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Perspectives on Precision Oncology

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Editorial and study commentary by Dr Angela George

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Abbreviations used in this issue

5-FU = 5-fluorouracil
ASCO = American Society of Clinical Oncology
CAP = College of American Pathologists
CI = confidence interval
COVID-19 = coronavirus disease 2019
CT = computed tomography
ctDNA = circulating tumour deoxyribonucleic acid
EDTA = ethylenediaminetetraacetic acid
EGFR = epidermal growth factor receptor
ER = oestrogen receptor
ESMO = European Society of Medical Oncology
HER2 = human epidermal growth factor receptor 2
HR = hormone receptor
IR = interventional radiology
MRD = minimal residual disease
NSCLC = non-small cell lung cancer
RR = relative risk
VAF = variant allele fraction

ctDNA – Can it live up to the promise of revolutionising care?

As we continue our review of guidelines relevant to precision medicine, this issue focusses on the use of ctDNA. In its first iteration, ctDNA provided the concept of a 'liquid biopsy', with the possibility of sparing patients an invasive biopsy and potential associated complications in favour of a simple blood test. As concepts go, it is perhaps one of the more attractive, especially for patients with disease not amenable to biopsy by the usual means. However, for many patients, detecting ctDNA can be like looking for the proverbial needle in a haystack, despite much refinement of protocols and technological advances.

New applications

There could be a real benefit to the health system if we can make these (ctDNA) programmes work

Over the last 5 years, we have seen a number of new applications accumulate evidence for the use of ctDNA beyond the original concept of diagnosis at baseline or relapse; these new applications include monitoring of MRD or early detection of recurrence. We have also seen huge interest in the use of ctDNA during the COVID-19 pandemic, when aerosol-generating procedures that would normally lead to a diagnosis were suspended for months at a time. Unprecedented pressure on interventional radiology added to delays, and we had a number of pilot schemes utilising ctDNA to allow patients to obtain a diagnosis and start treatment rather than wait many more months to do so. In this way, ctDNA clearly allowed a number of patients to receive treatment far earlier than they otherwise could have. We also have programmes in the UK that have been set up to see whether the use of ctDNA can help with the huge backlogs of patients in the community likely to have cancer, again by speeding up the diagnostic pathway or reducing pressure on the large numbers of people waiting for biopsies or procedures. Whilst there are clear differences in the chances of ctDNA detection by tumour type or site of disease, there could be a real benefit to the health system if we can make these programmes work. Here, we will review some of the guidelines and emerging evidence for ways in which this technology can be harnessed to alter the patient pathway.

Current guidelines

The joint ASCO and CAP guidelines from 2018 are still a good outline of the potential applications of ctDNA,[1] although there is now more evidence for most of these. Nevertheless, as a general background, these guidelines provide a thorough review of some of the pathways that have subsequently become more widely used, as well as a caution regarding some of the pitfalls in interpretation, such as age-related clonal haematopoiesis, present in up to 10% of samples. It seems likely that there will be an update to these guidelines relatively soon, but given the rapid evolution of the evidence-base, they will almost certainly be out of date again soon after publication.

It is important that any ctDNA results are assessed in a molecular tumour board or genomics tumour advisory board to aid the interpretation and analysis of results

A more recent summary of the current uses of ctDNA in advanced solid tumours was published recently in the journal of the American Cancer Society. This review by Cheng and colleagues provides details on the uses of ctDNA that have been approved since publication of the ASCO/CAP joint guideline, by tumour type and application.[2] It predominantly focusses on the use of ctDNA to guide selection of precision medicines for patients, but also touches on the increasing interest in ctDNA for risk stratification, response assessment and resistance monitoring. These guidelines, written in 2020 and published in early 2021, mention two of the most commonly used commercially available assays, those from Foundation Medicine (FoundationOne®) and Guardant (Guardant 360®), partly because these were used in many of the trials quoted. There are also multiple assays that have been developed by individual institutions, often focusing on smaller panels of tumour-specific likely mutations (i.e., optimised for colorectal cancer ctDNA detection, or breast cancer) that often have the benefit of being cheaper to run per sample, but are less useful in a more tumour agnostic setting. Regardless of the assay used, it is important that any ctDNA results are assessed in a molecular tumour board or genomics tumour advisory board to aid the interpretation and analysis of results.

