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Standardizing data collection in adjuvant colon cancer trials: A consensus project from the IDEA and ACCENT international consortia and national experts

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ABSTRACT

Background: Despite contributions provided by the recent clinical trials, several issues and challenges still remain unsolved in adjuvant colon cancer (CC). Hence, further studies should be planned to better refine risk assessment as well as to establish the optimal treatment strategy in the adjuvant setting. However, it is necessary to request adequate, contemporary and relevant variables and report them homogeneously in order to bring maximal information when analyzing their prognostic value.

Material and methods: The project was devised to gain a consensus from experts engaged in the planning, accrual and analyses of stage II and III CC clinical trials, to identify mandatory and recommended baseline variables in order to i) harmonize future data collection worldwide in clinical trials dedicated to adjuvant treatment of CC; ii) propose guidance for Case Report Forms to be used for clinical trials in this setting. A total of 72 questions related

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to variables that should be reported and how to report them in adjuvant clinical trials were approved and then voted to reach a final consensus from panelists.
Results: Data items on patient-related factors, histopathological features, molecular profile, circulating biomarkers and blood analyses were analyzed and discussed by the whole expert panel. For each item, we report data supporting the acquired consensus and the relevant issues that were discussed. Nineteen items were deemed to be mandatory for resected stage III patients and 24 for resected stage II disease. In addition, 9 and 4 items were judged as recommended for stage III and II, respectively.
Conclusion: In our opinion, these 28 variables should be used and uniformly reported in more comprehensive CRFs as research groups design future clinical trials in the field of adjuvant colon cancer.

1. Introduction

Colon cancer (CC) is the second most common cancer worldwide [1]. For early stage tumors, surgery followed by up to six months of chemotherapy, according to risk stratification, still represents the gold standard treatment [2]. Currently, 3–6 months of a chemotherapy regimen combining a fluoropyrimidine and oxaliplatin with the option of stopping oxaliplatin after 3 months and continuing fluoropyrimidine in case of poor tolerability is the standard of care for stage III patients depending on disease prognosis (high vs low risk stage III patients) [2–7]. For stage II patients, again depending on poor prognostic risk features, treatment may vary from surveillance to the same combination chemotherapy or a fluoropyrimidines alone [2,8]. This underlines the importance of an accurate risk stratification for each individual patient as disease prognosis is directly influencing our therapeutic choices for both disease stages. Furthermore, the emerging importance of novel molecular markers indicates that they are not only relevant prognosticators [9–11], but also predictive markers with mechanistic matched new treatment options for some molecular subgroups, such as *MSI-H* or *BRAF* V600E mutant colon cancer in the metastatic setting. How they can be best integrated in future prognostic models, in the adjuvant setting, is still matter of discussion. [12–15]. Adjuvant trials, that we base our practice on, are now 15 + years old and variables previously collected may be less relevant likewise. Specifying contemporary variables will permit efficient data collection and strengthen the potential for meta/pooled-analysis.

Despite the advancement resulting from recent clinical trials in the adjuvant setting, several issues or challenges still remain unresolved. Further studies should be designed to refine the definition of factors linked to risk assessment as well as to establish the best adjuvant treatment option for each prognostic group. Clinical trials are likely to provide more robust data than observational studies due to their prospective design and rigorous data collection and quality assurance. As we increasingly recognize the heterogeneity of colon cancers, it is necessary to standardize the conduct of clinical trials so that they are prospectively designed to collect all known relevant variables and to report them homogeneously. For instance, we have observed through individual patient data collected in ACCENT and IDEA databases, that the selection and reporting of baseline variables is somewhat heterogeneous within the most relevant clinical trials dedicated to adjuvant treatment for CC. In some cases, even the case report forms (CRFs) developed by the same research intergroup does not report the same set of variables in two consecutives trials, though dedicated to the same patient population.

