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Guidelines for time-to-event end-point definitions in adjuvant randomised trials for patients with localised colon cancer: Results of the DATECAN initiative

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Appendix A.: Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2020.02.009.

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Abstract

Background: The variability of definitions for time-to-event (TTE) end-points impacts the conclusions of randomised clinical trials (RCTs). The Definition for the Assessment of Time-to-event Endpoints in CANcer (DATECAN) initiative aims to provide consensus definitions for TTE end-points used in RCTs. Here, we formulate guidelines for adjuvant colon cancer RCTs.

Methods: We performed a literature review to identify TTE end-points and events included in their definition in RCT publications. Then, a consensus was reached among a panel of international experts, using a formal modified Delphi method, with 2 rounds of questionnaires and an in-person meeting.

Results: Twenty-four experts scored 72 events involved in 6 TTE end-points. Consensus was reached for 24%, 57% and 100% events after the first round, second round and in-person meeting. For RCTs not using overall survival as their primary end-point, the experts recommend using disease-free survival (DFS) rather than recurrence-free survival (RFS) or time to recurrence (TTR) as the primary end-point. The consensus definition of DFS includes all causes of death, second primary colorectal cancers (CRCs), anastomotic relapse and metastatic relapse as an event, but not second primary non-CRCs. Events included in the RFS definition are the same as for DFS with the exception of second primary CRCs. The consensus definition of TTR includes anastomotic or metastatic relapse, death with evidence of recurrence and death from CC cause.

Conclusion: Standardised definitions of TTE end-points ensure the reproducibility of the end-points between RCTs and facilitate cross-trial comparisons. These definitions should be integrated in standard practice for the design, reporting and interpretation of adjuvant CC RCTs.

Keywords

Guidelines; Colon cancer; Adjuvant; Chemotherapy; Randomised controlled trials; Time-to-event end-points

1. Introduction

In randomised phase III cancer clinical trials, the most objectively defined time-to-event (TTE) end-point is overall survival (OS). The desire to reduce clinical trial duration and cost and meet end-points efficiently with the fewest possible number of patients has led to the use of surrogate end-points of OS to measure treatment efficacy, such as disease-free survival (DFS), recurrence-free survival (RFS), progression-free survival (PFS) or time to recurrence (TTR). These criteria are composite end-points combining different events such as local and distant recurrences and occurrence of a second cancer, death or severe toxicity.

The variability of definitions for a particular TTE end-point can strongly impact the trial by affecting both statistical power and study conclusions. This issue was highlighted by Birgisson *et al.* in the context of colorectal cancer (CRC) [1]. The authors demonstrated that the inclusion of a second primary cancer other than CRCs as an event in the definition of DFS significantly impacted the results. The estimated DFS rate for patients with stage I–III disease was 62% after 5 years if second primary non-CRC was not counted as an event, compared with 58% if it was. Furthermore, the results of the PETACC (Pan European Trial Adjuvant Colon Cancer)-3 study were either statistically significant or not significant depending on whether second primary tumours were included in the DFS definition [2]. The recognition of the lack of standardised definitions for TTE end-points, as recommended by the International Conference on Harmonisation (ICH) guidelines and the CONSORT (Consolidated Standards of Reporting Trials) statement [3,4], led to the publication of international guidelines, including a template for colon cancer adjuvant trials [5]. However, the absence of a formal consensus process and the fact that the process did not seek the input of international academic groups in these studies may explain why existing guidelines are not consistently used by researchers designing trials.

The international Definition for the Assessment of Time-to-event Endpoints in CANcer (DATECAN) initiative has been set up to provide recommendations to standardise definitions of TTE end-points used in randomised cancer clinical trials, using a formal consensus process [6]. Here, we report guidelines for the definition of TTE end-points used in adjuvant randomised clinical trials (RCTs) for patients with localised colon cancer. This research work is registered on the international clinical trials registry (ClinicalTrials.gov Identifier: NCT03676010).

2. Methods

The DATECAN methodology has been published in an earlier communication [6]. As of today, the DATECAN initiative has led to the publication of international guidelines in several cancer sites, notably pancreatic, breast and kidney cancer and sarcoma/gastrointestinal stromal tumour [7–10].

2.1. Literature review

We conducted literature reviews to assess the development of guidelines for TTE end-points and listed TTE end-points reported in RCTs, either as primary or secondary end-points, as well as events included in the definition of these TTE end-points. We limited our search to

articles published in English from January 2007 to December 2018. The research algorithms are available in Appendix A1 (online only).

