Circulating tumour DNA in oligometastatic oesophago-gastric cancers: applications, challenges, and future directions

Antonella Cammarota[1,2], Alberto Puccini[1,3], Christopher M. Jones[4,5], Peter S.N. van Rossum[6,7], Florent Mouliere[8], Hanneke W.M. van Laarhoven[7, 9*]

[1]Department of Biological Sciences, Humanitas University, Pieve Emanuele, Milan, Italy

[2]Hepatobiliary Immunopathology Laboratory, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy

[3]Medical Oncology and Hematology Unit, Humanitas Cancer Center, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy

[4]Department of Oncology, University of Cambridge, Cambridge, UK

[5]Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK

[6] Department of Radiation Oncology, Amsterdam University Medical Center, Amsterdam, the Netherlands

[7]Cancer Center Amsterdam, Cancer Treatment and Quality of Life, Amsterdam, the Netherlands

[8]Cancer Research UK National Biomarker Centre, University of Manchester, Manchester, UK

[9] Department of Medical Oncology, Amsterdam University Medical Center: location University of Amsterdam, Amsterdam, the Netherlands

*Corresponding author: h.vanlaarhoven@amsterdamumc.nl

Keywords: circulating tumour DNA; liquid biopsy; oesophageal cancer; oligometastatic disease.

Abstract

Oesophago-gastric cancer (OGC) is associated with a poor prognosis, with most patients presenting with or ultimately developing metastatic disease. Oligometastatic disease (OMD) represents an intermediate disease state characterised by a limited metastatic burden and, in selected patients, a more indolent clinical course. Increasing evidence suggests that carefully selected patients with OMD may benefit from local metastasis-directed therapies combined with systemic treatment.

The OligoMetastatic Esophagogastric Cancer (OMEC) consortium has recently proposed a standardised consensus definition of OMD in OGC. However, this definition is primarily imaging-based, and conventional imaging may lack sensitivity for occult systemic disease and does not fully capture underlying tumour biology. Circulating tumour DNA (ctDNA) is a promising biomarker in OGC, with demonstrated value across locally advanced and metastatic settings. In the oligometastatic setting, ctDNA may provide a biological complement to imaging-based classification, enabling detection of molecular residual or occult systemic disease, improved prognostic stratification, and identification of patients most likely to benefit from local therapy.

In this review, we summarise current evidence for the management of OMD in OGC and the evolving role of ctDNA in this disease. We discuss how ctDNA could refine prognostic stratification, therapeutic decision-making, and response assessment in oligometastatic OGC. Finally, we highlight key biological and methodological challenges and outline future directions, including the integration of ctDNA into OMD trial design to improve patient selection and response assessment.

1. Introduction

Oesophago-gastric cancer (OGC), encompassing oesophageal, gastroesophageal junction, and gastric tumours, is a major cause of cancer-related morbidity and mortality worldwide[1]. Across both adenocarcinoma and squamous cell histologies, a substantial proportion of patients present with unresectable or metastatic disease at diagnosis, while around half of those treated with curative-intent approaches ultimately recur[2,3]. For patients with inoperable or metastatic disease, systemic anti-cancer therapy (SACT) remains the mainstay of treatment, aiming to prolong survival, control symptoms, and preserve quality of life.

For patients with advanced disease, treatment strategies are histology-specific but share common principles, such as the use of chemotherapy backbones[4-7]. Immune checkpoint inhibitors (ICIs) are also now standard for most patients, with programmed death-ligand 1 (PD-L1) expression guiding access to ICIs in both adenocarcinoma and squamous cell carcinoma, and mismatch repair deficiency/microsatellite instability (dMMR/MSI) identifying a subgroup with exceptional sensitivity to ICIs[8]. In oesophago-gastric adenocarcinoma, HER2 and Claudin-18.2 further shape first-line choices, supporting the respective addition of trastuzumab and zolbetuximab to chemotherapy[4,5].

With these advances, median overall survival (OS) has improved to 12-20 months in contemporary trials and up to 39 months in dMMR/MSI-H tumours[9-13]. However, for patients with inoperable disease outcomes vary substantially. This reflects the limitations of conventional tumour-node-metastasis (TNM) staging, which groups otherwise biologically heterogeneous metastatic disease that ranges from rapidly progressive polymetastatic spread to limited and more indolent metastatic states[14]. Within this spectrum, oligometastatic disease (OMD) has gained attention as an intermediate state between widely disseminated and truly localised cancer[15]. Some patients with OMD have a favourable prognosis, and tumours with more restricted metastatic capacity may benefit from combining local and systemic therapies[16,17]. While consensus definitions have attempted to harmonise OMD criteria for distinguishing genuine or *de novo* OMD from induced or repeat disease[15,18], identifying patients with truly limited metastatic potential remains challenging and is not currently supported by validated biomarkers.

Circulating tumour DNA (ctDNA), the tumour-derived fraction of cell-free DNA detectable in blood, is an emerging biomarker in oncology[19]. In OGC, ctDNA detection is associated with adverse outcomes, and changes over time can track treatment response and disease progression[20,21]. While

most clinical evidence relates to detecting persistent molecular residual disease (MRD) in patients after resection of the primary tumour, ctDNA kinetics may also have clinical utility in OMD.

In this review, we summarise the evidence for OMD management and ctDNA use in OGC, discuss how ctDNA could refine prognostic stratification and therapeutic decision-making in oligometastatic settings, and define the challenges that must be addressed for its clinical implementation.

2. Oligometastatic disease: prevalence and management in oesophago-gastric cancers

There is increasing focus on the potential benefits of local metastasis-directed treatment in OGC, given that retrospective series suggest that 7%-25% of patients with metastatic OGC present with oligometastatic disease[22,23]. In most cases, OMD involves a single metastatic site, most commonly the liver or extra-regional lymph nodes[22,23].

