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The Need for Early Detection of Chemotherapy Resistance in Ovarian Cancer

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ABSTRACT

Background: Ovarian cancer has a high mortality rate due to late stage detection and the development of chemotherapy resistance in ovarian cancer cells. Platinum based chemotherapy is initially very effective in treating ovarian cancer, but recurrence and treatment resistance are major problems that arise. Aim: This paper shows the importance of detecting ovarian cancer early to mitigate chemotherapy resistance with an emphasis on liquid biopsy, circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), and molecular biomarkers.

Method: By reviewing several papers on PubMed, NCBI, and clinical trial registries with keywords such as ovarian cancer, liquid biopsy, and chemotherapy resistance, information was gathered. Studies relevant to diagnostic tools, biomarkers, and chemotherapy mechanisms were analyzed and clinical trials were compared to evaluate the current applications of ctDNA and other liquid biopsy approaches.

Results: Liquid biopsies are minimally invasive and highly informative for not only early detection, but also monitoring chemotherapy resistance. Biomarkers involving BRCA1/2, TP53 are associated with resistance pathways based on research. Ongoing clinical trials are evaluating whether ctDNA can detect recurrence, treatment response, and residual disease earlier than conventional monitoring but these studies by themselves do not establish clinical benefit.

Conclusion: Liquid biopsy may complement conventional assessment because it could provide molecular information during and also after treatment. Further validation is needed to establish when these tests will be able to reliably identify clinically actionable resistance and be able to improve patient management.

KEYWORDS: *Ovarian Cancer, Chemotherapy Resistance, Liquid Biopsy, Early Detection, Circulating Tumor DNA, Circulating Tumor Cells, Gynecologic Cancer*

INTRODUCTION

Ovarian cancer is a type of gynecologic cancer which generally causes mortality because of a late stage diagnosis. Symptoms can include abdominal discomfort, bloating, and change in appetite which are

nonspecific, making it difficult to diagnose. Because of this, patients are usually diagnosed in advanced stages.

Current methods used to detect ovarian cancer include serum cancer antigen 125 (CA-125), transvaginal ultrasounds, imaging, and tissue biopsy. However, these methods are limited when it comes to early detection. Ultrasounds can identify abnormalities without knowing for sure if it is malignant while CA-125 levels can also be higher without the risk of cancer. CA-125 alone does not have enough sensitivity and specificity to be used as a population wide screen test. [1,2]

A different type of test, liquid biopsies, are being investigated as another approach. Liquid biopsies analyze tumor associated material found in bodily fluids such as ctDNA, CTCs, cell free RNA, proteins, and extracellular vesicles. Samples such as plasma, urine, cervical or vaginal specimens, and uterine lavage are being studied for early detection. [3,4]

This review mainly talks about the potential use of liquid biopsy to monitor tumor evolution and also investigate treatment resistance in patients who are already diagnosed with ovarian cancer. Platinum based chemotherapy and taxanes are important treatments, but some tumors grow even though the patient is getting treated. Molecular changes involving DNA repair, apoptosis, drug transport, and other pathways can contribute to resistance. [5] The central question of this review is: How can liquid biopsy approaches help monitor molecular changes associated with treatment resistance in ovarian cancer, and what evidence is needed before these approaches can guide clinical decisions?

METHODS

The methods used to compile this narrative literature review of liquid biopsy approaches for monitoring ovarian cancer after diagnosis was finding information on databases such as PubMed, ClinicalTrials.gov, and NCBI. Some search strategies used was using keywords such as ovarian cancer, liquid biopsy, circulating tumor DNA, circulating tumor cells, platinum resistance, PARP inhibitor resistance, treatment response, minimal residual, recurrence, BRCA reversion, extracellular vesicles, multiomics, and artificial intelligence. The dates around which these databases were searched is from July 2025 - December 2025. These studies were selected if they examined liquid biopsy methods, molecular biomarkers, treatment response, recurrence, minimal residual, or mechanism of platinum chemotherapy and PARP inhibitor resistance in ovarian cancer. The abstracts of the papers were read and if deemed relatable to the topic, they would be read fully to determine the usefulness for this paper.