2.2. The consensus process

A formal consensus method was used to develop these guidelines (for a full description of the methodology of the consensus process, refer to the study by Bellera et al. [6]). Four committees of experts were involved in this process: the coordinating committee (CC), the steering committee (SC), the rating committee (RC: 20–30 experts representative of international academic groups chosen by the RC with the help of the SC) and the peer-review committee (PRC). Two experts of the DATECAN methodology (DATECAN founders) were included in the CC and the SC (C.B. and S.G.). All RC experts had to be a current or past principal investigator of at least one phase III adjuvant colon cancer study or to be the first or last author of at least one phase III trial publication reporting phase III trial results.

Briefly, we relied on a modified Delphi consensus method, with two rounds of online questionnaires and a final in-person meeting to discuss items for which consensus has not been reached after the two rounds of rating. For the first round, all RC experts received the questionnaire elaborated by the SC and were asked to score from 1 (totally disagree) to 9 (totally agree) whether each event should be included or not in the definition of each TTE end-point. For the second round, experts were asked to rescore items for which no strong consensus had been reached during the first round (*i.e.* inclusion of an event in the TTE end-point definition if median score ≥7 and all scores ≥7; no inclusion if median score ≤3 and all scores ≤3; up to 2 missing responses or outliers were tolerated for the second round; see Appendix A2 [online only]). By design, the formal consensus process aims to guide experts to take a position, while accurately determining their opinion. Items for which no strong consensus had been reached during the 2 rounds of rating were discussed during a final in-person meeting.

3. Results

3.1. Selection of time-to-event end-points to be defined and clinical events of interest

During the literature review process, 32 RCTs published from January 2007 to December 2018 were identified (Appendix A3, online only). A total of 5 distinct TTE end-points which included 12 distinct events (*i.e.* 60 events to be scored; Table 1) were reported. Variations were observed for the definition of all TTE end-points except TTR that was used in only one trial. Discrepancies were notably observed in the definition of DFS. Among 25 trials using DFS as their primary end-point, 80% included second primary CRC as an event for DFS and 40% included second primary non-CRC (Appendix A3, online only). During the development of the questionnaires, the SC proposed to discuss an additional TTE end-point named colon cancer–specific survival (C-CSS) that, to our knowledge, had never been reported in published trials but might be more relevant than cancer-specific survival (CSS). This methodology led us to score 72 events. Owing to some variability in the choice of the reference date (‘t0’) in the literature, a supplementary question was added to the questionnaires to obtain the experts’ opinion.

3.2. Experts for the scoring process

The CC drafted a list of 45 international experts that were representative of academic research groups. Of the 24 experts who completed the first questionnaire, 20 (83%) also answered the second round (4 experts did not participate in the second round of rating despite several reminder emails sent during a 6-week period). They were mainly medical oncologists (19 of 20), working at academic institutions in multiple countries (Appendix A4, online only). Multiple cooperative groups were represented: AIO CRC study group (Arbeitsgemeinschaft Internistische Onkologie), Alliance for Clinical Trials in Oncology, Canadian Cancer Trials Group (CCTG), Dutch Colorectal Cancer Group, European Organisation for Research and Treatment of Cancer, Gastrointestinal group (EORTC GI), Fédération Francophone de Cancérologie Digestive (FFCD), French Multidisciplinary Group in Oncology (GERCOR), Italian Group for the Study of Gastrointestinal Cancer (GISCAD), Hellenic Oncology Research Group (HORG), Japan Clinical Oncology Group (JCOG), NRG Oncology (National Surgical Adjuvant Breast and Bowel Project [NSABP]/ Radiation Therapy Oncology Group [RTOG]/Gynecologic Oncology Group [GOG]), Unicancer Gastrointestinal Group (UCGI).

3.3. Standardised definitions of the time-to event end-points

After the first round of rating, there was a strong consensus on 17 items out of 72 items (24%). Thus, 55 items were submitted to the rating process for the second round. After the second step of the rating process, the group reached a strong consensus on 41 additional items (57%; Table 2 and Appendix A5, online only). Therefore, the attendees (12 experts: 7 from the RC, 2 from the CC and 3 from the SC) discussed the 31 items where consensus had not become apparent during the face-to-face meeting (Appendix A6, online only).

Events to be included in the definition of each TTE end-point after the consensus process are summarised in Table 3. After consensus, the definition of DFS included all causes of death as an event as well as second primary CRCs, and both anastomotic and metastatic relapses. Events included in the RFS definition were as follows: all types of death, as well as anastomotic and metastatic relapse. TTR definition includes anastomotic and metastatic relapse as well as death with evidence of recurrence and death from colon cancer.

The definitions of CSS and C-CSS (which had been added to the questionnaire by the SC) were identical: death with evidence of recurrence, death related to protocol treatment and death from colon cancer. In the experts' opinion, with respect to adjuvant colon cancer trials, the relevant end-point should be designated as 'colon cancer–specific survival' rather than 'cancer-specific survival'.