In oesophageal squamous cell carcinoma (OSCC), the highest-level evidence is provided by the Chinese multi-centre phase II ESO-Shanghai 13 trial, which randomised 104 patients with OMD to SACT alone or SACT plus local therapy to all metastatic lesions[24]. Adding local therapy, which for 83% of patients was radiotherapy, significantly improved progression-free survival (PFS) from 6.4 months with SACT alone to 15.3 months (stratified hazard ratio, HR 0.26; 95% CI 0.16-0.42; log-rank $p<0.0001$). This trial built on an earlier single-arm phase II study supporting stereotactic ablative radiotherapy (SABR) feasibility in oligometastatic OSCC[25]. An alternative approach for the management of OMD in OSCC was reported in the Chinese phase II ChiCTR2000040533 trial[26]. Treatment with intensity-modulated radiation therapy resulted in favourable median PFS and OS of 6.9 and 12.8 months, respectively[26]. However, the proposed immunomodulatory doses of 40Gy in 20 fractions to primary tumours and 30Gy in 10 fractions to growing oligometastases are substantially lower, and the hypofractionation markedly less pronounced, than dose-fractionation regimens employed in SABR.

In gastric or gastroesophageal junction adenocarcinoma, evidence on the added value of oligometastasis-directed treatment remains less certain. Small prospective studies have suggested potential benefit[27-29]. However, two phase III studies, the Asian REGATTA and the German RENAISSANCE (FLOT-5) failed to demonstrate a survival advantage with the addition of local therapies to SACT compared with SACT alone[30,31]. Unlike ESO-Shanghai 13, both studies used surgery for local control[30,31]. Of note, in REGATTA, the most frequent metastatic site was peritoneal disease (75%)[30], and in RENAISSANCE, subgroup analyses suggested improved OS with local therapy

in patients with retroperitoneal lymph node metastases (30 vs 17 months) but not in those with peritoneal disease (12 vs 19 months)[31]. The interpretation of these studies is complex. In both studies, the surgery arm had shorter systemic therapy exposure. In RENAISSANCE, survival curves crossed, resulting in opposite OS trends at early and late time points, and there were substantial rates of incomplete resection (46%) and non-trivial postoperative mortality (8% at 90 days)[30,31]. These data contrast with the earlier phase II stratified AIO-FLOT3 trial, which shared many of its inclusion criteria with RENAISSANCE and demonstrated a favourable median OS of 22.9 months in patients who proceeded to local tumour plus oligometastases resection following SACT[32]. Other phase III trials are ongoing to test different multimodal strategies incorporating local therapies into current systemic treatment regimens (e.g., NCT04248452, NCT07000253, NCT06922279). As outlined in Table 1, which provides an overview of the main studies evaluating treatment strategies for OMD OGC, these studies used cross-sectional imaging to define OMD and characterise response to treatment[24-33].

Despite increasing efforts to profile and study OMD in OGC, a major challenge remains the limited sensitivity of current clinico-radiological criteria. Radiological parameters alone may not adequately capture true metastatic burden and underlying disease biology, leading to heterogeneity in OMD definitions and outcomes after metastasis-directed treatment[31-33]. In this context, the OligoMetastatic Esophagogastric Cancer (OMEC) consortium has developed a consensus definition of OMD in OGC that defines OMD as the maximum involvement of one organ with up to three metastases, or one extra-regional lymph node station[17]. Peritoneal metastases are not considered to represent OMD[17]. Future clinical trials are likely to rely on this definition, though more refined, biologically-informed stratification tools are needed to improve patient selection and to better align treatment intensity with individual disease dynamics.

3. Circulating tumour DNA in oesophago-gastric cancers

3.1 Technical considerations for ctDNA detection

In OMD, ctDNA represents a promising adjunct, offering a biologically informed approach to detect molecular residual or occult disease, quantify tumour burden, and capture early molecular progression[19]. Given its short half-life (~1-2.5 hours), ctDNA can provide near real-time insights into tumour dynamics. To fulfil a meaningful role in supporting treatment decision-making in

oligometastatic OGC, however, ctDNA assays will need to demonstrate high analytical sensitivity. Current ctDNA detection approaches are influenced by tumour biology, assay design, sequencing methods, and the analytic pipelines used[19]. For instance, tumour-agnostic assays can have broad indications, as they do not require prior tumour tissue sequencing, but distinguishing germline from somatic variants and filtering confounding signals from clonal haematopoiesis of indeterminate potential (CHIP) is challenging[34,35]. Addressing these issues requires sequencing of patient-specific peripheral blood leukocytes from matched plasma samples or approaches not based on the analysis of mutations. On the other hand, tumour-informed approaches, which detect ctDNA by matching plasma variants with those identified in tumour tissue can achieve higher sensitivity[19,36]. One such example that has been used in OGC ctDNA studies is Signatera, enabling longitudinal tracking of patient-specific tumour-derived variants in blood identified through tumour exome or genome sequencing[36]. Machine-learning-based approaches have also led to refined variant calling, improving the integration of multimodal signals and the detection of sequencing artefacts and other background noise. One of these platforms reported a limit of detection sufficiently low to capture ctDNA shed from precancerous lesions in the colon[37]. Yet, reliance on tissue has limitations, as it may fail to capture spatial and temporal heterogeneity and constrains ctDNA analysis to more limited clinical applications (such as MRD tracking, follow-up, and detection of recurrence)[35].

The performance of ctDNA assays is further challenged by the low disease burden that characterises OMD, as the shedding rate of tumour-derived cell-free DNA (cfDNA) is closely related to tumour extent[38,39]. To retain clinical utility in OMD, ctDNA platforms will need to demonstrate robust performance across different treatment modalities (including chemotherapy, chemo-immunotherapy, and chemoradiotherapy (CRT)) as well as across various OGC subtypes.