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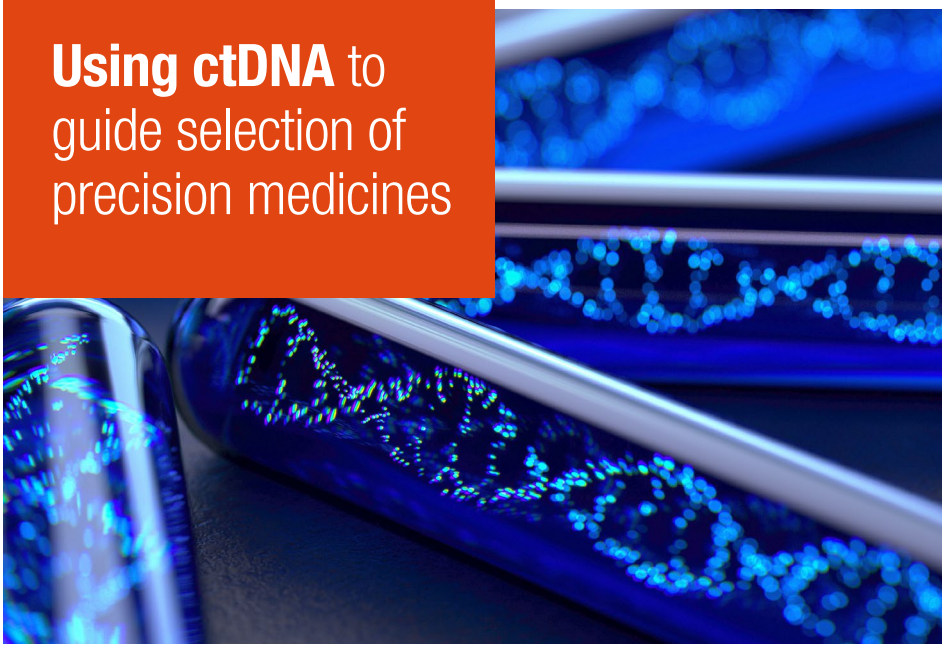
Using ctDNA to guide selection of precision medicines



Considering metastases

When considering the use of ctDNA in a specific tumour type, it is important to take into account both the potential tumour type and the metastatic site. We commonly see lower rates of ctDNA detection in tumours such as ovarian tumours, where haematological spread typically occurs late; or brain tumours, where the blood/brain barrier prevents circulating fragments. From personal experience, we also often see negative ctDNA reports from patients with a single site of metastatic disease, especially if it is based in the lung or brain, or if it is particularly small. Bando et al., looked in more detail at this in patients with metastatic colorectal cancer who had only a single site of metastasis and compared tumour testing with ctDNA (Guardant 360®) across metastatic sites.[3] As may have been expected, those with liver or lymph node metastases had the best concordance between tests, with lung-only or peritoneum-only metastases having lower concordance. Of note, the VAF (proportion of cells in which the mutation is seen) was also lower with the latter two sites, meaning that the mutation may potentially be present in ctDNA but at levels lower than the detection level set for the test. This is also helpful in interpreting results and potentially identifying patients who may be better with tumour-based testing rather than ctDNA when assessing for targeted treatments.

As a tool for predicting risk of recurrence

The annual ASCO meeting in 2022 included a wealth of studies reporting on a variety of clinical applications for ctDNA. One of the most exciting was the Australasian DYNAMIC study in stage II colorectal cancer, assessing the presence versus absence of ctDNA to identify those at higher risk of recurrence.[4] In this study, patients were randomised to have the decision for adjuvant treatment guided by either the presence/absence of ctDNA or standard clinicopathological criteria. In patients for whom ctDNA guided treatment, the use of adjuvant chemotherapy (15%) was around half that in those using traditional risk factors to give chemotherapy (28%). Despite this, there was no reduction in the 2-year recurrence-free survival rate, suggesting that this may be a more sensitive way of detecting those with stage II disease who truly benefit from chemotherapy, and allowing those with fewer molecular risk factors to avoid treatment that may be unnecessary. Of note, most of those receiving chemotherapy in the ctDNA-guided group were given combination treatment with oxaliplatin, suggesting that the presence of ctDNA after surgery may have made clinicians more

The idea that we may in future be able to better define the group who truly benefit from adjuvant treatment is hugely exciting

likely to offer chemotherapy seen as more effective than a 5-FU-based treatment alone. Those in the ctDNA-guided group who received adjuvant chemotherapy had higher disease-free rates in this study than have been historically reported, and it would be interesting to further evaluate the relative benefit of treatments in this group, presumed to be higher risk. The idea that we may in future be able to better define the group who truly benefit from adjuvant treatment is hugely exciting, both in terms of reducing mortality and morbidity in this group, but also reducing the cost of adjuvant treatments across health systems.