In other cases, the same variable is collected differently, hampering cross study comparisons. For example, the actual number of positive and examined lymph nodes was collected in some trials, while other studies collected nodal status as an aggregated categorical variable based on AJCC-UICC staging criteria (N1a/b/c, N2a/b). This data collection diversity, challenges the effective integration of serial studies into statistical models, resulting in significant limitations on our ability to draw conclusive inferences across clinical trials performed in identical or similar patients. This situation ultimately hinders the potential identification of crucial prognostic subgroups and the customization of adjuvant treatments in international multi-trial pooled analysis such as the IDEA or ACCENT collaboration.

Therefore, the goal of this project was to find a consensus on which baseline variables are important to be included in a CRF and to provide guidance for future adjuvant trials dedicated to CC. For each variable we considered the best format (or coding) based on the panel recommendation. Hence, this project records the outcome of a think-tank dedicated to clinical research in this specific setting, and is not necessarily meant to be required for the daily care of patients treated outside of clinical trials. This project may help to identify the variables that are mandatory and recommended, but also which are the variables that seem useless to the international panel of experts and that can be discarded from future CRFs.

2. Material and methods

A multinational expert panel was assembled, and a modified Delphi method was applied to reach consensus in identifying mandatory and recommended baseline variables. The main objectives of the study were: i) to harmonize future data collection in clinical trials worldwide dedicated to adjuvant treatment of CC ii) to propose a reference standard for CRFs that could be used by any research group performing a clinical trial in this setting.

In the first phase, the Study Steering Committee selected 22 experts in the field of adjuvant treatment of CC. The experts were chosen from the lower GI ESMO faculty working group for localized CC, the ACCENT group (devoted to pooled analyses of clinical trials in the field of adjuvant treatment of CC trials since two decades ago) and the IDEA consortium that have generated the IDEA pooled analysis on more than 12,000 patients recruited from 12 different countries. These experts treat patients in Europe, Asia, Oceania, and North America. Several experts were part of 2 or 3 of these groups. All members (clinicians or statisticians) had wide experience in clinical trial design, including the development of CRFs and in the analysis of clinical trial data. The project itself consisted of 2 key rounds. During the first round, 22 voting-members completed an online survey establishing which variables should be reported in future clinical trials dedicated to adjuvant treatment in CC, and how to best report them. The survey was structured in electronic form using the online platform, *SurveyMonkey*™.

Overall, 72 statements were approved and clustered in two main topics. During the first step, panellists answered 49 questions to quote which variable should be reported in clinical trials conducted on adjuvant CC patients. A 4-point scale was used to rank the agreement or the negative consensus for each of the proposed statements: *mandatory* (1), *recommended* (2), *optional* (3), *useless* (4) for the first round of the study. Detailed questions about the first step are shown in the supplemental material file (Suppl. Table1). In the second step, 23 additional questions were addressed on how to best report each variable in future CRFs (Suppl. Table 2).

The second round was held through two consecutive web-based meetings at scheduled intervals. In the first meeting, all panellists examined and discussed the results obtained from the web-based survey. In the second meeting, the statements endorsed with only partial agreement were voted upon again after thorough discussion through the

meetings and final recommendations were made based on the opinions of the majority of respondents. All responses were summarized through descriptive analysis. Descriptive statistical analyses were performed with *SurveyMonkey*™ and STATA (StataCorp. (2015) Stata Statistical Software: Release 14.2. College Station, TX: StataCorp LP). A consensus was declared achieved if more than 75% recipients agreed on the same statement.

3. Results

3.1. The first-round online survey on the variables that should be reported in (neo)adjuvant clinical trial

Panel members were asked if they considered 49 items mandatory/recommended/optional or useless. Overall, 22 answers were collected for all items (no missing answer). Results are summarized in Suppl Fig. 1. After first round voting, 21 out of 49 items were considered as mandatory items. Of note, bowel obstruction, bowel perforation, tumor grade and venous, lymphatic and perineural invasion (VELIPI) were considered mandatory in the first-round survey only for stage II patients. As for the remaining questions, the answers were more heterogeneous (see Suppl Fig. 1) and were debated during the second-round web-meeting.