LIQUID BIOPSY

Liquid biopsy is a minimally invasive technique which analyzes tumor associated material in bodily fluids. Unlike a tissue biopsy, a liquid biopsy can provide information about the tumor material from different areas of the body and can also be repeated throughout treatment. [3,4]

CIRCULATING TUMOR CELLS

Circulating tumor cells (CTCs) are cancer cells that detached from a primary tumor and entered into the bloodstream. They are helpful in detecting how likely the cancer is to spread and also how large the tumor is. CTCs can be detected by immunomagnetic separation and microfluidics, which will be very helpful in guiding treatment [6,7].

A challenge with CTC analysis is that CTCS are pretty rare in the bloodstream. Their detection varies depending on the isolation method and also the characteristics of the tumor cells. However, CTCs are being investigated as biomarkers for disease progression and treatment resistance. Recent reviews emphasized their potential for tumor heterogeneity and drug resistance but also acknowledge the technical challenges to isolate and characterize these cells. [6,7]

CIRCULATING TUMOR DNA

ctDNA are fragments of DNA that are released by tumor cells into the bloodstream. They carry tumor specific genetic information along with epigenetic alterations. In the case of ovarian cancer, ctDNA has been used for early detection, treatment monitoring, relapse prediction, and the detection of molecular alterations that are associated with treatment resistance. [4,8]

ctDNA can be detected using techniques like polymerase chain reaction (PCR), digital PCR, and next generation sequencing (NGS). A major advantage of ctDNA is that blood samples can be collected repeatedly which means changes in tumor biology can be monitored over time. [8]

However, there are limitations to ctDNA. Early stage tumors can release small amounts of tumor derived DNA into the bloodstream which causes the detection to be difficult. The biological variety between patients and the differences in laboratory methods also affects sensitivity and specificity. ctDNA is promising for a complementary tool, but more validation is needed before it can replace the conventional methods of ovarian cancer detection. [3,4,8]

CHEMOTHERAPY

Chemotherapy is a common way to treat ovarian cancer. Generally, platinum based drugs and taxanes are used to kill cancer cells. The platinum drugs damage the DNA of the cancer cells while taxanes stop cancer cells from pulling apart when they divide. Platinum and taxane chemotherapy is an important foundation of ovarian cancer treatment. [5]

Chemotherapy resistance can develop through multiple ways. One way is developed when DNA repair proteins start fixing the damage caused by platinum based drugs and taxanes. Damaged cells generally

die, but cancer cells do not die even after facing damage from chemotherapy. The cancer cells push the chemotherapy drugs out and the drug isn't enough to work to fight the cancer cells. Other ways resistance can develop is through apoptosis, drug transport, cellular signaling, and drug detoxification. These mechanisms allow cancer cells to survive treatment which would normally kill them. [5,9]

Epigenetic modifiers also play a role in resistance. DNA methylation, histone acetylation, and noncoding RNAs can alter gene expression without changing the DNA sequence. They can influence pathways involved in DNA repair, apoptosis, cell regeneration, and drug response. Due to different populations of cells having different genetic and epigenetic characteristics, the alterations may contribute to tumor heterogeneity and treatment resistance. [9,10]

BRCA1 AND BRCA2

BRCA1 and BRCA2 are important genes involved in homologous recombinant repair, a pathway which repairs certain types of DNA damage. Ovarian tumors with defective BRCA1/2 function may be sensitive to platinum chemotherapy. However, these mutations should not simply be classified as markers of chemotherapy resistance. In some patients, these tumors can acquire reversion mutations that restores BRCA function and homologous recombination repair. These reversions have been associated with acquired resistance to PARP inhibitors and can also affect the sensitivity to DNA damaging treatments. [11]

Serial ctDNA analysis was used to identify BRCA reversion and other molecular changes that are associated with developed resistance in patients with BRCA mutated ovarian cancer. These findings could help researchers monitor tumor evolution and changes with PARP inhibitor resistance. However, detection of a molecular alteration alone does not establish that changing treatment will improve the outcomes. [11]

TP53

TP53 is a tumor suppressor gene that is involved with cell cycle regulation, DNA damage responses, and apoptosis. TP53 mutations are really common in serous ovarian cancer and are important characteristics of the disease's molecular biology. [12]

However, TP53 mutations alone should not be considered as a definitive marker of chemotherapy resistance. Instead, their alterations can provide tumor specific information that will allow researchers to identify and monitor tumor derived DNA.