Considering the reference date (surgery or date of randomisation), the experts agreed that date of randomisation should be used in RCTs for adjuvant treatment in localised colon cancer to maintain the notion of intention to treat.

3.4. Validation of the guidelines and peer review

The minutes of the face-to-face meeting, which included the final guidelines, were validated by email by all the participating experts. After this preliminary review, the first draft of the

manuscript of guideline recommendations was sent to the experts and then submitted to a peer-review group for external comments. This group provided a formal, advisory opinion on the content and form of the initial version of the guidelines, in particular their applicability, acceptability and readability.

4. Discussion and conclusion

It is desirable to standardise the methodology of RCTs that enrol patients with cancer to harmonise the reporting of clinical research, especially for colon cancer studies, the second most common cancer killer worldwide. The experts involved in this study were drawn from the leadership of international cancer clinical trial cooperative groups and had coordinated clinical trials in the setting of the adjuvant treatment of colon cancer. We also had experts in the use and application of the DATECAN methodological framework. We believe that this approach will enhance the reproducibility of the end-points between studies and facilitate the comparison of results across different RCTs.

We intentionally did not include recommendations about the censoring process. Indeed, events that are not included in the TTE end-points can be censored, ignored or accounted for (using competing-risk analysis) in the statistical analysis, and the selected method is study-specific depending on the trial's objectives [5,11].

Considering DFS, strong consensus was already obtained for 5 events after the 2 steps of the rating process: anastomotic and metastatic relapse, death with evidence of recurrence, death related to treatment protocol or death from colon cancer cause. The experts agreed that DFS should include all causes of death as an event, to avoid bias in the interpretation of the cause of the death. A consensus emerged to include second primary CRCs in the definition of DFS. During the last decade, second primary CRCs were included in the definition of DFS, with the exception of NCCTG N0147, CALGB 89803, CALGB 9581 and in a study of the Norwegian Gastrointestinal Cancer Group (NGCG) [12–15]. The potential difficulty to distinguish second primary CRCs from anastomotic relapse was one of the reasons for this unanimous decision. Second primary non-CRCs were discussed at length. It has been included in the definition of DFS in 10 of 27 trials (PETACC-3, FNCLCC Accord 02, NASBP C-07, NASBP C-08, NASBP-C09, JCOG0205, JMC33–0502, JCOG0910, SACURA and ECKINOXE) using DFS as the primary or secondary objective since 2007 [2,12–16,16–41]. Importantly, in the PETACC-3 trial, 45 patients (4.3%) in the LV5FU2 group and 55 patients (5.3%) in the irinotecan plus LV5FU2 group had a second primary malignancy other than colon cancer that was recorded as a DFS event, with potential impact on the trial's conclusions [2]. Considering the presumed absence of relationship between adjuvant therapy for colon cancer and the occurrence of second primary non-CRC, the experts decided not to include this item in the definition of DFS for adjuvant colon cancer trials.

For the definition of RFS, strong consensus had been reached during the rating process not to include second primary non-CRCs. This has not been defined as an RFS event in trials reported in the last decade with the exception of PETACC-3, X-ACT, CALGB 89803 and XELOXA studies [2,13,23,38]. In published trials, death of any cause was considered as an

event for RFS in almost all trials, except in X-ACT and XELOXA where it was limited to ‘treatment-related or cancer-related death if relapse had not been reported’, and in CALGB 89803 in which only ‘death with documented cancer relapse’ was included in the definition of RFS [13,23,38]. Finally, as well as for DFS, the experts agreed to include all causes of death in the definition of RFS: given the difficulty in defining the true cause of death, all deaths, whatever the cause, should be considered events for ‘survival’ TTE end-points, except for (colon) cancer-specific survival.

In the only trial (NCCTG N0147) that used TTR as an end-point, the events included in the TTR definition were recurrence or death with recurrence [12]. Strong consensus was obtained for these 2 items, as well as for death caused by colon cancer. All other causes of death, as well as second primary cancers, were not considered as events to be considered in the definition of time to recurrence. TTR might be useful for populations for which death from non-colon cancer cause and from unknown cause might compete with cancer relapse events, such as the elderly, who may die before cancer relapse, or patients with stage II colon cancer, whose risk of recurrence is low. TTR may also be more informative than DFS for biomarker association analyses.

