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REVIEW

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Circulating tumor DNA (ctDNA) in adjuvant therapy of early stage colon cancer: current status and future perspectives

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ABSTRACT

Background: This article reviews the current knowledge on circulating tumor DNA (ctDNA) in early stage colon cancer and ongoing trials on ctDNA-guided treatment in the adjuvant setting.

Methods: A literature search of Pubmed was performed to identify studies on ctDNA in early stage colon cancer and neoadjuvant or adjuvant treatment. For ongoing trials, we searched clinicaltrials.gov and the Australian New Zealand Clinical Trials Registry (ANZCTR).

Results: Several studies show that ctDNA is a strong predictor for recurrence and survival after surgery and adjuvant chemotherapy. The specificity of this marker is extremely high, and the sensitivity is increasing with the development of technology. Recurrences can be detected very early and the analysis can potentially be used to guide neoadjuvant and adjuvant treatment. Ongoing and planned studies are now looking into escalation and de-escalation of therapy according to ctDNA-status after surgery.

Conclusion: Serial measurement of ctDNA shows great promise as a marker for both prognosis and response to treatment in early colon cancer. Future studies will show whether we can use this analysis for tailoring treatment for patients in the adjuvant and neoadjuvant setting. With improved technology, ctDNA has the potential of becoming a 'game-changer' in the treatment of early stage colon cancers.

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KEYWORDS
ctDNA; colon cancer; adjuvant; neoadjuvant; ongoing trials

Background

Colon cancer is the third most common malignancy in Sweden and the incidence is rising. The mortality is, however, declining which may be due to more effective treatments over time [1] and earlier stage of disease at diagnosis [2]. Worldwide, colon cancer is the second most common cause of cancer death and the fourth most common cancer with over one million new cases per year [3].

The principal treatment of early stage disease is still curative intent surgery followed by adjuvant chemotherapy (ACT) in patients with high risk of recurrence. Recently, neoadjuvant chemotherapy (NAC) followed by surgery has emerged as an alternative strategy to treat certain cases with localized colon cancer [4].

Twenty to 30% of patients with early-stage colon cancer relapse despite surgical and oncological treatment. A few prognostic and predictive factors are known, but we need to improve our ability to select patients with high risk of recurrence for additional, tailored therapies and avoid overtreating cases that are most likely cured by surgery alone. Known prognostic factors for recurrence are clinical stage according to the TNM classification [5] and pathological stage of the surgically removed tumor [6]. The tumor marker carcinoembryonic antigen (CEA) may be used as a complement for risk assessment but has limited specificity and sensitivity [7].

Another prognostic and possibly predictive factor in early colorectal cancer is tumor microsatellite instability (MSI), which is the result of a deficiency in the mismatch repair genes of the cell. Around 15–20% of patients with newly diagnosed colorectal cancers have sporadic or inherited, that is, Lynch syndrome, deficiency of the mismatch repair protein [8–12].

Furthermore, there is evidence that an immunoscore-based approach with analysis of tumor CD3+ and cytotoxic CD8+ T lymphocyte densities, is associated with survival and response to chemotherapy in stage III colon cancer [13].

A novel factor to take into consideration is the level of circulating fragments of DNA. All healthy individuals harbor cell-free DNA (cfDNA) in plasma which originates from apoptotic, necrotic and shedding from living cells. In patients with cancer, a fraction of the cfDNA originates from cancer cells, i.e., circulating tumor DNA (ctDNA) [14,15]. The levels of ctDNA at diagnosis vary greatly between different types of

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tumors, among individual patients and different stages of the disease. High levels can usually be found in patients with metastases and detectable levels after surgery indicate the presence of minimal residual disease (MRD) [16]. Early reports from smaller prospective studies suggests a very high prognostic value of detectable postoperative ctDNA in patients with colon cancer [17–20].