Recent advances have broadened detection beyond mutations by integrating multimodal profiling that exploits ctDNA biological features and multi-analyte profiling that incorporates complementary tumour-derived signals such as RNA or proteins, either within extracellular vesicles or released into the bloodstream[37,40-45]. Examples include the shorter fragment length distribution of ctDNA (typically below 150 base pairs) relative to cfDNA[40] and cancer-specific methylation signatures[41,42]. Simultaneous evaluation of genomic and fragmentomic features using consensus calling based on genome-wide long-read nanopore sequencing allowed the detection of tumour fractions as low as 0.24%[43]In another multimodal platform, incorporation of software capable of deriving fragment-end composition, ctDNA size, and tumour fraction from standard whole genome sequencing (WGS)

achieved 82% detection accuracy and an area under the receiver operating characteristic curve (AUROC) of 0.96 across multiple cancer types, including OAC[44]. In addition to detecting tumour-derived signals, such approaches leveraging epigenetic or fragmentomic features can inform on cfDNA derived from immune and microenvironmental cells, thereby complementing purely tumour-informed sequencing. These novel platforms may help overcome the anticipated challenges with ctDNA testing in oligometastatic OGC.

3.2 Clinical applications of ctDNA

Early proof-of-concept studies demonstrated that tumour-derived variants could be detected in the plasma of patients with OGC with reasonable concordance with tumour tissue, and that ctDNA levels broadly correlated with tumour stage, preceded radiological recurrence and were associated with worse survival[46-50]. Collectively, these findings provided the basis for evaluating ctDNA as a tool for monitoring treatment response, tracking disease burden, particularly for detecting MRD after curative-intent therapies, and identifying actionable alterations for precision medicine.

In the palliative setting, cohort studies in both oesophago-gastric adenocarcinoma and squamous cell carcinoma demonstrated that ctDNA was detectable in the majority of cases and correlated with tumour burden, despite heterogeneity in panels used and thresholds adopted to define ctDNA-response[47,50-53]. In a cohort of 72 patients, most of whom had OAC, residual detectable ctDNA after 9 weeks of treatment was associated with worse survival outcomes (OS: HR 4.95, 95% CI 1.53-16.04; p=0.008; PFS: HR 4.08, 95% CI 1.31-12.75; p=0.016)[50]. Evidence of ctDNA clearance during therapy was a surrogate of radiological response and was also associated with reduced risk of progression or death in cohorts treated with chemo-immunotherapy regimens[51,53].

Most efforts in tracking disease burden have focussed on detection of MRD prior to adjuvant therapy or disease recurrence during surveillance. In the context of OGC with adenocarcinoma histology, an exploratory analysis of the CRITICS trial showed that ctDNA positivity (45%) within nine weeks of curative-intent surgery predicted recurrence in 50 patients with gastric cancer[54]. Similarly, in the OCCAMS cohort, among 97 patients with OAC treated with neoadjuvant chemotherapy and surgery, postoperative ctDNA positivity (16%) was associated with shorter disease-free survival (DFS: HR 2.35, 95% CI 1.18-4.72; p=0.01) and cancer-specific OS (HR 5.55, 95% CI 2.42-12.71; p=0.0003)[55]. Both studies used small, tumour-agnostic fixed cancer gene panels with CHIP filtering[54,55]. In CRITICS and OCCAMS, CHIP-related variants were identified in 62% and 23% of cases, respectively,

and frequently involved *TP53*, a highly prevalent driver gene in OGC. Importantly, CHIP-uncorrected ctDNA analyses were not prognostic in CRITICS[54]. Even with filtering, sensitivity for recurrence remained modest, reaching only 35% in the OCCAMS cohort[55].

In a cohort of patients with OAC treated with neoadjuvant CRT, both baseline and pre-surgery ctDNA detection through a tumour-informed platform that combined ctDNA mutations with tumour fraction estimated from shallow WGS, were associated with an increased risk of recurrence[56]. Applying different tumour-informed strategies, postoperative ctDNA positivity ranged from 25% to 47.4% and was consistently associated with significantly worse OS in two Asian cohorts of patients with stage II-III gastric cancer[57,58]. However, assay performance was limited, with a sensitivity for recurrence of 42.4% within the MRD window[46], possibly influenced by the use of fixed cancer gene panels to track tumour-specific variants in plasma.

In a follow-up OCCAMS analysis applying the patient-specific Signatera assay to 20 individuals with resected OAC, postoperative ctDNA positivity was detected in 20% of cases and was strongly associated with shorter DFS ($p<0.0001$) and OS ($p=0.0027$), achieving a sensitivity of 80% and specificity of 100% for recurrence detection[59]. In chemoimmunotherapy cohorts, exploratory analyses of the phase II ICONIC and PANDA trials, both using Signatera, showed ctDNA detection before adjuvant therapy in 10.5-25% of patients[60,61]. In ICONIC, ctDNA positivity prior to adjuvant therapy was associated with shorter median PFS (12.9 months vs not reached; HR 27, 95% CI 3.0-241; $p<0.0001$)[51]. In PANDA, pre-surgery ctDNA complemented recurrence risk stratification by pathological response. In patients without pCR, ctDNA positivity was associated with the highest risk of relapse or death (DFS: HR 11.06, 95% CI 0.99-124.23) followed by those who were ctDNA-negative without pCR (HR 3.87, 95% CI 0.40-37.36), each compared with the ctDNA-negative and pCR group[52]. The PLAGAST study further examined the value of longitudinal ctDNA monitoring using personalised assays in 62 patients with gastric and gastroesophageal junction adenocarcinoma[21]. Besides predicting inferior outcomes after surgery, ctDNA detection during neoadjuvant therapy (DFS: HR 6.17, 95% CI 1.99-19.12; $p=0.002$; OS: HR 4.71, 95% CI 1.24-17.86; $p=0.022$) and after completion of neoadjuvant therapy (DFS: HR 5.26, 95% CI 1.96-14.12; $p=0.001$; OS: HR 7.35, 95% CI 2.35-22.95; $p=0.001$) was also associated with significantly shorter DFS and OS compared with patients without ctDNA detection at these time points. Other early phase studies also suggested that pre-operative ctDNA dynamics correlate with depth of tumour response, aiding patient prognostic

stratification[62] and supporting their use as a complementary tool to identify clinical complete response in dMMR/MSI patients for non-operative management in the INFINITY trial[63].

