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Serum Tumor Markers Combined with 18F-FDG PET/CT Volumetric Metabolic Parameters in the Prognosis of Ovarian Cancer

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Abstract

Ovarian cancer (OC) is the most fatal gynecological malignancy, and identifying reliable prognostic indicators can help guide therapeutic treatment. Various tumor marker-guided treatment regimens can considerably improve patient prognosis with a better understanding of the molecular underpinnings of ovarian cancer recurrence and metastasis. Fluorine-18-fluorodeoxyglucose Positron emission tomography/computed tomography (18F-FDG PET/CT) is a molecular imaging tool that provides anatomical and functional information about the tumor, and its volume-based metabolic parameters allow for quantifiable observation of ovarian cancer recurrence, prognosis, and therapeutic efficacy. The combined utilization of serological and radiologic markers has been found to provide increased clinical benefit. This article reviewed the predictive value of serum tumor markers and 18F-FDG PET/CT volumetric metabolic parameters for the prognosis of patients with ovarian cancer.

Keywords

Ovarian Cancer (OC), Tumor Markers, PET/CT, Volume Metabolic Parameters, Prognosis

1. Introduction

Ovarian cancer (OC) is the most common cause of mortality in gynecologic carcinoma patients [1] [2]. Updated data from the American Institute for Cancer Research indicate that in 2023, roughly 19,710 new cases of ovarian cancer were diagnosed, accounting for 1.0% of all cancer cases. The estimated number of fatalities is 13,270, with a 5-year relative survival rate of 50.0% [3]. The majority of OC patients benefit from cytoreductive surgery combined with platinum-based

chemotherapy [4]. However, 70% of patients will recur and metastasize within 5 years, and the prognosis is poor. Therefore, a practical approach that can more accurately predict a patient's prognosis for epithelial ovarian cancer (EOC) is necessary, and stratifying patients according to potential survival outcomes can have an impact on management and therapy choices.

The presence or variation in biomarker concentrations can be used to determine the nature and progression of the disease. Aside from the conventional tumor markers carbohydrate antigen 125 (CA125) and human epididymis protein 4 (HE4), other biomarkers have become the hotspots of current research. In recent years, 18F-FDG PET/CT, as an advanced molecular imaging tool, has demonstrated significant clinical value in the diagnosis, staging, recurrence monitoring, efficacy assessment, and prognosis prediction of patients with multiple cancers [5]. Metabolic tumor volume (MTV), which is a volume measurement of tumor cells with high glycolytic activity, and total lesion glycolysis (TLG), which is the product of metabolic tumor volume (MTV) and mean standardized uptake value (SUV mean) of the lesion, both measure the overall change in tumor glycolysis. Additionally, WB-MTV and WB-TLG represent the sum of the metabolic burden of all lesions throughout the body, providing maximum multidimensional information of the lesions [6].

2. Serum Tumor Markers and Prognosis of Ovarian Cancer

2.1. CA125

CA125 is the most characteristic of the several ovarian cancer indicators. A vast number of researchers have done multiple studies on the role of CA125 in the prognosis of ovarian cancer, with promising results. A meta-analysis of 23 articles on the relationship between pretreatment CA125 levels and overall survival (OS) and progression-free survival (PFS) in ovarian cancer patients found that elevated pretreatment CA125 levels were significantly associated with a poor prognosis in ovarian cancer patients [7]. A prospective study by Chan *et al.* found that patients with early-stage, high-risk epithelial ovarian cancer who had normal baseline CA125 levels fared better in terms of survival [8]. Apart from focusing on the prognostic significance of CA125 concentration values, many academics have focused on the dynamic changes of CA125. Timmermans *et al.* [9] investigated perioperative CA125 alterations and found that patients with an 80% decrease in CA125 levels had a better OS than patients with a 50% decrease (HR = 0.45, 95% CI = 0.36 - 0.57). The study by Liao *et al.* [10], on the other hand, focused on OC patients who underwent surgery followed by chemotherapy, and the findings suggested that OC patients with a CA125 normalization time of more than 60 days had a poor prognosis. Furthermore, some authors have introduced the concept of CA125 half-life, demonstrating that it is an independent risk factor [11].

2.2. HE4

Human epididymal protein 4 (HE4), as the name suggests, was first discovered

in human epididymal epithelial cells. Compared with CA125, HE4 has similar sensitivity and higher specificity and is thought to be one of the more promising novel serum biomarkers for the diagnosis, monitoring, and prognosis of a variety of diseases [12] [13] [14]. Salminen *et al.* [15] performed a prospective study with 143 patients on a connection between HE4 concentrations at first recurrence and OS in high-grade serous ovarian cancer (HGSOC), indicating that HE4 serum concentrations > 199.20 pmol/l were substantially associated with poorer OS. This reveals that HE4 is an obtainable biomarker in the therapy monitoring and prognostic classification of HGSOC patients. An experiment was conducted to determine whether preoperative HE4 levels could predict death in OC patients, and it was discovered that preoperative serum HE4 levels were strongly related to mortality [16]. As an ovarian cancer promoter, HE4 is a valuable prognostic factor that may one day serve as a treatment target for the disease.