Panel members were also asked, through 23 questions, what is the best way to report each variable in clinical trials. Results are shown in Suppl Table 3. Briefly, a consensus (>75% of votes) was reached for only 3 of 23 questions (WHO-PS, *BRAF* status and primary tumor location reporting). Four additional questions reached over 70% of consensual answers (CEA, VELIPI, *RAS* status, and Ethnicity reporting). For all remaining questions, the answers were more heterogeneous and were debated during the second-round web-meeting (Suppl Table3).

3.2. The Second-round web meetings on variables that should be reported in (neo)adjuvant clinical trial

During the second-round of virtual meetings, all questions and answers from the first-round were re-examined to reach a consensus (Figure 1, Table 1). To facilitate comprehension of the team discussion on each non-consensual item, statements have been grouped and presented according to their topic.

3.2.1. Variable ranking

A summary of the final consensus on item classification as mandatory/recommended/optional and useless is shown in Figure 1.

3.2.1.1. Variables about patient-related factors and diagnosis of colon cancer. Age, sex, country of origin, race, height, weight, WHO/ECOG PS, date of surgery, date of histological diagnosis and primary tumor location should be considered mandatory in conducting adjuvant and neoadjuvant clinical trials.

As panelists widely discussed, the date of last CT scan was considered a recommended item to be entered in CRF, given that CT scan done within 8 weeks should be mandatory before study inclusion. A negative consensus was reached about body mass index (BMI) and body surface area (BSA), since they should be derived from height and weight, to minimize human mistakes or errors derived from differing calculation formulas. Finally, comorbidities and concomitant medication were considered optional by the vast majority of voting experts given the intricacy of collecting them in a systematic and unitary fashion among different trials, which ultimately can lead to misleading interpretations.

3.2.1.2. Variables about histo-pathological features. TNM classification based on American Joint Committee on Cancer/Union for International Cancer Control (AJCC/ UICC) system still represent the most relevant histological criteria for risk assessment [16]. However, overall disease