A large cohort study of 295 patients with operable oesophageal, gastroesophageal junction, and gastric cancers of either adenocarcinoma or squamous cell histology showed a similar prognostic effect of ctDNA detection[20]. Using Signatera, ctDNA was detected in 23.5% of patients within the MRD window, with the test yielding a sensitivity of 85.7% and specificity of 95.5% for recurrence detection at any time point after surgery. The risk of recurrence or death in patients with postoperative ctDNA detection within the MRD window (HR 10.7, 95% CI 4.3-29.3; p<0.0001) or at any time after surgery (HR 23.6, 95% CI 10.2-66.0; p<0.0001) was significantly higher compared to ctDNA-negative patients. In a subsequent analysis focussing on 42 patients with pathological complete response (pCR) or near-complete response within the same cohort, ctDNA positivity, detected in 13% of cases during the MRD window, was associated with shorter DFS (HR 6.2, 95% CI 1.0-37.6; p=0.049), with recurrence occurring in 67% of ctDNA-positive versus 15% of ctDNA-negative patients[64]. During surveillance, ctDNA positivity predicted recurrence in all patients and was associated with a very high risk of relapse or death (HR 37.6, 95% CI 4.3-325.6; p<0.001).

Detection of ctDNA carried a similar prognostic role in OSCC. Exploratory analyses of the phase II EC-CRT-001 trial showed higher rates of complete clinical response following definitive CRT and toripalimab in patients who were ctDNA negative during CRT (83%) or post-CRT (78%) using a tumour-informed non-personalised assay[65]. ctDNA detection during CRT and post-CRT correlated with shorter PFS (both p<0.01) and the assay yielded a sensitivity of 87% for predicting clinical complete response[65]. In post-hoc analyses of the preSINO trial (n=132), ctDNA detected after neoadjuvant CROSS CRT was associated with increased risk of systemic recurrence[66,67]. Post-operative ctDNA positivity independently predicted inferior DFS and OS in multivariable analysis (both p<0.001) and, notably, stratified benefit from adjuvant immunotherapy, with improved DFS observed only in ctDNA-positive non-pCR patients[67]. Across the platforms used for ctDNA detection, including a patient-specific tumour-informed assay (PROPHET), a tumour-informed fixed panel, and a tumour-agnostic panel, the personalised tumour-informed assay outperformed the others at all time points, achieving a sensitivity of 72.7% for detection of residual disease after CRT[67]. Table 2 summarises the main studies exploring ctDNA to track disease burden in OGC[20,21,54,55,57,59,61,64,65,67].

Applications of ctDNA in OGC can also extend to the detection of targetable alterations in plasma, complementing tissue testing and allowing real-time monitoring of treatment benefit[68,69]. While

targetable alterations in OGC remain primarily assessed with tissue-based approaches, liquid biopsy platforms can overcome discordant results from tissue testing linked to tumour heterogeneity and the need for repeat tissue biopsies to guide treatment sequencing. Exploratory analyses of the DESTINY-Gastric01 trial showed a concordance of 64% between tissue-based HER2 positivity and *ERBB2* plasma gene amplification, demonstrating benefit from trastuzumab-deruxtecan with both tissue and plasma-based HER2 stratification[70]. Large real-world cohorts also demonstrated high detection rates for ctDNA-derived MSI and HER2 amplifications, and corresponding clinical benefit from ICIs or anti-HER2 therapies[71,72]. Of note, in patients with concordant tissue- and blood-based HER2 assessment, benefit from anti-HER2 treatment was magnified[72].

4. Open challenges and future directions

The consistency and magnitude of the prognostic impact of ctDNA across disease stages, tumour histology, and treatment regimens in OGC[20,21,51-55,57-61,64-67] support the exploration of its value in OMD. In particular, ctDNA dynamics offer a compelling opportunity to refine patient selection, treatment strategies, and response monitoring in OMD (Figure 1). Distinguishing genuinely limited metastatic potential from early systemic dissemination remains a core challenge in OMD. By analogy with MRD in operable disease, ctDNA could provide a biological “stress test” of radiologically defined OMD. Patients with limited lesions but high ctDNA levels may represent higher-volume systemic disease less likely to benefit from upfront metastasis-directed interventions, whereas patients with low or undetectable ctDNA levels may be enriched for more indolent OMD amenable to durable control with metastasis-directed approaches. A potential framework for ctDNA-based OMD stratification could integrate baseline ctDNA levels with kinetic changes during initial systemic therapy. For instance, patients with undetectable ctDNA at baseline or rapid ctDNA clearance within 2-3 months of systemic therapy may represent “true” OMD with limited systemic burden, warranting consideration for metastasis-directed consolidation. Conversely, persistently high or rising ctDNA levels despite radiological stability may indicate occult systemic disease, favouring continuation of systemic therapy alone. Such a stratification approach requires prospective validation but could enhance patient selection beyond current radiological criteria.

However, several biological and technical aspects pose important challenges to the sensitivity and interpretation of ctDNA analyses in oligometastatic OGC (Figure 2). In this setting, ctDNA shedding is anticipated to be low or even undetectable with current assays, reflecting the low overall tumour burden and the heterogeneous shedding across metastatic sites[38]. For instance, peritoneal disease,

a common metastatic site in OGC that is often challenging to detect early with conventional imaging and that would fall outside OMEC criteria for OMD, has been shown to contribute minimally to ctDNA shedding[72]. In patients with radiologically defined OMD and occult peritoneal disease, ctDNA testing may not offer added value and may even be misleading, as false-negative results could underestimate the true extent of disease, incorrectly favour an oligometastatic classification, and drive management decisions towards inappropriate local interventions. This limitation is particularly relevant as ctDNA-informed OMD stratification moves beyond prognostic assessment towards clinical actionability. To guide tailored management, ctDNA testing must be supported by platforms with high accuracy. Emerging approaches have reported improved sensitivity by incorporating multimodal or multi-omic profiling, combined with machine-learning-based interpretation[37,40-42]. While these strategies hold promise, prospective validation in OMD settings will be essential.

