	< LLN vs Normal
Platelet count	<400 vs ≥ 400 x 10^9/L
Initially resectable metastatic disease	Yes or No
Lung-only disease	Yes or No
Peritoneal disease	Yes or No
Number of metastases	1 vs >1
Comorbidity or Fit vs Unfit patient	According to ESMO guidelines
Weight / BMI	Underweight (BMI<18.5 kg/m^2); Normal (18.5-24.9 kg/m^2), Overweight (25-29.9 kg/m2), Obese (≥30 kg/m2)
Weight loss	>5% or >10% during last 3 or 6 months
Symptomatic disease	Yes or No
For later line trials	
Truly refractory vs 'Just discontinued' prior treatments	
Time from diagnosis mCRC to start of treatment	< or ≥18 months
Response and PFS on prior treatments	best response to prior treatment: CR/PR, SD, PD; PFS: median, in months
Time from last treatment to start of trial	in months

CR/PR = complete or partial response. LLN = lower limit of normal. PD = progressive disease. PFS = progression-free survival. UNL = upper normal limit.