Circulating tumor DNA can be analyzed by a tumor-informed or panel-based method. The tumor-informed approach examines a certain number of mutations in the patient's own tumor, whereas the panel-based method does not require knowledge of the individual patient's mutations and can include alterations such as methylations.

In early stage colon cancer, there is, thus, a need to find better and more accurate ways to predict recurrence after surgery and assess response to ACT and NAC. Monitoring of ctDNA in the perioperative setting and during follow-up is emerging as a new and highly promising marker for prognosis as well as therapeutic efficacy. We herein review the current status of clinical trials and future perspectives of this exciting field in early colon cancer.

Methods

For this review, we performed a search of PubMed with the keywords 'colon cancer' or 'colorectal cancer' or 'colonic neoplasm' and 'ctDNA' or 'circulating tumor DNA' or 'liquid biopsy' and 'adjuvant' or 'neoadjuvant'.

For information regarding ongoing trials, we searched the US National Library of Medicine in clinicaltrials.gov and the Australian New Zealand Clinical Trials Registry (ANZCTR), with the use of the keywords 'colorectal cancer', 'colon cancer', 'ctDNA' or 'circulating tumor DNA'. Among the clinical trials, we choose to present trials on adjuvant or neoadjuvant treatment, which randomize participants to treatment according to ctDNA status. Information on the Dutch (MEDOCC-CrEATE), Japanese (CIRCULATE-Japan) and French/European (CIRCULATE-EUROPE) trials, has been obtained from the respective research group.

Results

Circulating tumor DNA as a prognostic and predictive marker in adjuvant treatment of Colon cancer

In colorectal cancer, ctDNA can be found at different levels before surgery, depending on tumor stage and sensitivity of the analysis. Levels of preoperative ctDNA vary from 63.8% to 88.5% in different studies [17,18]. Furthermore, several trials have demonstrated a strong influence of postoperative ctDNA status on survival [17,21,22]. These trials differ in setting, size, outcome measure and analysis (Table 1).

A Danish cohort study of 125 patients with colorectal cancer stage I–III, showed that patients with positive ctDNA were seven times more likely to relapse than ctDNA negative cases, hazard ratio (HR: 7.2). If ctDNA positiveness persisted after adjuvant chemotherapy, these patients were 17 times more likely to relapse than ctDNA negative cases (HR: 17.5) [17].

Likewise, this strong association between recurrence and ctDNA was corroborated in a study of 58 patients in Swedish hospitals with colorectal cancer stage I–III [21]. In this study, none of the 45 ctDNA-negative patients experienced relapse during a median follow-up of 49 months. Moreover, detection preceded clinical and radiological signs of recurrence by a median of 3 months in the 13 patients with positive ctDNA during follow-up.

An Australian study of 230 stage II colon cancer patients by Tie and coworkers, found that 20 out of 230 patients (8.7%) were ctDNA positive 4–10 weeks after surgery [20]. These patients had a markedly worse 3-year recurrence-free survival (RFS) than those with negative ctDNA (HR: 18), with RFS 0% for ctDNA positive patients versus 90% for ctDNA-negative cases. Postoperative ctDNA positivity had a greater influence on RFS than any one clinicopathological factor or any combination of these factors. The sensitivity of postoperative ctDNA to predict recurrence at 3 years was 48% and the specificity was 100%.

In yet another report by the Australian group, 96 patients with stage III colon cancer were studied and 21% were found to have detectable postoperative ctDNA [19]. The 3-year RFI (recurrence-free interval) with positive ctDNA in the circulation was 47% versus 76% for those with negative ctDNA (Figure 1). Furthermore, the samples taken after ACT were associated with a 3-year RFI of 30% for those with positive ctDNA and 77% for those with nonmeasurable levels of ctDNA (HR: 6.8).

Several studies have also shown that repeated measurements of ctDNA after surgery in patients with colon cancer can detect recurrence earlier than repeated testing of CEA and radiology exams [17–21]. However, all these trials have some methodological limitations, e.g., limited number of patients, discordancy of ctDNA sampling in relation to CT-scans and testing for CEA.