Longitudinal ctDNA monitoring could also facilitate OMD detection. In operable disease settings, ctDNA positivity has preceded radiological recurrence by several months[20,21,52,54,55,57-61,64-67], creating a window for intensified surveillance and earlier intervention. In OMD, this lead time may be particularly valuable, as progression may initially involve few sites that are still amenable to ablative approaches. As in other disease settings, where molecular response has informed treatment intensity[73], ctDNA dynamics may support adaptive strategies in OMD. Lessons from operable disease suggest that persistent ctDNA during peri-operative treatments reflects biological resistance and carries a particularly poor prognosis that is rarely mitigated by continuation of the same regimen in the adjuvant setting[20,21]. Similarly, in OMD, detectable ctDNA after metastasis-directed approaches might prompt early initiation of SACT, while ctDNA clearance could support de-escalation strategies or the delay of additional therapy[74]. Conversely, in patients treated with induction SACT, ctDNA persistence even without radiological progression may help identify those who are unlikely to benefit from further consolidative treatments and may instead benefit from an early switch in the systemic strategy[75]. In both contexts, real-time identification of targetable alterations in ctDNA may allow further treatment personalisation. Importantly, ctDNA should complement (rather than replace) imaging, particularly given its limitations in patients with peritoneal disease and the need to locate oligometastatic lesions to enable local therapies. Moreover, although serial ctDNA sampling may provide valuable complementary information for treatment stratification and tailoring in oligometastatic OGC, the optimal sampling time points remain to be established and must be balanced against resource implications and patient burden.

From a trial design perspective, incorporating ctDNA into OMD studies could improve patient selection by enriching for biologically favourable OMD or enabling stratified randomisation by molecular risk. ctDNA-based endpoints could serve as intermediate or composite endpoints and help define optimal timing and sequencing of systemic and local therapies. One example is the ongoing phase II OMEC-5 randomised trial (NCT07000253), which evaluates the optimal duration of systemic therapy before metastasis-directed treatment in patients with oligometastatic OGC and includes exploratory ctDNA analyses.

To realise the potential of ctDNA in OMD, several critical next steps are required. First, prospective observational studies should establish baseline ctDNA detection rates, optimal sampling time points, and prognostic thresholds specifically in oligometastatic OGC cohorts. Second, assay performance in low-burden settings must be rigorously benchmarked across platforms, with particular attention to site-specific shedding patterns. Third, interventional trials randomising patients to ctDNA-guided versus standard management strategies are needed to demonstrate clinical utility beyond prognostic value. Finally, integration of ctDNA with complementary biomarkers and imaging modalities should be explored in multimodal risk stratification frameworks. Only through such systematic validation can ctDNA transition from a promising research tool to a clinically actionable biomarker in oligometastatic OGC.

In summary, the utility of ctDNA in early-stage OGC provides a strong foundation for extending its evaluation to OMD. By adding biological resolution to current imaging-based OMD criteria, enabling earlier detection of progression, and supporting adaptive treatment strategies, ctDNA, potentially complemented by other liquid biopsy approaches, offers an opportunity to enhance the precision of oligometastatic OGC management and maximise the likelihood that local and systemic therapies are delivered to the right patient, at the right time, and in the right sequence.

Acknowledgements: AC is supported by a post-doctoral research fellowship funded by AIRC Foundation for Cancer Research (ID: 29542). CMJ is supported by a Clinical Lectureship part-funded by CRUK RadNet Cambridge [C17918/A28870]. FM is funded by Cancer Research UK (CRUK) via core-funding to the CRUK National Biomarker Centre and supported by the Manchester Experimental Cancer Medicines Centre, the CRUK Lung Cancer Centre of Excellence, and the NIHR Manchester Biomedical Research Centre.

Conflicts of interest: AP reports honoraria from GlaxoSmithKline, Takeda, Bayer, Daiichi Sankyo, MSD, Amgen, BeiOne, Pierre Fabre, Servier, BMS, Merck Serono for consultancy, advisory boards or invited speaker; research funding (to the Institution) from GlaxoSmithKline and Amgen; travel Grants from AstraZeneca, Merck Serono, Amgen. CMJ has consulted for Candesic. FM is coinventor on patents related to cfDNA analyses and has consulted for Roche Dx. FM has received support from Biomodal. HvL reports research funding and/or medication/material supply from: AMGEN, Auristone, BMS, Incyte, Merck, MyeloidTx, ORCA, Servier. Consultant/advisory role: AMGEN, Amphera, Astellas, AstraZeneca, Beigene, BMS, Boehringer, Daiichy, MSD, MyeloidTx. Speaker role: AstraZeneca, BMS, Congress Care, Daiichy, Medtalks, MSD, Uitgeverij JAAP, Travel Congress Management. Conflicts for all authors are unrelated to the work presented here. All other authors state no conflicts of interest.

References

1. Morgan E, Soerjomataram I, Rumgay H, et al. The Global Landscape of Esophageal Squamous Cell Carcinoma and Esophageal Adenocarcinoma Incidence and Mortality in 2020 and Projections to 2040: New Estimates From GLOBOCAN 2020. *Gastroenterology* 2022; **163**(3): 649–58.e2.
2. Sundar R, Nakayama I, Markar SR, et al. Gastric cancer. *The Lancet* 2025; **405**(10494): 2087–102.
3. Then EO, Lopez M, Saleem S, et al. Esophageal Cancer: An Updated Surveillance Epidemiology and End Results Database Analysis. *World J Oncol* 2020; **11**(2): 55–64.
4. Lordick F, Carneiro F, Cascinu S, et al. Gastric cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol* 2022; **33**(10): 1005–20.
5. Lordick F, Candia Montero L, Castelo-Branco L, Pentheroudakis G, Sessa C, Smyth EC. ESMO Gastric Cancer Living Guideline v1.4. 2024.
6. Obermannová R, Alsina M, Cervantes A, et al. Oesophageal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol* 2022; **33**(10): 992–1004.
7. Obermannová RL, Leong T. ESMO Clinical Practice Guideline interim update on the treatment of locally advanced oesophageal and oesophagogastric junction adenocarcinoma and metastatic squamous-cell carcinoma. *ESMO Open* 2025; **10**(2).
8. de la Fouchardière C, Cammarota A, Svrcek M, et al. How do I treat dMMR/MSI gastro-oesophageal adenocarcinoma in 2025? A position paper from the EORTC-GITCG gastro-esophageal task force. *Cancer Treat Rev* 2025; **134**: 102890.
9. Janjigian YY, Kawazoe A, Bai Y, et al. Pembrolizumab plus trastuzumab and chemotherapy for HER2-positive gastric or gastro-oesophageal junction adenocarcinoma: interim analyses from the phase 3 KEYNOTE-811 randomised placebo-controlled trial. *The Lancet* 2023; **402**(10418): 2197–208.
10. Shitara K, Ajani JA, Moehler M, et al. Nivolumab plus chemotherapy or ipilimumab in gastro-oesophageal cancer. *Nature* 2022; **603**(7903): 942–8.
11. Doki Y, Ajani JA, Kato K, et al. Nivolumab Combination Therapy in Advanced Esophageal Squamous-Cell Carcinoma. *New England Journal of Medicine* 2022; **386**(5): 449–62.

