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Review

# MicroRNAs as prognostic markers in ovarian cancer

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ABSTRACT

Ovarian cancer (OC) is the most lethal gynecological malignancy among women. Over 70% of women with OC are diagnosed in advanced stages and most of these cases are incurable. Although most patients respond well to primary chemotherapy, tumors become resistant to treatment. Mechanisms of chemoresistance in cancer cells may be associated with mutational events and/or alterations of gene expression through epigenetic events. Although focusing on known genes has already yielded new information, previously unknown non-coding RNAs, such as microRNAs (miRNAs), also lead insight into the biology of chemoresistance. In this review we summarize the current evidence examining the role of miRNAs as biomarkers of response and survival to therapy in OC. Beside their clinical implications, we also discuss important differences between studies that may have limited their use as clinical biomarkers and suggest new approaches.



**Contents**



*Abbreviations:* OC, Ovarian cancer; OS, overall survival; miRNAs, microRNAs; HG-SOC, high-grade serous OC; TCGA, The Cancer Genome Atlas; SNPs, single nucleotide polymorphisms; PFS, progression-free survival; FFPE, formalin-fixed paraffin-embedded; EMT, epithelial-to-mesenchymal transition; OSE, ovarian surface epithelium; RNAi, RNA interference; siRNA, small interfering RNA; EVs, extracellular vesicles.

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## 1. Introduction

Ovarian cancer (OC) is the fifth most common cancer and the most lethal gynecological malignancy among women in the Western world, leading to 22.400 newly diagnosed cancer cases and over 14.300 deaths every year in the US (Siegel et al., 2013). Basically, this poor prognosis is due to (a) the insidious asymptomatic nature of this disease in its early onset, (b) the lack of robust and minimally invasive methods to detect the disease at an early stage, and (c) the acquisition of tumor resistance to chemotherapy.

After a suspicious physical examination, CA-125 blood test and transvaginal ultrasound screening methods are performed in order to diagnose OC. Nevertheless, the final diagnosis is still performed at the time of the surgery. At the time that OC is diagnosed when the disease is still confined to the ovaries (stage I), the 5-year survival rate exceeds 90%; unfortunately, only 15% of all patients are diagnosed at early stage. The majority of patients (80%) are diagnosed at stage III or IV presenting distant metastases and, despite high initial responsiveness to chemotherapy are observed among them, survival rates remain poor (Siegel et al., 2013). In advanced OC, chemotherapy resistance develops in most (70%) of patients during their treatment (Markman and Bookman, 2000). The majority of patients relapse within 2–3 years following primary chemotherapy and subsequent treatment after relapse is usually less effective than primary treatment. Platinum-resistant, recurrent or persistent disease patients are treated by a variety of agents including topotecan, doxorubicin, gemcitabine, paclitaxel, and/or docetaxel, or liposomal doxorubicin (Stein et al., 2013; Lawrie et al., 2013; Su et al., 2013; Polyzos et al., 2005). Unfortunately, over the last 30 years, no single agent has demonstrated clear superiority in this setting, and response rates are generally less than 20% (Siegel et al., 2013). One of the greatest impediments to improve response rates, and subsequent outcome for patients with OC, is the incomplete understanding of the molecular underpinnings of OC cell chemosensitivity/chemoresistance and afterwards the correct selection of the best treatment for each group of patients (Fig. 1).

Therefore, there is an urgent need to discriminate between patients who will or will not benefit from chemotherapy and this will probably have significant clinical implications in the management of OC. Moreover, identification of the molecular pathways involved in primary and acquired drug resistance will play a prominent role in the establishment of rational therapeutic approaches aimed to circumvent or retard the acquisition of the drug-resistant phenotypes. Recently, epigenetic mechanisms like DNA methylation, histone modification, and microRNA (miRNA) regulation have been associated with the resistance of cancer cells to chemotherapy (Zhang et al., 2008).

## 2. Molecular events related with poor prognosis in ovarian cancer

A considerable number of prognostic factors have shown to predict prognosis in OC. Stage, age, grade, performance status and residual disease remain the most important. As far as residual disease is concerned, the presence or absence of macroscopic residuum is the best discriminator of outcome (Hoskins et al., 1994). Currently, the definition of optimal cytoreductive surgery (or debulking surgery) most widely accepted is the definition of residual disease equal to 0 cm (Vergote et al., 2010). Cytoreductive surgery is an important part of the management of advanced OC either prior to or after combination with chemotherapy, based on platinum/paclitaxel (Vergote et al., 2010).

In the last decades there has been a considerable advance in our ability to interrogate the molecular events of cancer. Modern technologies (next generation sequencing, methylation arrays, etc.) have allowed us to better understand changes in gene expression, gene mutation, pathway activation and regulation. With the same goal OC has been classified into four major histologic subtypes (serous, mucinous, endometrioid, and clear cell), with serous being the most common histologic type (70% of total OC cases) (Koonings et al., 1989; Seidman et al., 2004). Current data indicate that each of these histologic types are associated with distinct morphologic features, genetic alterations and prognosis (Bast et al., 2009).

Recently, The Cancer Genome Atlas (TCGA) Research Network has analyzed messenger RNA (mRNA) expression, miRNA expression, promoter methylation and DNA copy number in 489

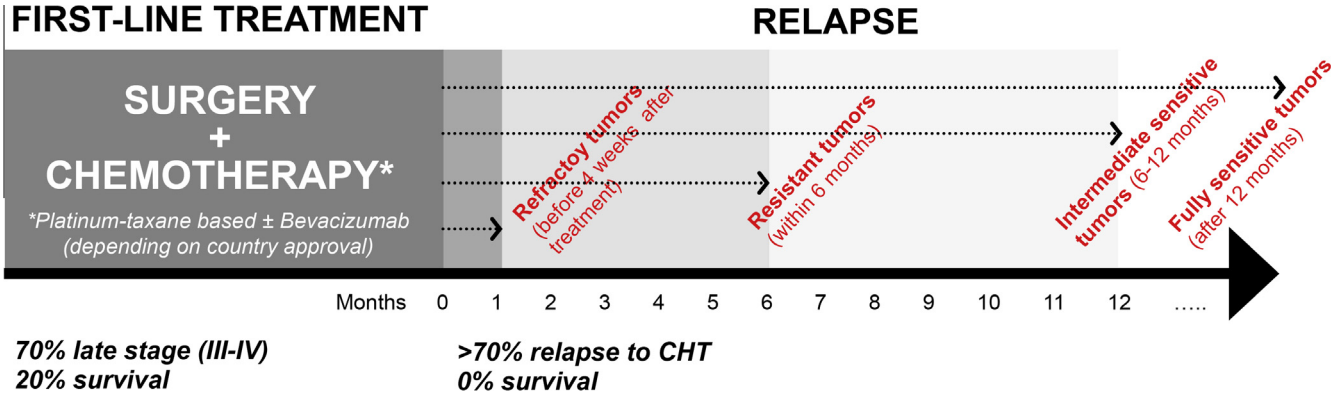


**Fig. 1.** Ovarian cancer outcome. Classification of ovarian cancer patients depending on their resistance/sensitivity to first-line treatment.