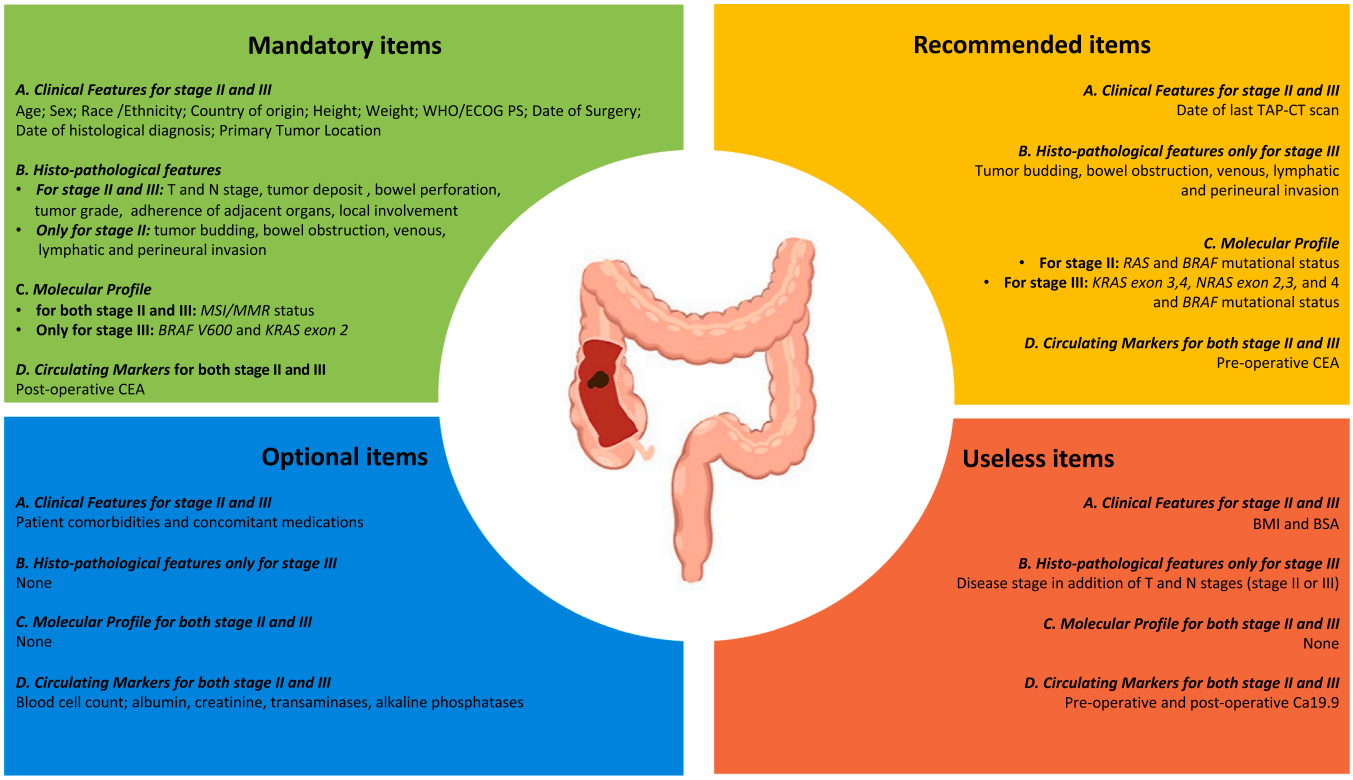

Fig. 1. Variables that should be collect in conducting adjuvant clinical trials. A total of 72 questions, grouped in patient-related factors, histo-pathological features, molecular profile, circulating biomarkers and blood analyses, were voted and discussed. The figure represents the first step of the survey: panel members were asked for 49 variables if they considered them mandatory, recommended, optional or useless.

stage was not recommended by panelists, since it can be derived from separate T and N stage. Given the continuous evolution of AJCC system over time, the "raw" data of T and N stages can provide the flexibility of standardizing comparisons even in the case where changes occur in stage classifications over time. Moreover, the panel endorsed as mandatory variables bowel obstruction (defined as clinical or radiological obstruction leading to emergency surgery and not according to colonoscopy criteria), and perineural invasion, vascular invasion as well as lymphatic invasion only for N0 tumors (i.e., current stage II per AJCC 8th edition), since their presence is strongly associated with worse DFS and OS [17–19]. In contrast, given their limited role in N + tumors, these same factors were judged as "recommended" for patients with current stage III disease per AJCC 8th edition. In addition the presence or absence of bowel perforation, local carcinomatosis resected "en bloc" during surgery (if allowed by the protocol inclusion criteria) and tumor grade were considered mandatory for both stage II and III [20–22].

Beyond standard histological features, tumor deposits were deemed mandatory as they could provide additional prognostic information in addition to that provided by positive and total lymph node counts. Indeed, the presence of tumor deposits (clusters of tumor cells in the pericolic fat, without identifiable residual lymph node tissue) has been associated with poorer DFS and OS in several studies [23–27]. In fact, the 7th and 8th editions of the AJCC TNM staging categorizes tumor deposits present in the tissues adjacent to N0 tumors as N1c disease [27]. Interestingly, the combined analysis of IDEA-France and CALGB/SWOG 80702 studies, demonstrated that a higher number of tumor deposits combined with the number of metastatic lymph-nodes was correlated with shorter survival outcomes [28,29]. In addition, this item is still often missing in the source pathological reports and its reporting needs to be encouraged as highlighted by several members of the panel.