12. Shitara K, Lordick F, Bang YJ, et al. Zolbetuximab plus mFOLFOX6 in patients with CLDN18.2-positive, HER2-negative, untreated, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma (SPOTLIGHT): a multicentre, randomised, double-blind, phase 3 trial. *Lancet* 2023; **401**(10389): 1655–68.
13. Shah MA, Shitara K, Ajani JA, et al. Zolbetuximab plus CAPOX in CLDN18.2-positive gastric or gastroesophageal junction adenocarcinoma: the randomized, phase 3 GLOW trial. *Nat Med* 2023; **29**(8): 2133–41.
14. Amin MB, Greene FL, Edge SB, et al. The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. *CA Cancer J Clin* 2017; **67**(2): 93–9.
15. Hellman S, Weichselbaum RR. Oligometastases. *J Clin Oncol* 1995; **13**(1): 8–10.
16. Dellinger Barney JC, E. J. Adenocarcinoma of the Kidney with Metastasis to the Lung: Cured by Nephrectomy and Lobectomy. *Journal of Urology* 1939; **42**(3): 269–76.
17. Kroese TE, Bronzwaer S, van Rossum PSN, et al. European clinical practice guidelines for the definition, diagnosis, and treatment of oligometastatic esophagogastric cancer (OMEC-4). *Eur J Cancer* 2024; **204**: 114062.
18. Guckenberger M, Lievens Y, Bouma AB, et al. Characterisation and classification of oligometastatic disease: a European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus recommendation. *Lancet Oncol* 2020; **21**(1): e18–e28.
19. Landon BV, Annapragada AV, Niknafs N, Velculescu VE, Anagnostou V. Liquid biopsies across the cancer care continuum. *Nature Medicine* 2025; **31**(12): 4006–21.
20. Huffman BM, Aushev VN, Budde GL, et al. Analysis of Circulating Tumor DNA to Predict Risk of Recurrence in Patients With Esophageal and Gastric Cancers. *JCO Precis Oncol* 2022; **6**: e2200420.
21. Zaanan A, Didelot A, Broudin C, et al. Longitudinal circulating tumor DNA analysis during treatment of locally advanced resectable gastric or gastroesophageal junction adenocarcinoma: the PLAGAST prospective biomarker study. *Nature Communications* 2025; **16**(1): 6815.
22. Kroese TE, Christ SM, van Rossum PSN, et al. Incidence and survival of patients with oligometastatic esophagogastric cancer: A multicenter cohort study. *Radiother Oncol* 2022; **173**: 269–76.
23. Down B, Lakunina S, Maynard N, Markar SR, Gordon-Weeks A. Oncological outcomes of patients with oligometastatic oesophagogastric cancer. *Eur J Surg Oncol* 2024; **50**(4): 108231.
24. Liu Q, Chen J, Lin Y, et al. Systemic therapy with or without local intervention for oligometastatic oesophageal squamous cell carcinoma (ESO-Shanghai 13): an open-label, randomised, phase 2 trial. *Lancet Gastroenterol Hepatol* 2023.
25. Liu Q, Zhu Z, Chen Y, et al. Phase 2 Study of Stereotactic Body Radiation Therapy for Patients with Oligometastatic Esophageal Squamous Cell Carcinoma. *Int J Radiat Oncol Biol Phys* 2020; **108**(3): 707–15.
26. Zhao W, Ke S, Cai X, et al. Radiotherapy plus camrelizumab and irinotecan for oligometastatic esophageal squamous cell carcinoma patients after first-line immunotherapy plus chemotherapy failure: An open-label, single-arm, phase II trial. *Radiother Oncol* 2023; **184**: 109679.
27. Cui Y, Yu Y, Zheng S, et al. Does resection after neoadjuvant chemotherapy of docetaxel, oxaliplatin, and S-1 (DOS regimen) benefit for gastric cancer patients with single non-curable factor? a multicenter, prospective cohort study (Neo-REGATTA). *BMC Cancer* 2023; **23**(1): 308.
28. Norén N, Rouvelas I, Lundell L, et al. Curative treatment for oligometastatic gastroesophageal cancer- results of a prospective multicenter study. *Langenbecks Arch Surg* 2024; **410**(1): 10.