Table 1. Results of trials on ctDNA as a prognostic and predictive marker in early stage colorectal cancer.

Study	Reinert et al. [17]	Tie et al. [20]	Tie et al. [19]	Wang et al. [21]
Disease and stage	Colorectal cancer, st.[a] I–III	Colon cancer, st. II	Colon cancer, st. III	Colorectal cancer, st. I-III
Setting	Pre- and postop.[b]	Pre- and postop.	Pre- and postop.	Pre- and postop.
Analysis	Multiplex PCR and NGS (HiSeq 2500 system®[1])	Safe-SeqS®[2]	Safe-SeqS®	Safe-SeqS®
Number of patients	125	230	96	58
Outcome measure	Measurement of ctDNA, clinical recurrence and recurrence-free survival (RFS)	Measurement of ctDNA, RFS	Measurement of ctDNA and recurrence-free interval (RFI)	Measurement of ctDNA, comparison to CT[c] and CEA levels, detection of recurrence

[1,2]Illumina Inc, San Diego, CA, USA.
[a]st = stage, [b]op = operative, [c]CT = computed tomography.

Furthermore, there are indications that repeated ctDNA measurements during treatment could be used as a predictive marker to guide therapy in colorectal cancer. Data from prospective studies with serial ctDNA measurements show that some patients can convert from ctDNA positivity to negativity after ACT, but if ctDNA remains positive, the recurrence risk is very high [18,20]. Moreover, the dynamics of ctDNA testing seem to give early indications of response and resistance to systemic therapy. This suggests an opportunity to intensify or change treatments in patients who remain ctDNA positive during ACT.

Ongoing and planned randomized clinical trials on ctDNA and adjuvant treatment

European trials

There are several newly started European trials on ctDNA as a predictor of therapeutic response and on escalation or de-escalation of ACT (Table 2). The large German/Austrian/Swiss CIRCULATE-AIO trial is an ongoing randomized adjuvant trial in patients with stage II microsatellite-stable (MSS) colorectal cancer (Table 2 and Figure 2) [23]. Circulating tumor DNA is measured at inclusion and patients are grouped according to ctDNA status. Patients with positive postoperative ctDNA are randomized 2:1 to chemotherapy with investigator's choice of chemotherapy: Capecitabine (Cape) for 6 months or Capecitabine and Oxaliplatin (CapOx) for 3 or 6 months, or follow-up. The ctDNA-negative patients are randomized 1:4 to follow-up within or outside the trial. The primary endpoint is disease-free survival (DFS).

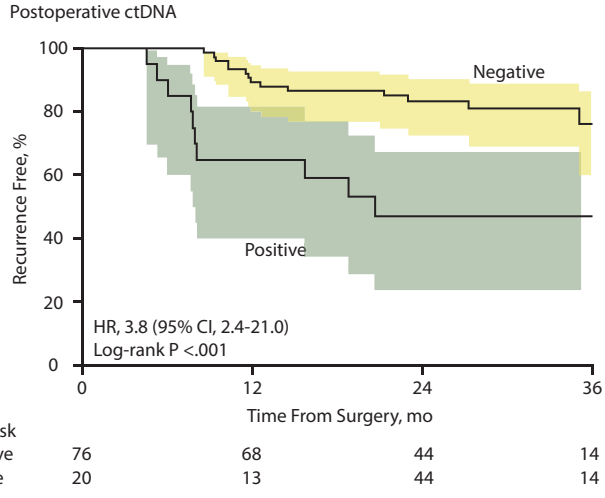

Figure 1. Recurrence-Free Interval (RFI) in stage III colon cancer patients according to post-operative ctDNA, Kaplan-Meier Estimates (published with permission, Tie et al. JAMA Oncol 2019).

