



Development of novel approaches to detect ovarian cancer recurrence

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Ovarian cancer is also known as the “silent killer” because this type of cancer spreads widely without the occurrence of any symptoms (1). Currently, ovarian cancer accounts for approximately 5% cancer deaths among women in the United States (2). Worldwide statistics from 185 countries indicated 295,414 new cancer cases and 184,799 deaths from this disease in 2018 (3). High-grade serous carcinoma is the most common histological type accounting for the majority of advanced ovarian cancers. This subtype is likely to be diagnosed at a later stage with large-volume ascites and peritoneal dissemination (1). Although only 20% of ovarian cancer cases can be detected at stage I or II by conventional examination, which is combined with serum carbohydrate antigen 125 (CA125) measurement, gynecological examination and transvaginal sonography, the prognosis of those patients is generally good with a 5-year overall survival rate of 90% and 70%, respectively. Nevertheless, patients with tumors spread throughout the abdominal cavity and further can be cured in less than 20% of cases due to the disease recurrence as a result of resistance to platinum chemotherapy (4). Once platinum-resistant recurrences are developed, only a few successful therapeutic options exist. Further chemotherapy treatments show responses in the range of 15% to 20% and a median progression-free survival rate of approximately 4 months (5). However, there are several novel drugs under development, and some have been tested in ongoing clinical trials to improve the poor outcomes of recurrent ovarian cancer patients (6,7). These novel agents might extend the lifetime of patients if treatment is started at an appropriate timing. While it remains unclear whether an earlier detection of

recurrent ovarian cancer can improve the overall survival rate of patients, they are given more time and more opportunities to receive such novel agents if recurrence is identified earlier. In that sense, the establishment of an early detection method for cancer recurrence would be definitely beneficial for patients.

Since the discovery of CA125 in 1981, it has been most extensively used not only to monitor the response to treatments but also to detect ovarian cancer recurrence. CA125 value reflects disease progression and is often increased at 2–5 months prior to the recurrence is clinically detected (8). The Society of Gynecologic Oncologists (SGO) recommendations described that the sensitivity and specificity of the CA125 level to detect a recurrence range from 62% to 94% and from 91% to 100%, respectively (9). For instance, Yang *et al.* reported that the area under the receiver operating characteristics curve (AUC) of the serum CA125 for diagnosing epithelial ovarian cancer recurrence was 0.897, and the sensitivity and specificity were 67.39 and 86.79% at a threshold of 35 U/mL (10).

Recent studies have revealed new biomarkers for predicting the relapse of ovarian cancer. One promising candidate is human epididymis protein 4 (HE4). Several studies have shown that HE4 is a useful biomarker for monitoring ovarian cancer treatment and recurrence (11). In addition, HE4 may complement CA125 in monitoring a patient's relapse. A recent clinical trial reported that HE4 can detect recurrent ovarian cancers with a 74% sensitivity and 100% specificity when HE4 levels exceed a threshold of 70 pM. Furthermore, the examination of HE4 plus CA125 improved overall sensitivity to 77% and specificity to

100% (12). Therefore, this combination may provide a better sensitivity for the detection of recurrent ovarian cancer than either marker alone.

Recently, a new generation of biomarkers, called “liquid biopsy”, has emerged alongside the development of the whole genome and RNA sequencing using next generation sequencing. The liquid biopsy includes microRNAs (miRNAs), circulating tumor cells (CTCs) and circulating tumor DNA (ctDNA). miRNAs are small (19–25 nucleotides) non-coding endogenously expressed RNAs. miRNAs downregulate protein expression of target genes by suppressing mRNA transcription. miRNAs have been found in the body fluids of different cancer types patients including ovarian cancer and several miRNAs have been proposed as biomarkers for recurrent ovarian cancers (13,14). Among miRNAs, the miR-200 family (miR-141, miR-200a, -200b and -200c, miR-429) has been extensively analyzed. For example, Gao *et al.* examined serum samples from 74 epithelial ovarian cancer patients and discovered that patients who had a high miR-200c level accomplished a significantly higher 2-year survival rate compared with the other group, whereas the low miR-141 patients displayed a significantly higher survival rate (15). Günel *et al.* showed that the serum expression of miR-1273g-3p was significantly downregulated in recurrent ovarian cancer patients compared with that of healthy controls groups. Serum miR-1273g-3p levels could distinguish between recurrent ovarian cancer patients and healthy controls, with an AUC of 0.7 (16). Two sources of tumor DNA can be noninvasively assessed in the circulation alongside with the progresses of techniques for identifying small quantities of DNA from small quantities of blood samples: ctDNA and CTCs. Pereira *et al.* collected tumor and serum samples at the time of surgery from 44 gynecological cancers including 22 ovarian cancer patients and showed that patient/tumor-specific mutations in the serum can be identified using a droplet digital PCR (17). They reported that ctDNA indicated the presence of a tumor at surgery with an AUC of 0.91, and that sensitivity and specificity were 81% and 99%, respectively. Six patients had detectable levels of ctDNA without apparent CT imaging results and were afterward identified to have tumors, suggesting the utility of ctDNA for the early detection of ovarian cancer recurrence. Li *et al.* collected whole blood from a total of 54 ovarian cancer patients including 24 primary patients and 30 recurrent patients (18). They defined CTCs as an EpCAM and DAPI positive, and CD45-negative feature and found that CTCs can be detected in 98.1% (53/54) of

the cases and that CTC-cluster is positivity correlated with platinum resistance. Thus, the expression level of CTCs can be proposed as a biomarker to predict recurrent ovarian cancer.

