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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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From their meta-analysis, of 28 studies, Callesen *et al.*[1] cited 10 studies demonstrating a correlation between post-ablation circulating tumor DNA (ctDNA) and a shorter recurrence-free survival (RFS) (pooled HR = 4.5, 95% CI: 3.4–6.1) (Figure 4(c)). (1) The length of RFS is the time between post-ablation therapy and the detection of recurrence and is commonly referred to as the 'lead-time'.[1] However, detecting ctDNA should not be conflated with recurrence (which is typically diagnosed by imaging) and can only be interpreted in the context of when imaging is done relative to the ctDNA timepoints.

For example, if ctDNA is detected 3 months after ablative therapy and a scan done the next day demonstrates recurrence, the lead-time is 1 day. If the first scan is instead not done until a year later, the RFS is 1 year.

Nearly all studies of ctDNA in colorectal cancer, including the meta-analysis reported by Callesen *et al.*[1] report lead-times with imaging being done not concurrently with the increasing DNA, but rather when the patient has clinical evidence of progression or as part of standard of care surveillance imaging timepoints after curative intention therapy. As a result, a longer lead-time does not necessarily reflect a smaller disease burden at the time of the ctDNA detection.[1,2–9]

Yet, a smaller disease burden often does predict a higher likelihood of preventing recurrence with systemic therapy. For example, adjuvant systemic therapy reduces recurrence risk when there is no radiographic evidence of recurrence, but once disease is detectable on imaging, it is only rarely curable with systemic therapy.

The RFS lengths reported by Callesen *et al.*[1] using ctDNA assays should not be interpreted as evidence of superior sensitivity of detecting recurrence using ctDNA assays compared to scanning done at standard of care timepoints. Studies designed to determine if detectable ctDNA assays are superior to standard of care methods to detect recurrence should include concurrent scanning once the ctDNA is detectable.

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Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contribution(s)

Steven Sorscher: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

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Competing interests
Dr. Sorscher previously was briefly (nine months) employed by Invitae, Corp.

Availability of data and materials
All data/statements in this perspective are either referenced in the text or the opinion of the author (SS). The data that support the findings/statements in this perspective are openly available in the references provided.

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