ERCC1

ERCC1 is involved with nucleotide excision repairs and has been investigated as a potential biomarker of platinum response. Because platinum chemotherapy causes DNA damage, researchers have examined whether or not increased DNA repair using ERCC1 can contribute to resistance. However, evidence collected remains inconsistent. Therefore, it should be considered as an investigation biomarker instead of a confirmative indicator or platinum resistance.

RECURRENCE AND MINIMAL RESIDUAL MONITORING

An early diagnosis is critical as delaying it can cause it to spread. As tumors grow, genetic and epigenetic changes also grow making clones in the tumor. These clones have traits which make them resistant and less sensitive to chemotherapy. [9] However, early detection does not directly prevent chemotherapy resistance. Instead, it allows treatment to begin earlier and monitors the disease closer before significant progression happens. After systemic treatment, serial ctDNA measurements may help investigators assess whether or not tumor material is detectable and if it appears again during the follow up.

Liquid biopsy offers more value by enabling repeated measurement of tumor associated changes during treatment. For example, ctDNA dynamics and emerging resistance mutations can provide earlier signals of progression than conventional imaging. [8,13] DNA methylation studies also support this approach because abnormal methylation patterns in cell free DNA can detect tumor associated changes even when other markers are limited. [14] However, earlier molecular detection does not mean that survival rates become higher. This depends on whether these findings can meaningfully guide treatment decisions which requires validation in prospective studies.

DETECTING CHEMOTHERAPY RESISTANCE

Liquid biopsy is particularly hopeful when identifying emerging chemotherapy resistance. Serial ctDNA analysis can track tumor evolution during treatment. In BRCA mutated ovarian cancer, ctDNA studies have identified multiple resistance mechanisms to PARP inhibitors such as restoration of homologous recombination, replication fork stabilization, altered survival pathways, target loss, and drug efflux. [11]

CTCs provide complementary information because they are intact tumor cells, allowing deeper analysis of tumor heterogeneity and resistance biology. [6,7] Extracellular vesicles also show potential. A 2025 study identified differences in EV associated proteins between platinum sensitive and platinum resistant ovarian cancer, including TMEM205 and CFH as candidate resistance markers. [15]

MULTIOMICS AND ARTIFICIAL INTELLIGENCE

Multiomics and AI tools help improve detection and also prediction of resistance. Multiomics is the combined analysis of genomics, transcriptomics, proteomics, metabolomics, and epigenomics and with AI, it is changing how ovarian cancer can be detected and monitored for chemotherapy resistance. AI does this by analyzing complex data that would be very difficult for humans to interpret. [16] Machine learning algorithms can identify small patterns in blood biomarkers and be able to tell if cancer is present or not and also the likelihood of developing chemotherapy resistance during treatment. Yet, there are still challenges to be faced. These AI technologies require much approval since they are still relatively new and are not very reliable yet. Approval is required in order to minimize risks such as overdiagnosis, false positives, and algorithmic bias.

CLINICAL TRIALS

A table below shows ongoing clinical studies pertaining to ctDNA and other liquid biopsy approaches in ovarian cancer that may be useful for further research. These trials do not establish clinical benefit.

Clinical Trial	ClinicalTrials.govID	Study Type	Main Application	Key Approach
CtDNA as a Novel Biomarker of Treatment Efficacy in Patients With Ovarian Cancer	NCT05027828	Prospective observational	Treatment efficacy and early recurrence monitoring	Serial plasma ctDNA during chemotherapy and PARP-inhibitor maintenance
Sequential Profiling of Tumor-Derived ctDNA in Advanced Ovarian Cancer (SPEED)	NCT06071286	Observational	Minimal residual disease, recurrence, and disease progression	Sequential ctDNA blood sampling
Circulating Tumor DNA Monitoring in Platinum-resistant Ovarian Cancer	NCT05976932	Prospective observational	Monitoring response to treatment in platinum-resistant disease	ctDNA analyzed by NGS and compared with imaging and CA-125
Circulating Tumor	NCT03691012	Prospective	Residual	Serial ctDNA collection