The prognostic role of tumor budding (up to four cancer cells at the invasive margin), has been widely studied and currently influences decision making for patients with pT1 and stage II CC. Consistently, voting-members decided to classify tumor budding as a mandatory variable for stage II patients. However, it was voted only as "recommended" for patients with stage III disease. The panel believes that although the results obtained from a recent post-hoc analysis on the IDEA-France trial demonstrated the prognostic role of tumor budding in stage III CC, further evidence is necessary to better establish the reproducibility of this variable [30–34]. However, it should be reported according to the criteria adopted by the 2016 International Tumor Budding Consensus Conference (ITBCC2016) (number of buds per 0.785 mm2 in the hot-spot), as BD1 (0–4: low), BD2 (5–9: intermediate), and BD3 (≥10: high).

3.2.2. *Molecular profile*

The prognostic and predictive role of the microsatellite instability high (MSI-H) and mismatch repair deficient status (*dMMR*) phenotypes have widely been established as relevant to outcomes and decision making in the adjuvant treatment of CC, especially for stage II patients. Therefore, MMR status is categorized as a mandatory variable in all guidelines for both Stage II and III trials performed in this setting [2,30,35]. Mounting evidence supports a DFS and OS benefit with the addition of oxaliplatin to fluoropyrimidine compared with fluoropyrimidine alone in stage III CC patients with *MSI-H* tumors, with a prognostic impact in low-risk stage III (pT1–3, N1). [36,37].

Besides MMR assessment, other molecular markers like *BRAF V600E* and *RAS* are not currently recommended in the routine management of non-metastatic CC patients. While studies on the prognostic value of RAS mutation have been mixed, a recent meta-analysis conducted on nine trials (QUASAR 2, PETACC-8, N0147, CALGB-89803, NSABP-C07, NSABP-C08, PETACC-3, QUASAR, MOSAIC) with more than 8000 stage III patients with molecular annotations for both gene mutations, showed worse OS and DFS for patients with *KRAS* exon 2 or *BRAF V600E* mutated tumors [11,38,39]. Voting-members considered *BRAF* V600E and K*RAS* exon 2 as mandatory for stage III disease, after long discussion and a third voting session. Though these markers do not currently influence the clinical management of early CC patients in routine practice, their demonstrated prognostic value will make them necessary for any relevant multivariable analyses on DFS or OS in stage III patients. Though very few data are available on *KRAS* exons 3 and 4 and *NRAS* exons 2,3 and 4, they are also recommended as they are generally tested together with *KRAS* exon 2 and *BRAF V600E*. In addition, the efficient therapies targeting these mutations, already successful in the metastatic setting, are moving to the adjuvant and neoadjuvant settings and will possibly make these markers move to routine practice in the near future. It has been also highlighted that, as these tests are not reimbursed in non-metastatic disease, they have to be funded by the study sponsor and shall not hampered the start of an academic trial not able to fund them. Considering stage II disease, as the level of evidence is lower for these patients the vote was only recommended.

3.2.2.1. Biomarkers assessed in analyses from blood samples. During the virtual conference panelists discussed the utility of circulating tumor DNA and RNA and tumor related proteins. Reporting of post-operative CEA, confirming the highly recognized prognostic role of post-operative CEA levels, was voted as mandatory. In fact, adjuvant studies revealed a linear relation between post-operative CEA and death or recurrence [40–43], especially in the first 12 months after surgery [44]. In contrast, reporting of pre-operative CEA levels was voted as recommended only, as the current literature is scarce as compared to reported importance of post-operative CEA. However, having both pre and post-operative CEA levels increases the value of this marker as elevated preoperative CEA followed by normal post-operative CEA is more informative that only normal post-operative CEA for example.

On the other hand, pre- and post-operative Ca19.9 levels were not recommended based on literature data and the standard operating practices of the different centers that the expert panels represent. Blood analyses performed in routine clinical practice achieved a lower level of agreement as their baseline prognostic value is less consistent and trials sometimes use these factors as inclusion/exclusion criteria; in fact, members voted them optional issues at baseline assuming that they will be also collected in the CRF before the first and subsequent cycles of treatment or during the follow-up of patients.