CSS was used in 2 trials only [15,36]. The included event was death caused by colon cancer and also treatment-related death in one of these 2 trials. Importantly, a strong consensus to include death with evidence of recurrence (whatever the cause of the death) was obtained during the first round of rating by the experts. The 2 rounds of rating and the discussion during the final meeting brought to light the fact that CSS and C-CSS seemed similar to the experts. Of note, the definition of CSS by the National Cancer Institute is as follows: ‘the percentage of people in a study or treatment group who have not died from a specific disease in a defined period of time; patients who died from causes other than the disease being studied are not counted in this measurement’. Therefore, considering adjuvant colon cancer trials, the relevant indicator might be named C-CSS rather than CSS. CSS can be confusing in the context of trials of adjuvant therapy in colon cancer because of deaths due to non-CRCs. Importantly, strong consensus was obtained during the first round to include death with evidence of recurrence in the definition of C-CSS. This determination was made given the poor prognosis of relapsed CRC. The experts confirmed that death with evidence of recurrence should be considered as event for C-CSS. Besides, considering the fact that patients do receive anti-tumour treatment because of the disease and would have not received it if they have not been diagnosed with colon cancer, the experts consensually decided to integrate death related to protocol treatment in the definition of C-CSS.

Consensus was obtained for all items after this formal consensus rating with 2 rounds of rating and a final face-to-face meeting. Given its strong correlation with OS, the experts unanimously recommend using DFS, a surrogate end-point approved by the Food and Drug Administration, as primary end-point rather than RFS, TTR and C-CSS in adjuvant RCTs for patients with localised colon cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflict of interest statement

L.S. has received research funds from Taiho Pharmaceutical. M.S. has received honoraria for meetings/lectures from Roche, Merck, Sanofi, Servier and Amgen. R.C. has received honoraria from Amgen, Sanofi and Servier and travel fees from Sanofi. T.A. has served in a consulting/advisory role, and/or received honoraria from Amgen, Bristol-Myers Squibb, Chugai, HalioDx, MSD Oncology, Pierre Fabre, Roche/Ventana, Sanofi and Servier and has received travel accommodations and expenses from Roche/Genentech, MSD Oncology and Bristol-Myers Squibb. T.Y. has received funding from Novartis Pharma K.K., MSD K.K., Sumitomo Dainippon Pharma Co., Ltd., Chugai Pharmaceutical Co. Ltd., Sanofi K.K., Daiichi Sankyo Co. Ltd., PAREXEL International Inc. and Ono Pharmaceutical Co. Ltd. ADW reports personal fees from Bristol-Myers Squibb, Servier Suisse, Merck , Merck Sharp & Dohme, Bayer, EMD Serono, Lilly, Sanofi, and Celgene, non-financial support from AstraZeneca, AbbVie, Sanofi-Adventis Deutchland, SHIRE, and PFIZER. All remaining authors have declared no conflicts of interest.

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Table 1

Events and time-to-event end-points used as primary or secondary objectives in randomised trials published between 2007 and 2018.

Events	Time-to-event end-points
Anastomotic relapse	Overall survival
Metastatic relapse	Disease-free survival
Second primary colorectal cancer	Recurrence-free survival
Second primary non-colorectal cancer	Time to recurrence
Death with evidence of recurrence	Cancer-specific survival
Death without evidence of recurrence	Colon cancer–specific survival[a]
Death related to protocol treatment	
Death from colon cancer cause	
Death from non–colon cancer cause	
Death from unknown cause	
Death from any cause	
Loss to follow-up	

[a]The steering committee suggested including colon cancer–specific survival during the elaboration of questionnaires.

Table 2

Results of the 2 rounds of rating. OS: overall survival; DFS: disease-free survival; RFS: recurrence-free survival; TTR: time to recurrence; CSS: cancer-specific survival; C-CSS: colon cancer–specific survival. Strong consensus to include (green) or not to include (red) the item; relative consensus to include (light green) or not to include (light red) the item; no consensus or uncertainty: white.

	OS	DFS	RFS	TTR	CSS	C-CSS
anastomotic relapse						
metastatic relapse						
2nd primary CRC						
2nd primary non-colorectal cancer						
death with evidence of recurrence						
death without evidence of recurrence						
death related to protocol treatment						
death from colon cancer cause						
death from non-colon cancer cause						
death from unknown cause						
death from any cause						
lost of follow-up						

Table 3

DATECAN guidelines for events to be included in the definitions of time-to-event end-points in randomised clinical trials for adjuvant treatment in localised colon cancer. Green box: inclusion of the event; red box: events that should not be considered in the definition of the time-to-event end-point. OS: overall survival; DFS: disease-free survival; RFS: recurrence-free survival; TTR: time to recurrence; C-CSS: colon cancer–specific survival.

	OS	DFS	RFS	TTR	C-CSS
Anastomotic relapse					
Metastatic relapse					
Second primary CRC					
Second primary non-colorectal cancer					
Death with evidence of recurrence					
Death without evidence of recurrence					
Death related to protocol treatment					
Death from colon cancer cause					
Death from non-colon cancer cause					
Death from unknown cause					
Death from any cause					
Loss to follow-up					