Utility in identifying *EGFR* mutations

As with many precision medicine stories, lung cancer has been a leader in the use of ctDNA to help guide treatment. The first approved use of routine ctDNA was for *EGFR* testing in lung cancer patients as a faster way of identifying those with *EGFR* mutations at the time of diagnosis/suspected lung cancer diagnosis rather than waiting for bronchoscopy and biopsy. For those without *EGFR* mutations detected, standard sequencing on tumour could then be performed. Heitzer et al., report on the ESMO guidelines for the current uses of ctDNA in patients with metastatic lung cancer, where we see ctDNA testing in parallel with biopsy requests, with such tests being able to be omitted if a driver mutation is identified.[5] In these guidelines, ctDNA becomes a complementary strategy to standard tissue testing to aid faster treatment, and also as a tool to identify resistance mutations, such as those conferring resistance to EGFR inhibitors when these treatments stop working. The ESMO guideline has a pragmatic approach to ctDNA usage, and also highlights limitations and pitfalls of such approaches.

The ESMO guideline for the current uses of ctDNA has a pragmatic approach to ctDNA usage

Use in breast cancer

The third tumour type in which we are increasingly seeing the application of ctDNA is breast cancer. Breast cancer tends to produce ctDNA earlier and at higher levels than many other cancers, and there have been several small studies suggesting that use of ctDNA testing may identify patients relapsing much earlier than tumour markers or radiological imaging. This has raised the question: if there is a sufficiently robust way to detect true relapse at a microscopic level, could early and aggressive treatment of this potentially prevent macroscopic recurrence, and salvage patients for cure? Lipsyc-Sharf and colleagues presented their data on lead time between the presence of a positive ctDNA test and subsequent clinical recurrence at the ASCO 2022 conference.[6]

Monitoring of ctDNA may be the most accurate way to detect early recurrence

Their study of 103 patients with high-risk ER-positive, HER2-negative tumours who were at least 5 years out from recurrence performed tumour testing to develop a personalised ctDNA assay for each patient, looking specifically for mutations present in the original tumour cell. Eight patients became ctDNA positive during follow-up, six of whom later had a clinical recurrence, with two not yet recurred by time of reporting. One patient had a local recurrence and was not ctDNA positive, highlighting that this is probably only useful for distant disease. In their study, the lead time between positive ctDNA and clinical recurrence was again 1 year, in keeping with other studies. This suggests that monitoring of ctDNA may be the most accurate way to detect early recurrence, although we do not yet have any idea of the implications of whether early treatment would be helpful or harmful.

As an indicator of treatment benefit

Perhaps one of the most commonly asked questions in adjuvant treatment clinics as patients come to the end of their chemotherapy is 'Did the chemotherapy work?'. To date, this has been a question that can only be answered with 'we don't know', with only time telling whether or not the patient relapses. Now, ctDNA is starting to be assessed at different timepoints through treatment as a potential indicator of treatment benefit or subsequent treatment failure. Gouda et al., undertook assessment of 204 patients with a variety of advanced solid tumours undergoing treatment at the MD Anderson Cancer Center.[7] Patients had samples taken prior to treatment, through treatment and with re-staging imaging. There were significant differences in the dynamic changes in ctDNA detection and quantity between responders/non responders and in those who subsequently progressed, although further breakdown by tumour type would be helpful.

The potential clinical utility of integrating ctDNA into routine assessment of patients to detect those who will benefit most from adjuvant treatment or to potentially improve long-term cure rates is huge. This is a rapidly changing field, with multiple studies currently ongoing across a wide number of tumour types to consider MRD monitoring, long-term outcomes of selection of patients for treatment based on ctDNA, and diagnostic testing. There is such potential in the technology to change treatment paradigms and reduce the need for invasive tests or more blanket chemotherapy recommendations if we can further refine the definition of high risk, and improve detection of ctDNA in some tumour types for which it currently still performs poorly. I hope that the reality reflects this promise.

The potential clinical utility of integrating ctDNA into routine assessment of patients to detect those who will benefit most from adjuvant treatment or to potentially improve long-term cure rates is huge

We hope that you find this editorial and these articles of academic or clinical interest and welcome any feedback.

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REFERENCES:

These are summarised with additional commentary in our Key Publication Summaries Section.