3.3. *Variable reporting*

A summary of the consensual best way to report each variable is shown in Table 1.

3.3.1. *Patient related features*

Panelists discussed how best to report patients' age: as a continuous variable or by categories (i.e. >70 and <70). Date of birth was the

Table 1
Final consensus statement on the variables that should be reported in (neo)adjuvant clinical trial and how to report them.

Mandatory	Recommended	Optional	Useless

(*continued on next page*)

Table 1 (*continued*)

Variables	Stage II	Stage III	*How to report variables*
A. Patient related factors and diagnosis of colon cancer			
Age	M	M	Date of birth
Sex	M	M	M or F
Race /Ethnicity	M	M	Black, White, Asian or others
Country of origin (for multinational trials)	M	M	Name country
Height	M	M	Continuous in cm
Weight	M	M	Continuous in kg
WHO/ECOG-PS	M	M	0, 1, 2
Date of surgery	M	M	Date of surgery
Date of diagnosis	M	M	Date of diagnosis
Primary tumor location	M	M	caecum/ascending/hepatic flexure/ transverse/splenic flexure/ descending/ sigmoid/ rectosigmoid junction and upper rectal
Date of last TAP-CT scan	R	R	Date of last TAP-CT scan
Patients comorbidities	O	O	Cardiovascular disease, diabetes, chronic inflammatory disease, metabolic syndrome
BMI	U	U	Useless, just report height and weight
BSA	U	U	Useless, just report height and weight
Concomitant Medications	U	U	Useless (except for registration trials)
B. Histo-pathological features			
T stage	M	M	Tx, Tis, T0, T1, T2, T3, T4a, T4b
N stage	M	M	Number of examined lymph node and number of positive lymph node for N stage
Tumor deposit	M	M	Number of tumor deposits
Bowel perforation	M	M	Yes vs No
Tumor grade/differentiation	M	M	G1, G2, G3, G4
Tumor Budding	M	R	Bd1, Bd2, Bd3
Bowel obstruction	M	R	Yes vs No
Venous embolism	M	R	Individual and not as VELIPI and Yes vs No
Perineural invasion	M	R	Individual and not as VELIPI and Yes vs No
Lymphatic invasion	M	R	Individual and not as VELIPI and Yes vs No
Adherence to adjacent organs	M	M	Yes vs No
Local peritoneal involvement ("en bloc" resected)	M	M	Yes vs No
Disease stage in addition of T and N stages (stage II or III)	U	U	Useless

(*continued on next page*)

Table 1 (*continued*)

C. Molecular profile			
MMR/MSI status	M	M	MSI-H vs MSS vs ND **AND** dMMR vs pMMR vs ND + Deficient protein collected (MLH1, MSH2, MSH6, PMS2)
RAS mutational status	R	M	List of individual mutations in KRAS and NRAS
BRAF V600E mutational status	R	M	WT vs MT V600E vs MT others
D. Circulating markers and blood analyses			
Post-operative CEA	M	M	Continuous in ng/mL
Pre-operative CEA	R	R	Continuous in ng/mL
Blood cell count	O	O	Continuous (Hb g/dL, WBCC /mm3 or Giga/L)
Albumin	O	O	Continuous in g/L
Creatinine	O	O	Continuous in umol/L or mg/dL
Transaminases (TGO/TGP)	O	O	Continuous in UI/L
Alkaline phosphatases (ALP)	O	O	Continuous in UI/L
Pre-operative Ca19.9	U	U	Useless (continuous in UI/L when reported)
Post-operative Ca19.9	U	U	Useless (continuous in UI/L, when reported)

Legend: M: mandatory, R: recommended; O: optional; U: useless; M: male; F: female; BMI: body mass index; BSA: body surface area; MSI: microsatellite instability; MMR: mismatch repair; MSS: microsatellite stable; dMMR: mismatch repair deficiency, WT: wild type; MT: muted.

preferred option, and it should be the best one because it allows age to be calculated at different time-points. However, due to regulatory policies and privacy requirement, panelists decided to share, in future clinical trials, only year of birth as some regulatory policies limit the sharing of the full date of birth.

