Time for a lead-time definition? Author response to 'Why the length of recurrence free survival or "lead-times" can be misleading. Comment on: Callesen LB, Takacova T, Hamfjord J, et al. Circulating DNA in patients undergoing loco-regional treatment of colorectal cancer metastases: a systematic review and meta-analysis'

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We thank Dr. Sorscher for bringing attention to the *lead-time* aspects, as a commentary to our manuscript on circulating tumor (ctDNA) in patients undergoing loco-regional treatment of colorectal cancer (CRC) metastases.[1] In this, we presented results of a systematic review and meta-analysis addressing the prognostic value of ctDNA detection prior to or after local treatment for CRC metastases.

In the presented dataset and thus the resulting discussion, we used aggregated data provided by the respective authors of the individual analyses, and since the majority do not draw attention to the aspects on any *lead-time* data, this aspect has consequently also not been brought to discussion in the review.

We do however, agree that *lead-time* data, as they are currently presented in the literature, can in fact be somehow misleading, and that this is another important subject for discussion.

ctDNA presence after a curatively intended treatment for solid tumors is a strong prognostic marker, indicating a markedly high (if not 100%) risk of relapse of the disease.[2] This is commonly referred to as ctDNA *minimal residual disease* (MRD). In studies where ctDNA analysis is done later, during the follow-up period, the same prognostic value is reported[3,4] – but in addition, data can be used to describe a potential *lead-time* between the ctDNA-based definition of relapse and the standard assessment of recurrence, by clinical and/or imaging-based examinations. Figure 1 shows our suggestions for definitions of *lead-time* in curative and palliative situations. The magnitude of the *lead-time* reported in the literature can indeed be misinterpreted if the study is not prospectively designed to address the topic. The true sensitivity of ctDNA for detection of early recurrence can only be assessed from studies with direct comparisons with current standards (radiological and clinical definition of recurrence) at similar timepoints. It is natural to assume that imaging procedures in most retrospective observational studies are performed according to clinical practice, but there is still value in analyzing the intermittent ctDNA testing to describe the potential of such new observations.

An overview of the included studies in a previous review and meta-analysis in advanced disease reveals that in a significant number of the studies blood samples were drawn more frequently than the clinical/radiological evaluations, whereas other studies failed to report on the frequency of scans.[5] Review of our present overview regarding loco-regional treatment of metastases from CRC revealed that only few of the studies included presentation of a *lead-time* aspect, and this primarily as case reports on a limited number of pat ients.[6–13] The frequency of scans was presented in only three studies.[9,12,13] In two of these studies,