2.3. MicroRNAs (MiRNAs)

MicroRNAs (MiRNAs), a type of single-stranded short endogenous non-coding RNA (SncRNA), have recently become a research hotspot, with many scholars doing macroscopic and microscopic investigations on them. MiRNAs might regulate the expression of PI3K/Akt, WNT/-catenin, mTOR, MAPK, and EGFR pathways relevant to ovarian cancer and are implicated in carcinogenesis and progression, according to the findings [17] [18] [19]. Serum MiRNA levels are linked to a number of clinical disorders and can be used to predict OC prognosis [20] [21]. Yoshida *et al.* collected 210 pretreatment serum miRNA profiles from 175 HGSOC patients. MiR-1908-5p, miR-6727-5p, and miR-6850-5p were poor predictors of PFS, while high expression of miR-187-5p and miR-6870-5p was associated with poorer OS and PFS. Based on the expression data of miRNAs, the study also calculated prognostic indices for OS and PFS and determined that both indices were independent poor prognostic indicators (hazard ratios of 2.343 and 2.357 for OS and PFS, respectively) [22]. Suzuki *et al.* [23] studied patients with ovarian clear cell carcinoma (OCCC) and screened miR-150-3p, miR-3195, and miR-7704 for association with PFS and OS. Additionally, high expression of miR-200a and miR-200c was linked to a shorter survival time in EOC patients [18]. In summary, serum miRNAs offer significant potential as predictive biomarkers for patients with ovarian cancer, and further studies are necessary for their early clinical application.

2.4. CtDNA

Circulating tumor DNA (CtDNA) is a genetically modified DNA that not only has the same genetic alterations and epigenetic information as tumor tissue, but it can also be recovered from plasma or serum using non-invasive procedures [24] [25]. Beyond that, it can overcome the heterogeneity of tumors and reflect the body's tumor load, thus reflecting the patient's condition in a dynamic and

timely manner. Studies on CtDNA as a predictive factor in ovarian cancer have gained prominence in recent years; however, there are still significant research gaps. In a recent study, CtDNA samples taken from ovarian cancer patients before and after surgery as well as throughout ongoing surveillance were evaluated [26]. The findings demonstrated a strong negative correlation between a reduction in RFS and the presence of ctDNA in patients' plasma during surveillance (both at individual time points and longitudinally). In addition, a study by Chao *et al.* [27] focused on the presence of ctDNA mutations in ovarian cancer and showed that the presence of ctDNA mutations after surgery was an independent predictor of poorer PFS and OS.

2.5. aHIF

The concept of tumor microenvironment has received much attention in recent years, and from this point, the important role played by exosomes in the tumor microenvironment has been derived. Circulating serum exosome aHIF is a long-stranded non-coding RNA that inhibits apoptosis in epithelial ovarian cancer (EOC) by activating the mitochondrial apoptotic pathway under hypoxic conditions, thereby promoting tumor growth [28]. Tang *et al.* [29] proposed that preoperative serum aHIF was linked with OS independently in ovarian cancer.

3. Combination of Biomarkers and Ovarian Cancer Prognosis

There are studies being conducted at the national and international levels that focus on the combined use of biomarkers, the more well-known ones being HE4 and CA125, in addition to examining the predictive significance of individual tumor indicators [30]. In addition, the combination of novel biomarkers has been used to great advantage. As mentioned in an article by Nie *et al.* [31], the combination of serum DKK3 and circulating CD133 cells can provide a reliable prognosis for OC patients.

4. 18F-FDG PET/CT Volumetric Metabolic Parameters and Ovarian Cancer Prognosis

One of the significant improvements in diagnostic imaging in recent years has been the development and deployment of picture fusion technologies. PET/CT is a new imaging device that combines two advanced imaging technologies, PET (functional metabolic imaging) and CT (anatomical structure imaging), in an organic way. The mechanism is to inject trace amounts of positron tracer into the human body, then use a special in vitro probe (PET) to detect the distribution of these positrons in each organ of the body, and then use computed tomography to display the physiological and metabolic functions of the major organs of the human body. CT technology is also used to precisely localize the distribution of these nuclides, so that this machine combines the benefits of both PET and CT. 18F-FDG PET/CT uptake as a tumor glucose metabolism marker is widely utilized for ovarian cancer recurrence monitoring and prognosis prediction

and is a viable imaging test supported by ENAM recommendations.