The large French multicenter adjuvant trial, CIRCULATE 2-PRODIGE 70, has already included 300 stage II colon cancer patients, excluding T4b cases, and the researchers aim to recruit 2000 patients. Participants will follow a surveillance program according to current French guidelines and the 198 ctDNA positive patients will be randomized 2:1 to 6 months FOLFOX (5-FU and Oxaliplatin) or close follow-up (Table 2) [24,25]. The primary endpoint is DFS.

CIRCULATE 3-EUROPE is another large French randomized controlled adjuvant trial in its final stages of planning and approval (Figure 3). Two thousand patients with stage-III colon cancer will be recruited to receive different ACTs according to ctDNA status. The ctDNA-positive patients are randomized to either FOLFIRINOX (5-FU, Irinotecan and Oxaliplatin) or FOLFOX for 6 months, whereas the ctDNA-negative group will receive either CapOx for 3 months or Cape for 6 months.

Tracking Mutations in Cell Free Tumor DNA to Predict Relapse in Early Colorectal Cancer (TRACC) is a UK adjuvant trial. The investigators aim to include 1000 patients with high risk stage II or stage III colorectal cancer after R0 resection who have measurable ctDNA preoperatively (Table 2) [26,27]. Patients are randomized to either standard of care (SOC) ACT or ctDNA guided ACT. In the guided arm, ctDNA negative cases receive de-escalated ACT for 3 months with

Table 2. Ongoing European adjuvant trials in early stage colon cancer evaluating the use of ctDNA.

Name of study and country	CIRCULATE-PRODIGE 70, France	CIRCULATE Germany, Austria, Switzerland	IMPROVE-IT, Denmark	TRACC, United Kingdom	MEDOCC-CrEATE, The Netherlands	Pegasus, Italy, Spain
Disease and stage	Colorectal cancer, stage II	Colorectal cancer, stage II	Colon cancer, stage I-II	Colorectal cancer, high risk stage II or stage III	Colon cancer, low risk stage II	Colon cancer, high risk stage II or stage III
Analysis	ddPCR	Ultra-deep sequencing	NGS and ddPCR	ddPCR	PGDx elio platform®[1]	LUNAR1®[2]
Treatment	ctDNA-positive after surgery. Arm A: FOLFOX Arm B: Observation	Positive ctDNA: Cape or follow-up. Negative ctDNA: Follow-up	ctDNA-positive after surgery. Arm A: CapOx or FOLFOX Arm B: Intensified follow-up	ctDNA-positive before surgery. Arm A: SOC ACT. Arm B: Negative ctDNA: 3 months of Cape or no chemotherapy.	Arm A: Positive ctDNA: CapOx Negative ctDNA: Follow-up Arm B: Follow-up	Positive ctDNA: CapOx 3 months Negative ctDNA: Cape 6 months. Thereafter tailored treatment according to retesting of ctDNA.
Recruitment target	1980	4812	64	1000	1320	140
Phase	III	III	II	III	III	II
Status	Not yet recruiting	Recruiting	Recruiting	Recruiting	Recruiting	Recruiting

[1]Personal Genome Diagnostics Inc, Baltimore, MD, USA.
[2]Guardant Health Inc, Redwood City, CA, USA.