For race/ethnicity the panelists agreed to classify patients as Black, White, Asian or others.

A positive consensus was achieved on reporting WHO/ECOG-PS as 0,1, or 2 and not 0 vs> 0 as seen in some trials, since ECOG-PS has a linear association with prognosis.

As previously discussed, comorbidities were considered optional. If the study team choses to report them, we recommend that it be done in a simple category as cardiovascular, diabetes/metabolism, chronic inflammatory disease. Panelists judged that it is useless to collect data on concomitant medications outside of registration trials where regulatory authorities require those data. If necessary, they should be reported using their international non-proprietary name, the dosage and the date on which treatment was started and stopped.

3.3.1.1. Histo -pathological features. T and N stage remains the most relevant prognosticator and the gold standard used in clinical practice to establish adjuvant treatment for CC patients. Panelists commented on how to report T and N stage, concluding for the more accurate classification (Tx, Tis, T0, T1, T2, T3, T4a, T4b for T stage and number of examined lymph nodes and number of positive lymph nodes for N stage including N1c in case of lack of node metastasis but presence of tumor deposits) leading to correctly classify disease stage according AJCC system that could change over time and to calculate the lymph node ratio (LNR: number of positive lymph nodes/ number of examined lymph nodes) that has been reported to have the best prognostic value when dealing with lymph node invasion [45–48].

Based on the results from recent publications, the panel recommended to report the number of tumor deposits. Tumor grading as G1,2,3,4 (or the corresponding well differentiated, moderately differentiated, poorly differentiated, anaplastic) was judged as more informative compared to the other options. Pathological grading may be complex for mucinous tumors since CC is graded according to the degree of glandular differentiation and thus, they were mainly considered as high-grade according to the WHO 2000 classification. However, more recent WHO guidelines (2019) suggested no prognostic difference based on the degree of tumor differentiation compared with simply classifying the tumor as adenocarcinoma, although a differences are reported in response to anti-cancer treatment in the metastatic setting according to grade. [49,50].

Notably, the more exhaustive option for tumor location (caecum/ ascending/hepatic flexure/ transverse/splenic flexure/ descending/ sigmoid/ rectosigmoid junction and upper rectal) was confirmed as the preferred choice during the virtual meeting.

Current clinical trials reported venous, perineural and lymphatic invasion, in different ways, leading to differences on how they relate to prognosis. Most of the panelists, according to the survey' responses, decided to record venous embolism, perineural invasion and lymphatic invasion as separate items.

3.3.1.2. Molecular Profile. Panelists endorsed the determination of *MMR* status as mandatory, while they defined as recommended determination of *RAS* and *BRAF* status in non-metastatic colon cancer. Based on the recent breakthroughs in molecular biology, panelists reached a consensus to recommend detailed reporting of RAS and *BRAF* status because of the potential that such data will be relevant to determining future targeted treatment options and extend our knowledge of the prognostic importance of individual mutations:

- *For MSI*: *MSI-H* vs *MSS* vs ND and *dMMR* vs *pMMR* vs ND + Deficiency collected (MLH1, MSH2, MSH6, PMS2)
- *For RAS*: List of individual mutations in *KRAS* and *NRAS* exons 2,3 and 4.
- *For BRAF*: WT vs mutant V600E vs other mutations

3.3.1.3. Circulating markers and blood analyses. In the first part of the survey, panelists defined post-operative CEA assessment as a mandatory variable to report. Although the common cut-off used is 5 ng/mL, some studies have report a higher prognostic and predictive impact when the specified cut-off point was 2.35 ng/mL [40,51,52]. Hence, the lack of a reliable cut-off value for CEA assessment, and the different interval limits used among centers were considered relevant issues by the experts. To better refine its prognostic role in the future trials, panelists suggested that CEA should be reported as a continuous variable in ng/mL.