1. Merker JD et al. Circulating tumor DNA analysis in patients with cancer: American Society of Clinical Oncology and College of American Pathologists joint review. J Clin Oncol. 2018;36(16):1631-1641
2. Cheng ML et al. Circulating tumor DNA in advanced solid tumors: Clinical relevance and future directions. CA Cancer J Clin. 2021;71(2):176-190
3. Bando H et al. Effects of metastatic sites on circulating tumor DNA in patients with metastatic colorectal cancer. JCO Precis Oncol. 2022;6:e2100535
4. Tie J et al. Circulating tumor DNA analysis guiding adjuvant therapy in stage II colon cancer. N Engl J Med. 2022;386(24):2261-2272
5. Heitzer E et al. Recommendations for a practical implementation of circulating tumor DNA mutation testing in metastatic non-small-cell lung cancer. ESMO Open 2022;7(2):100399
6. Lipsyc-Sharf M et al. Circulating tumor DNA and late recurrence in high-risk hormone receptor-positive, human epidermal growth factor receptor 2-negative breast cancer. J Clin Oncol. 2022;40(22):2408-2419
7. Gouda MA et al. Longitudinal monitoring of circulating tumor DNA to predict treatment outcomes in advanced cancers. JCO Precis Oncol. 2022;6:e2100512

KEY PUBLICATION SUMMARIES

- ctDNA analysis in cancer patients
- ctDNA in advanced solid tumours
- Effect of colorectal cancer metastatic site on ctDNA
- ctDNA-guided adjuvant therapy for stage II colon cancer
- ctDNA mutation testing in metastatic NSCLC
- ctDNA and recurrence detection in breast cancer
- Monitoring ctDNA to predict treatment outcomes in advanced cancers

Circulating tumor DNA analysis in patients with cancer: American Society of Clinical Oncology and College of American Pathologists Joint Review

Authors: Merker JD et al.

Summary: This ASCO and CAP literature review assessed clinical ctDNA assays of genomic ctDNA variants based on 77 articles. The review concluded that ctDNA testing is best conducted on plasma collected in EDTA or cell stabilisation tubes, and that EDTA tubes should be processed within 6 hours of collection. Although ctDNA assays have clinical validity and utility for certain advanced cancers, this is not the case for most advanced cancers. ctDNA assays and tumour specimen genotyping can be discordant and require tissue genotyping to confirm undetected ctDNA results. There is limited evidence for the clinical utility and validity of ctDNA assays for early-stage cancer, treatment monitoring, or detection of residual disease. There is no evidence of clinical validity and clinical utility of ctDNA for cancer screening.

Comment: This is a good background paper on the logistics of using ctDNA with an excellent glossary and guide to practical considerations of ctDNA and the benefits/issues compared to standard somatic testing. However, it is important to note that it is now out of date with regard to the evidence for use of ctDNA and does need updating in this regard. Nevertheless, it is otherwise a well-balanced article and introduction to ctDNA, with a good explanation of considerations such as clonal haematopoiesis.

Reference: J Clin Oncol. 2018;36(16):1631-1641
Abstract

Circulating tumor DNA in advanced solid tumors: Clinical relevance and future directions

Authors: Cheng ML et al.

Summary: This literature review considered the role of plasma ctDNA assays in the oncology care of patients with advanced cancer. The review concluded that clinical decision-making is increasingly driven by molecular stratification of specific genomic biomarkers across different cancer types that guide the use of targeted therapies and other systemic treatments. Plasma ctDNA testing can enhance genomic profiling, especially where tumour samples are limited, and there are now robust commercial assays available for routine clinical use. Clinicians should understand the advantages and disadvantages of plasma ctDNA and tumour tissue assays and the potential for false-positives and false-negatives. Standard clinical plasma ctDNA testing is currently limited to treatment selection, but the ability for longitudinal profiling of patients and evaluation of dynamic changes in ctDNA may allow expanded clinical applications for advanced solid tumours. Future applications could include response assessment and resistance monitoring that is more nimble than imaging and that augments interpretation of equivocal scan results.

Comment: This is a very nice review that summarises some of the more recent evidence for ctDNA and is a follow-on article from the joint ASCO/CAP guidelines. It explains the more recent uses of ctDNA with relapsed disease to identify new potentially druggable mutations in patients. It also highlights the idea of following the presence of ctDNA to monitor response to treatment or confirm disease relapse.