4.1. Pretreatment 18F-FDG PET/CT

Ovarian cancer spreads metastatically in three ways: continuously through the peritoneum, through lymphatic drainage, and through the bloodstream. Pre-treatment 18F-FDG PET/CT can help assess the extent and severity of disease involvement. Pre-treatment PET/CT parameters for 22 patients with ovarian clear cell carcinoma (OCCC) were obtained using a fixed ratio technique by Ye *et al.* [32]. The threshold SUV to depict MTV was defined as 40%, 50%, or 60% of SUVmax. According to the findings, higher MTV40, TLG40, TLG50, and TLG60 have shorter PFS and OS. Yamamoto *et al.* [33], on the other hand, conducted a study in ovarian cancer patients treated with cytopenia followed by adjuvant platinum-based chemotherapy, and the findings suggested that the pretreatment 18F-FDG PETCT metabolic parameters MTV and TLG (particularly TLG) could serve as potential predictors of recurrence.

4.2. Post-Treatment 18F-FDG PET/CT

Ovarian cancer has multiple pathological kinds and a high post-treatment recurrence rate. Post-treatment 18F-FDG PET/CT can successfully monitor tumor recurrence and metastasis. The study by Kim *et al.* [34] included 56 patients with ovarian epithelial carcinoma who underwent 18F-FDG PET/CT scan at first recurrence, and the optimal threshold values for SUVmax, WB-MTV, and WB-TLG were determined by statistical analysis and were 14, 92, and 332, respectively; the 2-year Post-relapse survival (PRS) rate was estimated to be 80% for patients with low WB-MTV and low WB-TLG, while the 2-year PRS rate was 14% for patients with high WB-MTV and high WB-TLG; clearly, both WB-MTV and WB-TLG were important factors affecting the prognosis of patients. Similarly, increased TLG60 (60% of SUVmax as the SUV threshold) was found to be a negative predictor of OS in another study of 31 patients with OCCC who obtained PET/CT scans at the time of the first recurrence [35]. In a prospective observational trial, Vallius *et al.* [36] performed PET/CT in 29 patients with inoperable ovarian cancer before and after neoadjuvant chemotherapy (NACT) and concluded that post-treatment MTV and MTV reduction were associated with PFS.

The preceding study confirmed the importance of 18F-FDG PET/CT volumetric metabolic parameters in ovarian cancer prognosis, although it has certain drawbacks. For one thing, the best measurement methods and optimal threshold values of the quantitative parameters MTV and TLG were not unified; second, the volume-based parameters did not distinguish the location of recurrence or metastasis; and the prognostic value of MTV and TLG is likely to be stratified based on their anatomical location because metastasis at different sites has different effects on patients' prognosis.

5. Combination of 18F-FDG PET/CT and Tumor Markers

The combination of the imaging index 18F-FDG PET/CT and serum tumor markers to evaluate the prognosis of ovarian cancer patients has received little attention and is largely limited to the identification of recurrent metastases. Sun *et al.* [37] reviewed the data of 69 OC patients with suspected tumor recurrence and metastasis after standard treatment, including CA125, HE4, and 18F-FDG PET/CT. Analysis showed that the sensitivity and specificity of PET/CT combined with serum CA125 and HE4 for diagnosis were 100.00% and 100.00%, respectively. The SUVmax of recurrent metastatic lesions was significantly and positively correlated with serum CA125 and HE4 levels. The study also did not involve volume-based parameters of PET/CT. And Glickman's study linked serum HE4 and CA125 concentrations to tumor burden in patients with advanced high-grade EOC as assessed by 18F-FDG PET/CT volumetric metabolic parameters [38]. According to the results of the 66-patient study, WB-MTV and WB-TLG were significantly correlated with serum CA125 and HE4 concentrations, with the strongest correlation between HE4 and WB-MTV40 ($r = 0.62$), especially in the peritoneal metastasis subgroup, where the Pearson correlation coefficient between MTV40 and HE4 was 0.61. Studies can be actively done to investigate the combined predictive value of these three on the prognosis of patients with OC based on the correlation of volumetric metabolic parameters measured by 18F-FDG PET/CT with CA125 and HE4 and their combined application value in detecting recurrent metastasis.

Besides, one investigator explored the value of the combined use of CA125 and 18F-FDG PET/CT in the prognosis of ovarian cancer. Budak *et al.* [39] divided patients into four categories based on PET and CA125 results and then counted the mean OS time in each group, revealing that the OS of the group positive for both CA125 and PET was considerably shorter than that of the group negative for both. This suggests that in clinical practice, the management of patients can be optimized by combining CA125 and PET/CT findings.

6. Summary and Prospect

Overall, the capability of multiple tumor markers and 18F-FDG PET/CT volumetric parameters as prognostic factors for OC can help identify patients with poor prognosis who would benefit from any kind of additional or different treatment, or closer follow-up. In clinical practice, CA125 and HE4 are more routine serum tumor markers. Future research can take CA125, HE4, and PET/CT as a starting point to explore the predictive value of the combination of the three on the prognosis of patients with ovarian cancer in different states (post-treatment, pre-treatment, first recurrence), with the aim of being able to guide the treatment and follow-up of patients. Further, for some novel serum tumor indicators that have not been commonly utilized in clinical practice, prospective, multicenter studies can be actively conducted with the perspective of early clinical application.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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