Moreover, the panel member decided that reporting of the other blood analyses specified in Table 1 is optional. When reported, they should be recorded as continuous variables.

4. Conclusion

Data collection and reporting in clinical trials are critical and essential. However, collecting and reporting these data is both onerous and costly. It is critical to balance the collection of practical, scientifically based data while considering the efficiency and cost-effectiveness of a trial. Uniformity in reporting of baseline characteristics so that the data can be used to generate the most valuable information is critical to optimize the value that can be extracted from clinical trials.

Oncology is currently leading the way in investigating new anticancer therapies, treatment strategies and molecular biology. However, the selection and reporting of baseline variables is not standardized and uniformly reported among different clinical trials impairing reproducibility, the possibility of integrating data from different trials and therefore the results that can be obtained. In the last years, different initiatives and research platforms have been carried out, especially in the context of observational data, to allow harmonization, reproducibility, accessibility and findability of research data like OMOP [53] (*Observational Medical Outcomes Partnership)*, ontologies, the FAIR [54] (Findability, Accessibility, Interoperability, and Reuse of digital data) principles, the EU Open Science policy [55] and EHDS [56] (*European Health Data Space)*. Notably, AACR GENIE [57] (Genomics Evidence Neoplasia Information Exchange) is particularly focused on precisione medicine and PLCRC [58] (Prospective Dutch CRC cohort) provides real-world data on colorectal cancer. Due to the lack of national and international guidelines for guidance about which variables and how to report them, aim of this consensus is to guide researcher in requesting homogenously the variables in the CRF form, in particular, in the future adjuvant clinical trials dedicated to CC.

This team effort of worldwide renowned experts in the field judged the following 19 items to be mandatory: age, sex, country, race, height, weight, WHO-ECOG PS, date of surgery, date of diagnosis, primary tumor location, T stage, N stage, the presence or absence and number of tumor deposit(s), tumor grade, the presence or absence of bowel perforation, the presence or absence of adherence to adjacent organs, the presence or absence of “en bloc” resected juxta-tumoral peritoneal carcinomatosis (if allowed by the protocol inclusion criteria), post-operative CEA, and MMR status. In addition, 5 more items were defined as mandatory for patients resected from a stage II tumor only: the presence or absence of tumor budding, bowel obstruction, and venous, lymphatic or perineural invasion. These last items are all recommended but not specified as mandatory for stage III patients. Other recommended items were the date of pre-operative CT scan, pre-operative CEA, *RAS* status, *BRAF* status for both stage II and III patients.

In our opinion all these items should be included as common data points in future CRFs constructed to record patient and tumor characteristics in adjuvant treatment trials for CC, in order to generate optimal information at the time of trial analysis and to allow pooled analyses dedicated to rare subtypes of the disease.

The identification and refinement of prognostic factors that have utility for understanding the behavior of locally confined, non-metastatic CC is a rapidly evolving landscape. ctDNA, to track minimal residual disease, digital pathology as artificial intelligence tools, to generate accurate prognostication from image analysis of simple pathological slides of the tumor, are developing quickly and will be very probably used in the near future. However, first results almost always show that traditional clinicopathological items can improve the performances of these new approaches when used properly and need thus to be adequately collected in clinical trials [59–61]. We will now have to study these new prognosticators through ongoing trials and implement them in future versions of this consensual work in coming years. Indeed, a more homogeneous and standardized collection of all the old and new items relevant to disease prognosis and prediction of therapy efficacy is needed to optimize data extraction from current and future trials so that they can translate in improvements in clinical practice.

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no founding to declare.

CRediT authorship contribution statement

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Declaration of Competing Interest

All authors declare no competing interest regarding this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2024.114118.

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