29. Day F, Sridharan S, Johnson C, et al. Esophageal chemoradiotherapy with concurrent nivolumab: Pilot results in the palliative treatment of oligometastatic disease. *Asia Pac J Clin Oncol* 2024; **20**(3): 416–22.
30. Fujitani K, Yang H-K, Mizusawa J, et al. Gastrectomy plus chemotherapy versus chemotherapy alone for advanced gastric cancer with a single non-curable factor (REGATTA): a phase 3, randomised controlled trial. *The Lancet Oncology* 2016; **17**(3): 309–18.
31. Salah-Eddin Al-Batran SL, Jorge Riera, Karel Caca, Christian Mueller, Daniel E Stange, Thomas Zander, Claus Bolling, Nils Homann, Jochen Gaedcke, Peter C. Thuss-Patience, Patrick Michl, Wolfgang Blau, Kai Wille, Christine Koch, Claudia Pauligk, Daniel Wilhelm Mueller, Ulli Simone Bankstahl, Stefan Paul Monig, Thorsten Goetze. Effect of chemotherapy/targeted therapy alone vs. chemotherapy/targeted therapy followed by radical surgical resection on survival and quality of life in patients with limited-metastatic adenocarcinoma of the stomach or esophagogastric junction: The IKF-575/RENAISSANCE phase III trial. *Journal of Clinical Oncology* 2024; **42**: LBA4001.
32. Al-Batran SE, Homann N, Pauligk C, et al. Effect of Neoadjuvant Chemotherapy Followed by Surgical Resection on Survival in Patients With Limited Metastatic Gastric or Gastroesophageal Junction Cancer: The AIO-FLOT3 Trial. *JAMA Oncol* 2017; **3**(9): 1237–44.
33. Al-Batran SE, Goetze TO, Mueller DW, et al. The RENAISSANCE (AIO-FLOT5) trial: effect of chemotherapy alone vs. chemotherapy followed by surgical resection on survival and quality of life in patients with limited-metastatic adenocarcinoma of the stomach or esophagogastric junction - a phase III trial of the German AIO/CAO-V/CAOGI. *BMC Cancer* 2017; **17**(1): 893.
34. Hu Y, Ulrich BC, Supplee J, et al. False-Positive Plasma Genotyping Due to Clonal Hematopoiesis. *Clin Cancer Res* 2018; **24**(18): 4437–43.
35. Liu J, Chen X, Wang J, et al. Biological background of the genomic variations of cf-DNA in healthy individuals. *Ann Oncol* 2019; **30**(3): 464–70.
36. Abbosh C, Birkbak NJ, Wilson GA, et al. Phylogenetic ctDNA analysis depicts early-stage lung cancer evolution. *Nature* 2017; **545**(7655): 446–51.
37. Widman AJ, Shah M, Frydendahl A, et al. Ultrasensitive plasma-based monitoring of tumor burden using machine-learning-guided signal enrichment. *Nat Med* 2024; **30**(6): 1655–66.
38. Bettegowda C, Sausen M, Leary RJ, et al. Detection of circulating tumor DNA in early- and late-stage human malignancies. *Sci Transl Med* 2014; **6**(224): 224ra24.
39. Deveson IW, Gong B, Lai K, et al. Evaluating the analytical validity of circulating tumor DNA sequencing assays for precision oncology. *Nat Biotechnol* 2021; **39**(9): 1115–28.
40. van 't Erve I, Alipanahi B, Lumbard K, et al. Cancer treatment monitoring using cell-free DNA fragmentomes. *Nature Communications* 2024; **15**(1): 8801.
41. Nakamura Y, Kaneva K, Lo C, et al. A Tumor-Naïve ctDNA Assay Detects Minimal Residual Disease in Resected Stage II or III Colorectal Cancer and Predicts Recurrence: Subset Analysis from the GALAXY Study in CIRCULATE-Japan. *Clin Cancer Res* 2025; **31**(2): 328–38.
42. Paracchini L, Ancona L, Beltrame L, et al. ALMA platform: a Pan-cancer agnostic multi-modal liquid biopsy approach for enhanced MRD detection and therapy monitoring. *The Journal of Liquid Biopsy* 2025; **9**: 100337.
43. Chen LT, Jager M, Rebergen D, et al. Nanopore-based consensus sequencing enables accurate multimodal tumor cell-free DNA profiling. *Genome Res* 2025; **35**(4): 886–99.
44. Moldovan N, van der Pol Y, van den Ende T, et al. Multi-modal cell-free DNA genomic and fragmentomic patterns enhance cancer survival and recurrence analysis. *Cell Rep Med* 2024; **5**(1): 101349.