DNA as a Marker of Residual Disease & Response to Adjuvant Chemotherapy		multicenter	disease and recurrence	in stage I-IV ovarian, fallopian tube, and primary peritoneal cancers
Assessment of Minimal Residual Disease in Ovarian Cancer From ctDNA and Immune Repertoire	NCT03614689	Observational	Minimal residual disease and recurrence monitoring	ctDNA at diagnosis, during treatment, after treatment, and during follow-up

The NCT05027828 study is evaluating serial plasma ctDNA in patients with serous ovarian cancer receiving chemotherapy followed by PARP inhibitor maintenance. The study is specifically investigating whether ctDNA can predict treatment efficacy and detect recurrence earlier. [17]

The SPEED study, NCT06071286, is evaluating sequential ctDNA profiling in advanced ovarian cancer to determine whether or not ctDNA can detect minimal residual disease and early relapse. The study is currently listed as recruiting and is estimating their completion for 2026. [18].

NCT05976932 focuses specifically on platinum resistant ovarian cancer. The study is evaluating whether ctDNA can monitor response to pegylated liposomal doxorubicin and whether ctDNA findings correspond with imaging and CA-125 measurements. [19]

NCT03691012 is a prospective multicenter study examining whether detectable ctDNA after surgery or completion of chemotherapy is associated with subsequent recurrence. The study includes patients with stage I-IV epithelial ovarian, fallopian tube, and primary peritoneal cancers. [20]

The NCT03614689 study investigates the use of ctDNA and immune repertoire analysis to detect minimal residual disease in patients with ovarian cancer. The study collects blood samples at multiple points, including diagnosis, during treatment, after treatment, and during follow up. By monitoring these molecular changes over time, researchers can evaluate whether or not ctDNA can identify residual cancer or recurrence before it becomes clinically apparent. This study is relevant to the early detection of chemotherapy resistance because persistent or increasing tumor derived DNA may provide evidence of residual disease and tumor evolution before conventional methods detect progression. [21,22]

These studies can show that the clinical research landscape is moving towards using ctDNA not only just identifying cancer, but also for monitoring residual disease, recurrence, and treatment response. However, the existence of these studies does not establish that liquid biopsy is already clinically superior to

conventional monitoring. Their results will be important in determining whether biomarker guided monitoring can ultimately improve patient care.

FUTURE POSSIBILITIES

Gene therapy, immunotherapy, and nanotechnology are all possibilities in helping chemotherapy resistant patients. Gene therapy works to fix the defective genes in cancer. CRISPR Cas-9 is a technology which can work to fix mutations in tumor suppressor genes such as TP53 and BRCA 1 & 2. By fixing these gene functions, tumor cells could possibly be able to go through apoptosis, self programmed cell death, when it is damaged by chemotherapy. However, this is not an established method for overcoming chemotherapy resistance in ovarian cancer. [23]

Immunotherapy will use the body's immune system to target cancer cells. Specifically, in ovarian cancer, immune checkpoint inhibitors will block proteins such as PD-1 and PD-L1 which the tumors use to escape detection. When these checkpoints are inhibited, T-cells will be able to recognize and attack tumor cells. [24]

Nanotechnology is a way to deliver drugs precisely to tumor cells and minimize damage to healthy cells. Nanocarriers can encapsulate chemotherapy agents and direct them to the tumor site using tumor-specific markers. By using a targeted delivery, it can bypass drug efflux pumps which are a general mechanism of chemotherapy resistance. Early phase studies show that there is an improved drug accumulation in tumors and nanotechnology could play a role in overcoming chemoresistance. [24]

CONCLUSION

Ovarian cancer is usually lethal due to late diagnosis and emerging chemotherapy resistance. Current tools like CA-125 and imaging are important but are limited in early detection and for capturing molecular tumor changes. Liquid biopsies, using ctDNA, CTCs, and epigenetic markers help with earlier detection and also monitoring chemotherapy resistance. ctDNA can track tumor mutations and treatment response, and studies of BRCA reversion mutations serve as biomarkers of acquired resistance to PARP inhibitors. Ongoing clinical trials are testing whether ctDNA can detect minimal residual disease and relapse earlier than conventional methods, but it remains as a complementary tool due to low tumor DNA levels, tumor heterogeneity, and technical limitations. Future therapies such as gene editing, immunotherapy, and nanomedicine are being investigated for their potential ability to help with treatment resistance, but further research is still needed.

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