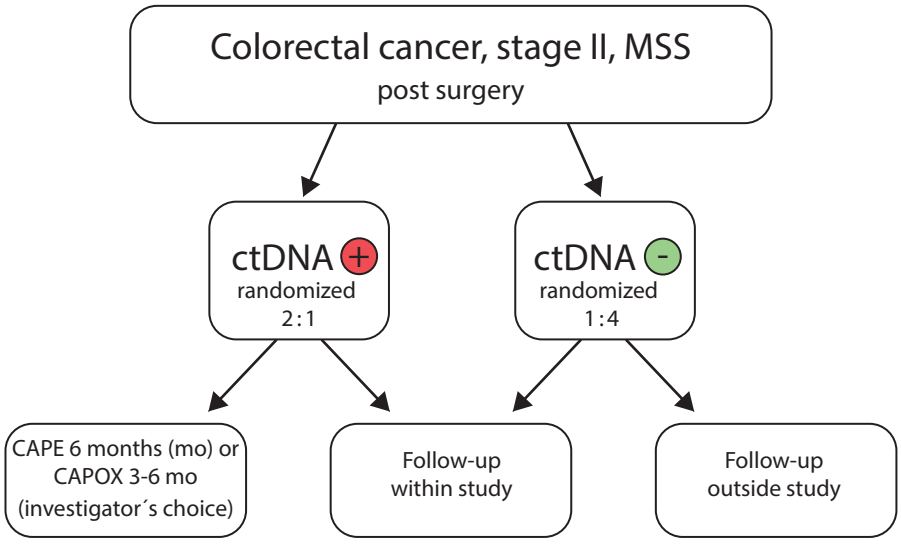

Figure 2. Simplified description of design of the ongoing CIRCULATE-AIO adjuvant trial in localized colon cancer ($n \approx 4800$).

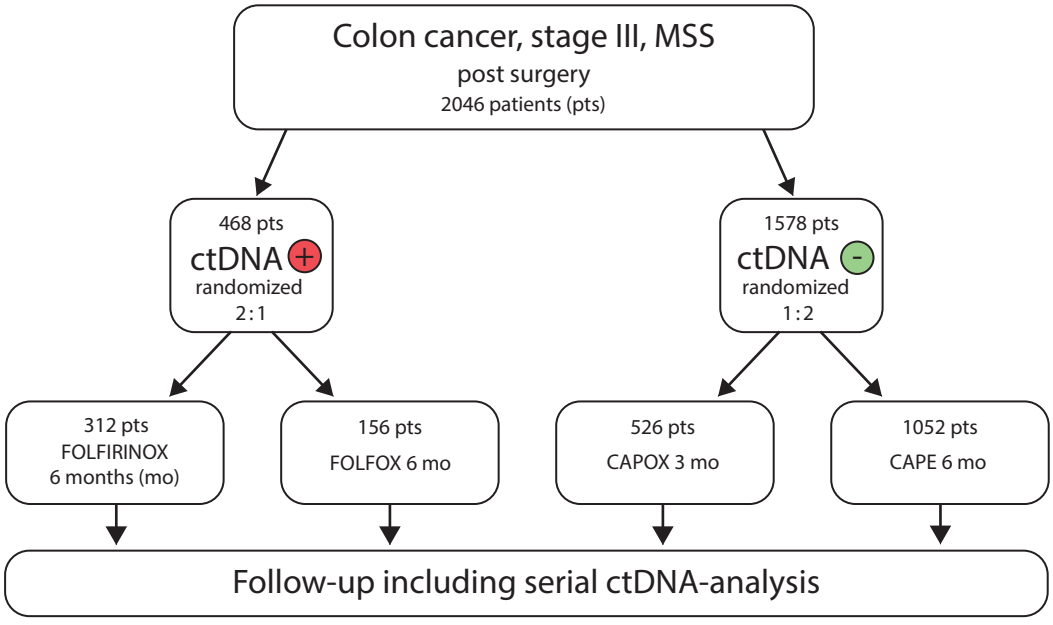

Figure 3. Simplified description of design of the proposed CIRCULATE 3-EUROPE adjuvant trial in early stage colon cancer ($n = 2046$).

single Cape, or no chemotherapy. Analysis of ctDNA is repeated at 3 months and if elevated, the patients are recommended the addition of 3 months CapOx. Investigators also aim to measure the incidence of positive ctDNA in this group of patients before surgery and examine the correlation between ctDNA levels and DFS postoperatively.