45. Casanova-Salas I, Aguilar D, Cordoba-Terreros S, et al. Circulating tumor extracellular vesicles to monitor metastatic prostate cancer genomics and transcriptomic evolution. *Cancer Cell* 2024; **42**(7): 1301–12.e7.
46. Ueda M, Iguchi T, Masuda T, et al. Somatic mutations in plasma cell-free DNA are diagnostic markers for esophageal squamous cell carcinoma recurrence. *Oncotarget* 2016; **7**(38): 62280–91.
47. Maron SB, Chase LM, Lomnicki S, et al. Circulating Tumor DNA Sequencing Analysis of Gastroesophageal Adenocarcinoma. *Clinical Cancer Research* 2019; **25**(23): 7098–112.
48. Yang J, Gong Y, Lam VK, et al. Deep sequencing of circulating tumor DNA detects molecular residual disease and predicts recurrence in gastric cancer. *Cell Death & Disease* 2020; **11**(5): 346.
49. Azad TD, Chaudhuri AA, Fang P, et al. Circulating Tumor DNA Analysis for Detection of Minimal Residual Disease After Chemoradiotherapy for Localized Esophageal Cancer. *Gastroenterology* 2020; **158**(3): 494–505.e6.
50. van Velzen MJM, Creemers A, van den Ende T, et al. Circulating tumor DNA predicts outcome in metastatic gastroesophageal cancer. *Gastric Cancer* 2022; **25**(5): 906–15.
51. Jin Y, Chen D-L, Wang F, et al. The predicting role of circulating tumor DNA landscape in gastric cancer patients treated with immune checkpoint inhibitors. *Molecular Cancer* 2020; **19**(1): 154.
52. Ng HY, Ko JMY, Lam KO, et al. Circulating Tumor DNA Dynamics as Prognostic Markers in Locally Advanced and Metastatic Esophageal Squamous Cell Carcinoma. *JAMA Surgery* 2023; **158**(11): 1141–50.
53. Mehta R, Rivero-Hinojosa S, Dayyani F, et al. Circulating tumor DNA informs clinical practice in patients with recurrent/metastatic gastroesophageal cancers. *Cancer* 2026; **132**(1): e70242.
54. Leal A, van Grieken NCT, Palsgrove DN, et al. White blood cell and cell-free DNA analyses for detection of residual disease in gastric cancer. *Nature Communications* 2020; **11**(1): 525.
55. Ococks E, Frankell AM, Masque Soler N, et al. Longitudinal tracking of 97 esophageal adenocarcinomas using liquid biopsy sampling. *Annals of Oncology* 2021; **32**(4): 522–32.
56. van den Ende T, van der Pol Y, Creemers A, et al. Genome-wide and panel-based cell-free DNA characterization of patients with resectable esophageal adenocarcinoma. *J Pathol* 2023; **261**(3): 286–97.
57. Yuan SQ, Nie RC, Huang YS, et al. Residual circulating tumor DNA after adjuvant chemotherapy effectively predicts recurrence of stage II-III gastric cancer. *Cancer Commun (Lond)* 2023; **43**(12): 1312–25.
58. Zhang M, Yang H, Fu T, et al. Liquid biopsy: circulating tumor DNA monitors neoadjuvant chemotherapy response and prognosis in stage II/III gastric cancer. *Molecular Oncology* 2023; **17**(9): 1930–42.
59. Ococks E, Sharma S, Ng AWT, Aleshin A, Fitzgerald RC, Smyth E. Serial Circulating Tumor DNA Detection Using a Personalized, Tumor-Informed Assay in Esophageal Adenocarcinoma Patients Following Resection. *Gastroenterology* 2021; **161**(5): 1705–8.e2.
60. Gerlinger M, Gordon A, Barber LJ, et al. Abstract 5591: Circulating tumor DNA for recurrence prediction and efficacy analysis in the ICONIC trial of peri-operative FLOT and avelumab (PD-L1) in localized esophago-gastric adenocarcinoma. *Cancer Research* 2023; **83**(7_Supplement): 5591–.
61. Verschoor YL, van de Haar J, van den Berg JG, et al. Neoadjuvant atezolizumab plus chemotherapy in gastric and gastroesophageal junction adenocarcinoma: the phase 2 PANDA trial. *Nature Medicine* 2024; **30**(2): 519–30.
62. Kelly RJ, Landon BV, Zaidi AH, et al. Neoadjuvant nivolumab or nivolumab plus LAG-3 inhibitor relatlimab in resectable esophageal/gastroesophageal junction cancer: a phase Ib trial and ctDNA analyses. *Nature Medicine* 2024; **30**(4): 1023–34.

63. Raimondi A, Lonardi S, Murgioni S, et al. Tremelimumab and durvalumab as neoadjuvant or non-operative management strategy of patients with microsatellite instability-high resectable gastric or gastroesophageal junction adenocarcinoma: the INFINITY study by GONO. *Annals of Oncology* 2025; **36**(3): 285–96.
64. Lander EM, Aushev VN, Huffman BM, et al. Circulating Tumor DNA as a Prognostic Biomarker for Recurrence in Patients With Locoregional Esophagogastric Cancers With a Pathologic Complete Response. *JCO Precision Oncology* 2024; (8): e2400288.
65. Chen B, Liu S, Zhu Y, et al. Predictive role of ctDNA in esophageal squamous cell carcinoma receiving definitive chemoradiotherapy combined with toripalimab. *Nat Commun* 2024; **15**(1): 1919.
66. Yang Y, Liu Z, Wong I, et al. Detecting residual disease after neoadjuvant chemoradiotherapy for oesophageal squamous cell carcinoma: prospective multicentre preSINO trial. *BJS* 2025; **112**(2).
67. Liu Z, Wang G, Yang Y, et al. ctDNA detects residual disease after neoadjuvant chemoradiotherapy and guides adjuvant therapy in esophageal squamous cell carcinoma. *Cell Reports Medicine* 2025; **6**(9).
68. Nakamura Y, Ozaki H, Ueno M, et al. Targeted therapy guided by circulating tumor DNA analysis in advanced gastrointestinal tumors. *Nature Medicine* 2025; **31**(1): 165–75.
69. Catenacci DVT, Moya S, Lomnicki S, et al. Personalized Antibodies for Gastroesophageal Adenocarcinoma (PANGEA): A Phase II Study Evaluating an Individualized Treatment Strategy for Metastatic Disease. *Cancer Discovery* 2021; **11**(2): 308–25.
70. Shitara K, Bang YJ, Iwasa S, et al. Trastuzumab deruxtecan in HER2-positive advanced gastric cancer: exploratory biomarker analysis of the randomized, phase 2 DESTINY-Gastric01 trial. *Nat Med* 2024; **30**(7): 1933–42.
71. Willis J, Lefterova MI, Artyomenko A, et al. Validation of Microsatellite Instability Detection Using a Comprehensive Plasma-Based Genotyping Panel. *Clin Cancer Res* 2019; **25**(23): 7035–45.
72. Maron SB, Chase LM, Lomnicki S, et al. Circulating Tumor DNA Sequencing Analysis of Gastroesophageal Adenocarcinoma. *Clin Cancer Res* 2019; **25**(23): 7098–112.
73. Tie J, Cohen JD, Lahouel K, et al. Circulating Tumor DNA Analysis Guiding Adjuvant Therapy in Stage II Colon Cancer. *New England Journal of Medicine* 2022; **386**(24): 2261–72.
74. Einstein DJ, Liang N, Malhotra M, et al. Assessment of Molecular Remission in Oligometastatic Esophageal Cancer With a Personalized Circulating Tumor DNA Assay. *JCO Precision Oncology* 2020; (4): 239–43.
75. Randon G, Lonardi S, Fassan M, et al. Ramucirumab plus paclitaxel as switch maintenance versus continuation of first-line oxaliplatin-based chemotherapy in patients with advanced HER2-negative gastric or gastro-oesophageal junction cancer (ARMANI): a randomised, open-label, multicentre, phase 3 trial. *Lancet Oncol* 2024; **25**(12): 1539–50.