Reference: CA Cancer J Clin. 2021;71(2):176-190
Abstract

Effects of metastatic sites on circulating tumor DNA in patients with metastatic colorectal cancer

Authors: Bando H et al.

Summary: This study used samples from 138 patients with metastatic colorectal cancer (mCRC) and single-organ metastasis (49 liver, 15 lymph node, 27 peritoneum, and 47 lung) in the SCRUM-Japan GOZILA study to investigate the relationship between metastatic site and ctDNA detection. Concordance of *RAS/BRAF* status next-generation sequencing ctDNA assay and tissue *in vitro* diagnostic tests was 95.9% for liver, 80.0% for lymph node, 56.0% for peritoneum, and 65.9% for lung metastases. ctDNA fraction (median maximum VAF)/median number of variants was 23.1%/5 for liver metastases, 6.0%/5 for lymph node metastases, 0.4%/3 for peritoneal metastases, and 0.4%/3 for lung metastases (all $p<0.001$ for the correlation between metastatic site and maximum VAF/number of detected variants). Very few patients with liver (2.0%) and lymph node (13.3%) metastasis had a maximum VAF <0.2% (required to ensure a detection limit of 95%), but maximum VAF <0.2% was more common in patients with lung (27.7%) or peritoneum (29.6%) metastases. Metastatic disease in the lung and peritoneum had lower ctDNA levels compared with other metastatic sites, suggesting lower clinical sensitivity for subclonal variants.

Comment: When using ctDNA, it is very important to realise that the chance of detecting ctDNA can depend on the stage of the cancer and the sites of metastatic disease. In this study we have a comparison of the ability to detect ctDNA at different metastatic sites in patients with colorectal cancer, which is one of the tumour types in which ctDNA is generally considered relatively reliable. This comes from the suggestion that, compared with other tumour types, ctDNA is present at earlier stages of colorectal cancer and in larger amounts. A potential benefit of ctDNA in those with metastatic colorectal cancer is the ability to detect RAS mutations, which can be acquired and subclonal (i.e., not present in all metastatic sites). That can lead to a failure to detect with standard somatic testing if the metastatic site with the mutation is not sampled, through chance or due to accessibility. With ctDNA, there is likely to be contributions from most metastatic sites, potentially leading to a higher chance of reflecting any subclonal mutations, although this study suggests a higher contribution from some sites than others.

Reference: JCO Precis Oncol. 2022;6:e2100535
Abstract

Circulating tumor DNA analysis guiding adjuvant therapy in stage II colon cancer

Authors: Tie J et al.

Summary: The DYNAMIC placebo-controlled trial was conducted to assess whether adjuvant chemotherapy using a ctDNA-guided approach (ctDNA-positivity at 4–7 weeks after surgery triggered oxaliplatin-based or fluoropyrimidine chemotherapy) could reduce adjuvant chemotherapy use in 455 patients with stage II colon cancer. Over a median follow-up of 37 months, the proportion of patients receiving chemotherapy was lower when treatment was guided by a ctDNA approach compared with standard management (15% vs 28%; RR 1.82; 95% CI 1.25–2.65). At 2 years, recurrence-free survival in the ctDNA-guided group was non-inferior to that in the standard management group (93.5% vs 92.4%; difference 1.1%; 95% CI –4.1 to 6.2). The 3-year recurrence-free survival rate was 86.4% in ctDNA positive patients who were treated with adjuvant chemotherapy compared with 92.5% in ctDNA-negative patients who did not receive adjuvant chemotherapy.

Comment: This is a hugely important study in taking us one step closer to being able to correctly identify high-risk patients who do benefit from chemotherapy, and potentially correctly identify lower-risk patients who do not need systemic treatment. The use of ctDNA as a marker of residual disease in these patients, all with normal post-operative CT scans and non-informative tumour markers, led to those receiving chemotherapy to be treated more aggressively, with better outcomes than would normally be seen. Interestingly, there were nearly twice as many patients receiving chemotherapy in the 'standard-risk-factor' group, suggesting that oncologists probably err on the side of caution in recommending chemotherapy when patients are borderline, without these more specific molecular markers. While longer follow-up is required, this study could set the standard for new approaches to adjuvant chemotherapy, certainly in colorectal cancer.

Reference: N Engl J Med. 2022;386(24):2261-2272
Abstract

Recommendations for a practical implementation of circulating tumor DNA mutation testing in metastatic non-small-cell lung cancer

Authors: Heitzer E et al.