The researchers of the ongoing Danish phase II trial IMPROVE-IT study patients with ctDNA positive stage I-II colorectal cancer, who are not eligible for ACT according to Danish guidelines and who have a clear postoperative PET scan (Table 2). Patients with a clear PET scan are randomized to chemotherapy with CapOx (or FOLFOX) or intensified follow-up [28]. Additionally, IMPROVE-IT2, is a randomized controlled trial where investigators look into ctDNA-guided surveillance as compared to standard surveillance with CT scans at 12 and 36 months after surgery according to Danish guidelines. The plan is to include 1800 patients and the primary endpoint is the number of patients with disease-recurrence who receive curative intended or local metastases-directed treatment [29].

Additional trials include the Italian Pegasus trial [30] and the Dutch MEDOCC-CrEATE study [31] (Table 2).

The Swedish CITCCA pilot study [32] has started recruitment in October 2020 and its purpose is to demonstrate the feasibility of prospective analysis of ctDNA in a cohort of 300–400 patients with colorectal cancer stage I–III. Our aim is to widely examine a great number of mutations for every patient in order to increase sensitivity. We will use a similar technique as Parsons and colleagues where tumor tissue will be sequenced using a broad pan-cancer targeted sequencing assay to enable MRD tracking, using a combination of mutations and structural variants [33]. Patient-specific tests will then be designed and used for the detection of ctDNA. Sampling of ctDNA will occur preoperatively, 4–6 weeks after surgery, after 3 and 6 months and after 1 and 2 years. If the study confirms the results of previous studies and is

successful in applying ctDNA profiling, we plan to initiate/participate in a large controlled trial, randomizing patients to adjuvant treatment according to ctDNA status.

Non-European trials

The Australian group has completed the recruitment of 459 patients in the DYNAMIC-II trial [34] (Table 3) which studies ctDNA guided ACT in stage II colon cancer versus SOC ACT. The primary outcome measure is RFS and the results of the trial are eagerly awaited. Patients randomized to arm A with positive ctDNA received ACT and those with negative ctDNA received no chemotherapy. Arm B patients were treated at their oncologist's discretion and doctors were, at least initially, blinded to the ctDNA results. Accepted chemotherapy regimens were 3–6 months 5-FU or Cape or doublet treatment with Oxaliplatin.

The DYNAMIC-III adjuvant trial [35] in stage III colon cancer has also recruited well, i.e., almost 600 patients, and the investigators aim to include 1000 participants (Table 3). The design is complex and involves comparing SOC ACT versus ctDNA-guided treatment. Researchers aim to assess the effect on RFS of ctDNA-guided escalation and de-escalation of treatment.

The Australian ACT trial in rectal cancer, DYNAMIC-rectal, is also recruiting well and has so far included over 200 patients, with the target of 408 participants [36]. Patients are randomized between SOC and ctDNA-guided treatment, where patients with a high-risk tumor and/or a ctDNA-positive result, receive chemotherapy with 4 months of Cape/5-FU with or without Oxaliplatin. The ctDNA-negative group will not receive ACT.

In the US, investigators will include 1400 patients with colon cancer stage IIA in the adjuvant COBRA trial (NRG-GI005) (Table 3) [37]. Arm A will undergo active surveillance and have blood stored for future ctDNA testing. Arm B will be tested for ctDNA at baseline and patients with positive ctDNA will receive ACT with FOLFOX for 6 months. Patients with negative ctDNA will undergo active surveillance. The researchers aim to examine ctDNA clearance after ACT and RFS for patients with positive ctDNA who have, or have not, received chemotherapy.

Moreover, CIRCULATE-US (NRG-GI008) is a trial where trialists, according to the preliminary design, will investigate ctDNA guided treatment in low risk, T1-3 N1, stage III colon cancer and plan to recruit around 1500 patients [38]. Patients will be randomized to treatment according to postoperative ctDNA status. The ctDNA negative patients will be randomized to either CapOx/FOLFOX or serial measurements of ctDNA. If a participant in the latter group should develop a positive ctDNA result during follow-up, the patient is then randomized to delayed ACT with either CapOx/FOLFOX or mFOLFIRINOX for 6 months. Patients with a postoperative positive ctDNA will be randomized to either CapOx/FOLFOX or mFOLFIRINOX for 6 months. The primary endpoint is ctDNA status and DFS and the investigators plan to start recruitment in q3 2021.