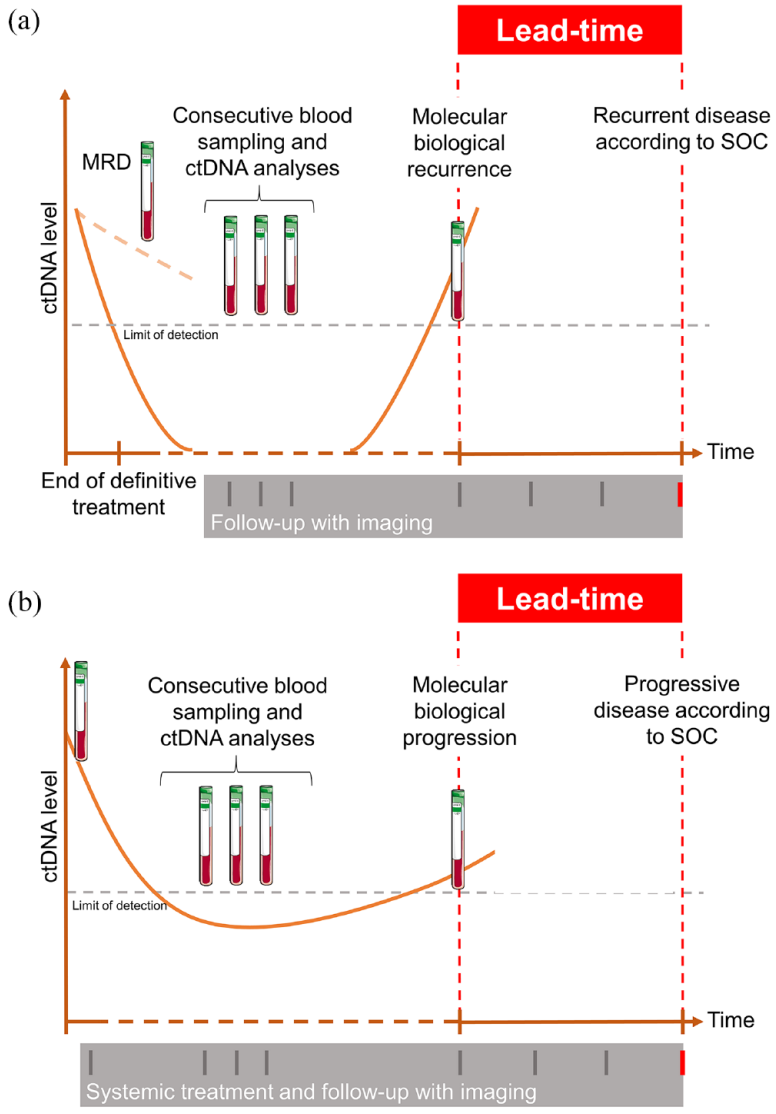

Figure 1. Schematic overview of definition of *lead-time* in the curative (a) and palliative (b) setting.
Clinical lead-time can be defined as the time between blood-based detected and clinical-detected recurrence/progression. The biological lead-time can only be defined if scans and blood samples are done at the same time.
MRD, minimal residual disease; SOC, standard of care.

scans were less frequent than ctDNA analysis.[9,12] The studies mentioned by the author show similar tendency. Tarazona *et al.* reported a median *lead-time* of 11.5 months based on 14 patients who underwent 6-monthly scans and blood sampling every 4 months.[14] Henriksen *et al.* reported a median *lead-time* of 9.8 months in 21 patients, and adequately addressed the issue of less frequently performed scans (i.e. 6-monthly or at 12- and 36-month compared to 3-monthly blood samples).[15] A shorter *lead-time* of 5.5 months was reported by Tie *et al.* but in this study both scans and sampling were performed with 3-monthly intervals.[16] To compare the results between studies, standardization in definitions and reporting of results is mandatory.

In summary, the true clinical value must be investigated in prospective carefully designed studies. Prospective observational studies should first be designed to compare the ctDNA analysis and imaging results at the same timepoints, blinded to the results from each modality. This will allow for a reliable quantification of the *lead-time* and results can thus be used to calculate the most relevant sample size for prospective randomized

trials. A few randomized studies have already been designed to investigating ctDNA as adjunct to standard follow-up programs, for example, in the Nordic trial of ctDNA guided follow-up in anal cancer (NOAC9 clinical trial.gov NCT05572801) or direct comparison of ctDNA based follow-up with standard of care in the IMPROVE-IT 2 study.[17] The results of these trials will provide valuable information to the field.

A natural consequence of the *lead-time* observations is the need for relevant intervention in ctDNA-positive patients. The first step should be additional and advanced clinical and radiological investigations, to confirm recurrence and, if possible, to identify the site of the recurrence. More advanced imaging, such as PET-based scans and/or artificial intelligence supported scan algorithms could add value in this situation. This may also prompt into a decision model, whether a local treatment strategy and/or systemic treatment should be the therapeutic consequence. However, in the case of no radiographic findings, the use of systemic treatment to eliminate ctDNA is also yet to be established.

In case of MRD, several studies have been designed to analyze the value of postoperative adjuvant chemotherapy in ctDNA-positive patients,[18] and data have shown successful ctDNA clearance in a fraction of patients during treatment.[16,19] Whether a ctDNA clearance is a true elimination or merely results in postponed tumor activity is also yet to be elucidated, but data are encouraging.

Finally, it is of high importance to liaise with patients' representatives in the design of ctDNA-based studies and to analyze the consequences in quality of life and fear of cancer aspects in such complex new clinical approaches. In addition, cost–benefit analysis should be performed when possible.

In conclusion, ctDNA analysis has shown immense potential in this disease and observational studies on *lead-time* aspects all point in the same direction toward a high sensitivity for early detection of recurrences. The use of consecutive blood sampling is attractive from both a patient and physicians' perspective and could contribute to better and more individualized follow-up strategies. However, the true clinical utility will only be established from carefully designed prospective observational studies and subsequent randomized trials.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contribution(s)

Karen-Lise Garm Spindler: Conceptualization; Investigation; Methodology; Supervision; Writing – original draft; Writing – review & editing.

Louise Bach Callesen: Conceptualization; Investigation; Methodology; Writing – review & editing.

Dirk Arnold: Conceptualization; Methodology; Supervision; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and material

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