Summary: This review examined current challenges and state-of-the-art applications of ctDNA mutation testing in patients with metastatic NSCLC. The authors considered the use of plasma ctDNA to identify actionable targets for NSCLC therapy. Clinical scenarios include complementary tissue and liquid biopsy testing to identify secondary resistance mutations, and ctDNA mutation testing to identify inter- or intra-tumour heterogeneity. ctDNA mutation testing may also identify possible targets missed by tissue biopsy, where insufficient samples are available or where tumour location makes biopsy difficult.

Comment: Lung cancer biopsies are often some of the smallest tumour biopsies received for diagnostic work-up and molecular testing due to the way in which the samples are often obtained and the difficulty in accessing some lung tumours. However, lung tumours have a wide range of druggable targets, and testing for all of these can sometimes be very difficult with the available tissue. There is also the inevitable wait for a bronchoscopy or IR-guided biopsy, which can delay the diagnostic process. For this reason, and because lung cancer is another tumour type that frequently produces positive ctDNA results relatively early in the disease process, clinicians have been early adopters of ctDNA as a diagnostic tool to potentially speed up the diagnostic pathway, or as a more convenient way to identify resistance mutations when patients progress. Given the relative cost of the diagnostic tests, it is currently also being formally assessed as a likely more cost-effective way to reach a diagnosis or find druggable targets in these patients.

Reference: ESMO Open 2022;7(2):100399
Abstract

Circulating tumor DNA and late recurrence in high-risk hormone receptor-positive, human epidermal growth factor receptor 2-negative breast cancer

Authors: Lipsyc-Sharf M et al.

Summary: This prospective study examined the prevalence and dynamics of ctDNA and its relationship with metastatic recurrence in 103 patients with high-risk early-stage HR-positive breast cancer ≥5 years after diagnosis. Overall, 85 patients had sufficient tumour tissue for analysis, of which 83 (97.6%) were successfully whole-exome sequenced. Personalised ctDNA assays targeted a median of 36 variants and tested 219 plasma samples. Median follow-up was 10.4 years with median time to first sample of 8.4 years. Eight patients (10%) were MRD positive at any time point, and 6 (7.2%) developed distant metastatic recurrence (all of whom showed MRD positivity before overt clinical recurrence, with a median ctDNA lead time of 12.4 months).

Comment: Breast cancer has been an early adopter of ctDNA in the relapsed disease setting to help identify mutations that would guide treatment choices, but ctDNA has also been increasingly utilised as a way of identifying sub-clinical relapse. To date, there have been several studies all suggesting the emergence of ctDNA approximately a year before radiological/clinical relapse in patients with metastatic breast cancer. This study specifically looked at ER-positive patients, and it is interesting to note that only 2% developed detectable *ESR1* mutations, a marker of resistance to standard endocrine treatments such as aromatase inhibitors. Most of the mutations detected were common mutations that occur early, such as *PIK3CA* or *TP53*. The obvious next step is to see whether there is benefit in early treatment to salvage cure in these patients.

Reference: J Clin Oncol. 2022;40(22):2408-2419
Abstract

Longitudinal monitoring of circulating tumor DNA to predict treatment outcomes in advanced cancers

Authors: Gouda MA et al.

Summary: This US study assessed the use of ctDNA for early assessment of systemic therapeutic response in 204 patients with advanced solid tumours. The ctDNA detection rate was higher in patients with progressive disease than those who did not progress (stable disease, partial response or complete response) at all time points ($p<0.009$). ctDNA detection was also associated with shorter median time to treatment failure ($p\leq0.001$). Changes in ctDNA quantity were more frequent in patients with progressive disease and were associated with a shorter median time to treatment failure. Increasing ctDNA quantity was predictive of clinical/radiologic progression in 73% of patients, with a median lead time of 23 days.

Comment: We routinely rely on a combination of clinical response, reduction in tumour markers or intermittent scans to determine response in patients with metastatic solid tumours, but none of these are perfect. Clinical response can be masked by treatment toxicity, or symptomatic response can be due to drainage of ascites or pleural fluid or better supportive medications rather than disease shrinkage. It is increasingly difficult for radiology departments to juggle the hugely increasing requests for imaging, making it challenging at times to get response scans. This study suggests that the use of both the presence/absence of ctDNA and the ctDNA quantity can potentially provide a more dynamic assessment of response, possibly reducing the burden on imaging and providing a more objective assessment than clinical evaluation.

Reference: JCO Precis Oncol. 2022;6:e2100512
Abstract

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