Kyriazi *et al.* described imaging modalities in a comprehensive review (19) and compared various modalities to evaluate therapy response, for the surveillance and detection of cancer recurrence including ultrasound (US), computed tomography (CT), positron emission tomography (PET)-CT, diffusion-weighted magnetic resonance imaging (MRI), dynamic contrast-enhanced MRI, and magnetic resonance spectroscopy (MRS). They concluded that CT has superior advantages including wide usefulness, high reproducibility, good cost-efficiency, and fast image scanning time; therefore, CT is the most routinely used imaging technique in the current clinical practice for the detection of ovarian cancer recurrence; however, its performance is sometimes insufficient for the discrimination of multifocal and low-volume disease. SGO recommendations described that CT scan can detect ovarian cancer recurrence at a sensitivity ranged from 40% to 93% and a specificity ranged from 50% to 98%, respectively (9). Recently, Danala *et al.* analyzed the feasibility of predicting the patients’ chemotherapeutic response using quantitative imaging landmarks computed from pre-treatment CT scan images (20). They reported an AUC value of 0.684 for overall prediction accuracy. The use of MRI showed equivalent detection rates to CT scans, while the increased costs limited its generalized use (21). Since CT scans sometimes lack the capability to detect the small size of recurrent tumors, PET-CT is recommended. The diagnostic accuracy rates approach a high of 95%, while the sensitivity and specificity vary from 45% to 100% and 40% to 100%, respectively (9). US has lower costs but a lower accuracy when compared to CT (22). Transvaginal sonography (TVS) has been shown to detect recurrence at a sensitivity between 45% and 85% and a specificity between 60% and 100% (9), although its accuracy is sometimes affected by the physician.

Imaging diagnosis with pattern recognition machine learning is making rapid progresses (23). Medical image analysis aims to help radiologists and clinicians to diagnose improve the treatment process. Deep learning (DL) mimics the human brain working, with a deep architecture composed of multiple layers of transformations. Computer-aided diagnosis can potentially make a differential diagnosis more accurately and less dependent on the skill of the observer. In addition to this, DL can extract the essential

Table 1 Some recent clinical studies to predict recurrent ovarian cancer

Reference	Source	Timing of analysis	Evaluable patients and lesions	Cut off value or specific features	Sensitivity (%)	Specificity (%)	AUC	Remarks
Salani (9), 2011	CA125	Postoperative	343	30 U/mL	86-94	91-100	NA	Summarized from 2 literatures
Yang (10), 2018	CA125	Preoperative	152	35 U/mL	67.4	86.8	0.89 (95% CI: 0.828–0.952)	
Schummer (12), 2012	HE4	Postoperative	34	70 pmol/L	73.5	100		
Pitteri (11), 2012	CA125, HE4	Postoperative	34	CA125 35 U/mL HE4 70 pmol/L	76.5	100	NA	
Gao (15), 2015	miR-200c miR-141	Preoperative	143	Relative quantity of the target miRNAs	miR-200c 72, miR-141 69	miR-200c 72, miR-141 72	miR-200c 0.79, miR-141 0.75	
Günel (16), 2018	miR-1273g	Preoperative	20	Log fold change value –1.406	NA	NA	0.7 (95% CI: 0.53–0.88)	
Pereira (17), 2015	ctDNA	Postoperative	44	10 copies/mL	81	99	0.80 (95% CI: 0.59–1.00)	
Gadducci (21), 2008	TVS	Postoperative	113	NA	45-85	60-100	NA	Summarized from 3 literatures
Salani (9), 2011	CT	Postoperative	358	Tumor size (5–10 mm)	79	84	0.8845	Summarized from 10 literatures
Danala (20), 2017	CT	Preoperative	91	Tumor characteristics	NA	NA	0.684	
Gadducci (21), 2008	MR	Postoperative	218	Tumor size	62-91	40-100	NA	Summarized from 7 literatures
Salani (9), 2011	PET-CT	Postoperative	452	18F-FDG dose (200–740 MBq)	91	88	0.9555	Summarized from 12 literatures
Fischerova (22), 2018	DL	Preoperative	245	Deep learning feature (16-dimension)	NA	NA	0.857 (95% CI: 0.815–0.897)	

TVS, transvaginal sonography; DL, deep learning.

characteristic of cancer imaging and provide a new imaging-based biomarker. Recently, Wang *et al.* (24) developed a novel DL network from preoperative CT images. They collected 8917 CT images from 245 patients with high grade serous carcinoma and trained a novel DL network to extract the prognostic biomarkers (DL feature). Kaplan-Meier's analysis successfully classified the two ovarian cancer patient groups with a high and low recurrence risk predicting a 3-year recurrence prediction with a power AUC of 0.772. Therefore, this DL feature showed a more

excellent prognostic value than clinical features, suggesting that DL can provide novel CT-based prognostic biomarkers for the prediction of ovarian cancer recurrence.

We are now at the turning point of the field of cancer biomarkers. Collectively, we summarized the current findings as *Table 1*. Novel biomarkers have the potential to overcome traditional biomarkers while their utilities have not been established by a randomized clinical trial with a large number of participants. Moreover, each novel biomarker alone may not be enough to predict recurrent

ovarian cancer. Therefore, the combination of conventional and novel biomarkers would be beneficial for predicting ovarian cancer recurrence and provide patients with more opportunities to receive more appropriate treatments.

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