Japanese researchers have initiated three parallel studies: GALAXY, VEGA and ALTAIR, which are included in a study platform called CIRCULATE-Japan [39]. GALAXY is an observational study that includes monitoring of ctDNA in stage I-IV colorectal cancer. VEGA (Table 3), is a randomized phase-III trial where high-risk stage II and low-risk stage III colon cancer patients who are ctDNA negative after surgery, are randomized to either no chemotherapy or CapOx for 3 months. The primary endpoint is DFS. Finally, ALTAIR is a randomized, double-blind phase-III study where patients with colorectal cancer stage II–III who are positive for ctDNA after surgery, receive either placebo or 6 months of Trifluridine/Tipiracil. In total, these studies will include 2500 patients.

Additionally, the US SU2C randomized phase-III trial will answer the question whether early treatment in ctDNA positive disease after ACT is of benefit [38,39]. Investigators plan to recruit around 500 patients with stage III colon cancer, measuring ctDNA after ACT. Patients with positive ctDNA will be randomized to either 5-FU and Irinotecan (FOLFIRI) or observation whereas ctDNA negative patients will be observed. A subgroup of ctDNA positive, MSI-H patients will receive immunotherapy with Nivolumab. Primary endpoints are DFS in ctDNA positive patients and ctDNA clearance.

Discussion and future perspectives

Serial measurement of ctDNA has emerged as a highly promising method to detect MRD after surgery in patients with early stage colon cancer and to guide ACT in real-time. Several studies have shown excellent specificity and increasing sensitivity for ctDNA detection.

There are, however, several challenges in the detection of ctDNA.

Firstly, the cfDNA concentration in plasma is low, typically $<$10 ng/ml which represents $\sim$3000 genome copies. Furthermore, the fraction of ctDNA in cfDNA is low in localized cancer, commonly 0.01−0.0001, which requires advanced technologies for detection [41]. Thus, the efficiency has to be high to minimize the loss of genome copies in the laboratory process to, in turn, maximize sensitivity in relation to the limited starting volume of blood. However, the low biological signal also requires high specificity, below the technical error rates of conventional high throughput sequencing technologies. This has spurred the introduction of molecular barcodes whilst preparing the DNA for sequencing [42]. The use of molecular barcodes make it possible to determine which DNA molecules originate from the same original DNA molecule after polymerase chain reaction (PCR). This, in turn, allows for error correction and lowering of the technical noise below the biological signal [41].

The half-life of ctDNA in patients with colon cancer is short, that is, 114 min [43], which allows for real-time analysis. While multiple technologies may be adopted for detection of ctDNA in localized cancer such as beaming or digital droplet PCR [33,44], these are commonly limited to a predefined set of somatic alterations at certain positions [45]. High-throughput sequencing, on the other hand, may be adopted to interrogate all somatic variants detected from tumor tissue, thereby increasing the sensitivity with several orders of magnitude [33].

Table 3. Ongoing non-European adjuvant trials in early stage colon cancer evaluating the use of ctDNA.

