

LIQUID BIOPSY IN GYNECOLOGIC ONCOLOGY: CURRENT STATUS AND FUTURE PERSPECTIVES

Rajabova Nodira Makhmud kizi

Scientific supervisor: PhD

Karimova Nargiza Mansurovna

General Oncology Department Tashkent State Medical University

Abstract. Liquid biopsy has rapidly evolved from a research concept into a clinically relevant approach for capturing tumor-derived information through minimally invasive sampling, most commonly from blood but increasingly from other fluids that are highly relevant to gynecologic malignancies. By analyzing circulating tumor DNA (ctDNA), circulating tumor cells, extracellular vesicles, and circulating RNA species, liquid biopsy can complement tissue pathology by offering real-time molecular insights, enabling longitudinal monitoring, and potentially detecting relapse earlier than conventional methods.

Keywords: liquid biopsy, circulating tumor DNA, gynecologic oncology, ovarian cancer, endometrial cancer.

INTRODUCTION

Gynecologic cancers remain a major source of morbidity and mortality worldwide, with outcomes often shaped by stage at diagnosis, tumor biology, and the capacity to tailor therapy over time. Although tissue biopsy and surgical pathology remain the cornerstone of diagnosis and molecular classification, traditional tissue sampling has persistent limitations in this field. Tumors can be spatially heterogeneous, metastatic deposits may differ genetically from the primary lesion, and repeated tissue biopsies are frequently impractical due to anatomical constraints, procedural risks, or limited accessible disease. These challenges are especially evident in high-grade serous ovarian cancer, where disease can disseminate widely within the peritoneal cavity, and in recurrent settings where treatment selection increasingly depends on up-to-date molecular information rather than archival specimens.

MATERIALS AND METHODS

Liquid biopsy is best understood as an umbrella term describing several analyte classes and technological strategies. In gynecologic cancers, plasma ctDNA has been the most studied, but circulating tumor cells, extracellular vesicles (including exosomes), microRNAs, and tumor-educated platelets are also being explored, alongside sampling from ascites, urine, and cervicovaginal fluids that may be particularly informative for certain disease sites. Each analyte reflects a different biological layer: ctDNA provides

a genomic and sometimes epigenomic readout; CTCs can enable cellular phenotyping; extracellular vesicles and circulating RNA species may reflect transcriptional programs and microenvironment interactions. Translating these signals into clinical action requires careful attention to biology (tumor shedding, clearance, and timing), technology (limits of detection, error profiles), and clinical context (what decision the test is meant to inform) [1].

RESULTS AND DISCUSSION

A recurring lesson across studies is that pre-analytical and analytical factors are not details; they determine whether a result is trustworthy. Plasma processing time, tube type, storage temperature, and the interval from draw to centrifugation can alter cell-free DNA quality and lead to leukocyte DNA contamination. On the analytical side, sensitivity is bounded by the fraction of tumor-derived DNA in circulation, which can be extremely low in early-stage disease or in tumors that shed minimally. Even when a highly sensitive assay is used, false negatives remain possible; conversely, false positives can arise from clonal hematopoiesis of indeterminate potential (CHIP), where age-related blood cell clones carry mutations that may be misattributed to the tumor if matched white blood cell sequencing is not performed. These constraints help explain why guidelines emphasize that tissue testing is still preferred in many scenarios, and why non-informative ctDNA results often warrant reflex tissue testing if feasible.

Clinically, the most mature application of liquid biopsy is molecular profiling in advanced cancer when tissue is unavailable, unsafe to obtain, or insufficient for comprehensive genotyping. In gynecologic oncology, this is relevant when recurrent disease is not easily accessible, when a patient's condition makes invasive procedures high risk, or when rapid turnaround is needed to guide therapy. Even in these cases, liquid biopsy should be interpreted as complementary: detection of a targetable alteration can be highly informative, but non-detection does not exclude its presence, particularly if tumor fraction is low. The implication for clinicians is practical—use ctDNA as a tool for speed and feasibility, but maintain a pathway for tissue confirmation or broader profiling when results do not fit the clinical picture [2].

Ovarian cancer illustrates both the promise and complexity of liquid biopsy. High-grade serous ovarian carcinoma often harbors ubiquitous TP53 alterations, which makes ctDNA tracking conceptually straightforward, and serial measurements may reflect tumor burden dynamics. Liquid biopsy has been investigated for earlier detection of relapse compared with conventional markers and imaging, for prognostication, and for monitoring therapy response. It also offers a route to study acquired resistance mechanisms, including secondary alterations that restore homologous recombination function in BRCA-mutant tumors exposed to PARP inhibitors. However, ovarian cancer also demonstrates practical limitations: peritoneal-

dominant disease may yield variable ctDNA shedding into plasma, and early-stage disease may have ctDNA levels below reliable detection thresholds. As a result, although evidence supports clinical potential—especially in recurrence monitoring and resistance biology—routine decision-making algorithms based solely on ctDNA remain an area where institutions often proceed cautiously, aligning use with specific clinical questions rather than broad, unsupervised testing.

Endometrial cancer is a second domain where liquid biopsy is gaining traction, particularly because risk stratification and post-treatment surveillance remain challenging for subsets of patients. Contemporary endometrial cancer management increasingly incorporates molecular classification, and ctDNA could serve as a longitudinal companion to that classification by enabling detection of molecular relapse or by reflecting residual disease after surgery and adjuvant therapy. Early studies and emerging reviews suggest ctDNA may support prognostication and earlier detection of recurrence, but the overall evidence base is still smaller than in some other solid tumors, and the key unanswered question is not whether ctDNA can predict relapse—it often can—but whether acting on that information improves outcomes [3].

CONCLUSION

Liquid biopsy has reached an important transitional stage in gynecologic oncology. The technology can now deliver clinically useful molecular information in selected settings, particularly for genotyping in advanced disease when tissue is limited and for longitudinal monitoring in research-informed clinical pathways. Ovarian, endometrial, and cervical cancers each present distinct opportunities: ovarian cancer for treatment monitoring and resistance discovery, endometrial cancer for risk stratification and relapse prediction, and cervical cancer for tumor-specific viral DNA tracking.

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