Name of study and country	DYNAMIC II Australia, New Zealand	DYNAMIC III Australia, New Zealand	COBRA United States	CIRCULATE-Japan, VEGA Japan
Disease and stage	Colorectal cancer, stage II	Colorectal cancer, stage III	Colon cancer, stage IIA	Colon cancer, stage II high risk and stage III low risk, ctDNA negative
Analysis	Safe-SeqS®[3]	Safe-SeqS®	LUNAR®[4]	Signatera®[5]
Treatment	Arm A: Positive ctDNA: ACT. Negative ctDNA: No chemotherapy. Arm B: Treatment at oncologist's discretion: 3–6 months 5-FU or Cape +/− Oxaliplatin	Arm A: Treatment at oncologist's discretion. Arm B: ctDNA-informed arm. De-escalation or escalation of chemotherapy based on clinician's choice of regimen before randomization.	Arm A: Active surveillance Arm B: Positive ctDNA: FOLFOX. Negative ctDNA: Active surveillance	Arm A: No chemotherapy Arm B: CapOx 3 months
Recruitment target	450	1000	1408	1240
Phase	II	II	III	III
Status	Completed	Recruiting	Recruiting	Recruiting

[3]Illumina Inc, San Diego, CA, USA.
[4]Guardant Health Inc, Redwood City, CA, USA.
[5]Natera Inc, San Carlos, CA, USA.

Several independent research groups have detected MRD in patients with colon cancer with the use of high-throughput sequencing. However, the number of genes analyzed differ, which is reflected in the reported variable degrees of sensitivity [17,20,21]. Furthermore, cfDNA preserves the epigenetic imprint of the originating tissue [46]. Recently reported data indicate that assessing the methylation status of informative regions may be applied for early detection of localized cancer, including colorectal cancer. This may enable MRD-assessment without a priori knowledge of the mutation status [47,48]. However, high-dimensional epigenetic profiling requires large training and validation sets to establish assay properties and potentially clinical utility. It is not clear, at this stage, how such assays perform compared to tracking somatic alterations.

In our CITCCA pilot trial [32], we plan to further improve sensitivity by broad genomic profiling which we hope will perform better than techniques used in previous studies.

Currently, many studies are exploring the concept of escalation and de-escalation of ACT according to ctDNA status (Tables 2 and 3). The results of these studies will deepen our understanding of this approach and hopefully lead to more informed treatment decision-making in patients with early colon cancer.

After the initial results of the FOxTROT study on NAC in early colon cancer [4], we may also have the alternative to recommend neoadjuvant chemotherapy prior to surgery in a selected group of high-risk patients. The preliminary results show that 6 weeks of NAC followed by surgery lead to a reduction in incomplete surgical resections. Results on the primary end-point, DFS at 2 years, are expected to be updated in the near future. The FOxTROT data probably need to be considered in the planning of upcoming trials on ctDNA in early colon cancer. Indeed, the future trials FOxTROT 2 and 3 may include monitoring of ctDNA during NAC. Although preoperative treatment is not a good setting to assess MRD *per se*, it is possible that the efficacy of NAC could be monitored and guided by the dynamics of ctDNA levels.

As mentioned previously, microsatellite instability has emerged as a prognostic and possible predictive marker in early stage colon cancer and should be considered part of the treatment algorithm in these patients. Patients with stage II and low risk stage III, MSI-High (MSI-H) colon cancer appear to have a lower risk of recurrence than cases with MSS tumors. Results from several studies have also suggested a lack of benefit of ACT with single fluorouracil (5-FU) in patients with MSI-H cancers [8–12].

Also, therapies targeting Her-2, NTRAK fusion, KRAS G12C or BRAF-mutation may be included in future personalized treatment algorithms for subgroups of patients with suitable tumor characteristics for these treatments, as there are studies that suggest efficacy in the palliative setting [49–51].

Concerning follow-up and prediction of survival, longitudinal ctDNA measurements seem to outperform CEA in RFS prediction according to early results that were presented at GI ASCO 2021 [52]. However, results from additional trials need to prove the relation of clearance of ctDNA during ACT and DFS/OS.

Conclusion

Analysis of ctDNA shows great promise as a marker for both prognosis and response to treatment in colon cancer. Future studies will show whether we can use this technique to tailor treatment for patients in the adjuvant and neoadjuvant settings and whether this will translate into improved survival. Although ctDNA presently has some limitations, it has the potential to revolutionize treatment for patients with early stage colon cancer.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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