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New Progress of CA125 Surveillance in Diagnosis and Treatment of Ovarian Cancer

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Abstract

The fatality rate of ovarian cancer (OC) is the highest, and the 5-year survival rate is only 50.8%. For more than 40 years, CA125 has been the most concerned and widely used biomarker of OC in clinical practice. In recent years, many researchers have proposed a reliable strategy of multiple markers combined with CA125 to screen OC to make up for the lack of accuracy of CA125, redefine the biochemical recurrence threshold of CA125, and use mathematical model scores to provide help for the feasibility of treatment and survival prognosis. To fully understand the role of CA125 in OC screening, initial treatment, and recurrence prediction, and summarize the limitations of CA125, this review has summarized the new progress of CA125 in the diagnosis and treatment of OC in recent years which can also provide a reference for clinicians.

Keywords

CA125, Epithelial Ovarian Cancer

1. Introduction

Ovarian cancer (OC) is the third most common malignant tumor of the female reproductive tract, with a 5-year survival rate of only 50.8% [1]. There were 313,959 new cases of OC in the world in 2020, and 207,252 women died of OC worldwide [2]. The 5-year survival rate of patients with early stage of OC (FIGO I and II) is about 92%, while that of patients with advanced OC (FIGO III and IV) is only 29% [3]. Many biomarkers of OC have become popular research topics, among these biomarkers, CA125 plays the most important role in the screening, monitoring, and treatment of OC. CA125, also known as carbohydrate antigen 125, is a high molecular mucinous glycoprotein found on the surface of OC cells. It is quantitatively detected in the serum of patients with OC. In 1981, Bast

described CA125 for the first time [4]. In 1983, CA125 was first proposed as a tumor marker for the diagnosis of epithelial ovarian cancer (EOC) [5]. The common measurement of CA125 is the electrochemiluminescence immunoassay method (ECLIA), and the reference interval of serum CA125 detection may be different due to different methods, instruments, and reagents. Each laboratory should establish its reference interval according to reagent instructions and clinical practice; however, most of them use 35 U/ml as the threshold of serum CA125. CA125 was positively correlated with tumor load and FIGO stage, which can be reflected that serum CA125 levels increased in 50% of patients with early OC and 92% of patients with advanced OC [6]. Since CA125 was used in the clinical diagnosis and treatment of OC, its research on OC screening, efficacy monitoring, and recurrence prediction has been continuously deepened. Up to now, as the most representative biomarker of OC, CA125 may still have great potential value to be explored. This review aims to summarize the new progress of CA125 in the diagnosis and treatment of OC in recent years and provide clinicians with guidance strategies for reference.

2. CA125 Screening for Ovarian Cancer

Patients with early stage have few symptoms, and a series of non-specific symptoms will appear with the progress of the disease, including abdominal distension, abdominal pain, frequent urination, urgent urination, and so on. To advanced ovarian cancer, there may be significant weight loss and intestinal obstruction [7]. CA125 is one of the biomarkers used to monitor EOC. It has been used to screen patients of OC in general women and to distinguish malignant ovarian diseases from benign ovarian diseases. A variety of tumor biomarkers, imaging examination, and risk of ovarian malignancy algorithm (ROMA) are the focus of early diagnosis of OC. ROMA index makes up for the deficiency of the single use of CA125 and reduces missed diagnosis: compared with the single use of CA125, ROMA improves the sensitivity of identifying ovarian cancer from benign gynecological diseases. For every 10 patients with OC, ROMA could detect one more missed diagnosis of patients with OC caused by the single use of CA125. In addition, some related studies pointed out that the sensitivity of ROMA in identifying FIGO I and II of malignant ovarian tumors was improved by 10% compared with the single use of CA125. However, the performance of CA125 in postmenopausal women was better than that of ROMA and HE4: in the study by Van Gorp, the performance of ROMA and HE4 did not improve the diagnosis of OC [8]. Compared with CA125, ROMA performed better in premenopausal women, which may be because the HE4 of premenopausal women in benign diseases did not increase [9].

Many physiological factors would affect the serum concentration of CA125. Pauler analyzed the factors leading to CA125 fluctuations in healthy women. African and Asian women, caffeine intake, smoking, and post-hysterectomy CA125 levels were lower, among which race was an independent factor affecting

CA125 levels [10]. Pelvic and abdominal inflammatory stimulation is related to the increase of CA125 level, so CA125 can be used as routine monitoring for the diagnosis of moderate and severe endometriosis [11]. Excessive adipose tissue is related to the increase in CA125 level. Obese women lose weight successfully after laparoscopic sleeve gastrectomy, and the CA125 level decreases significantly [12]. In addition, elevated CA125 was also observed in heart failure, liver cirrhosis, and coronary heart disease [13]. In the Moss study, 80% of women with elevated CA125 levels were healthy and without OC [14]. Therefore, there is a high false positive rate in screening OC with CA125, which may bring unnecessary psychological burden to healthy women.

To improve the accuracy of CA125 diagnosis, many studies began to explore the combination of CA125 and other biomarkers for screening. Many studies have shown that human epididymal protein 4 (HE4) is more specific and sensitive than CA125 in diagnosis [15] [16]. However, the level of HE4 increases with age, and the level of HE4 in postmenopausal women is often higher. The reason is that HE4 is more effective in premenopausal women and CA125 is better in postmenopausal women [17]. CA125 combined with HE4 is still the most effective biological diagnostic tool for OC [18]. Besides, a multivariate index of five markers (CA125, transferrin, transthyretin, apolipoprotein AI, and beta 2 microglobulin) [19], second-generation multivariate index of five new markers (CA125, transferrin, apolipoprotein AI, follicle-stimulating hormone, and HE4) [20], symptom index of several non-specific symptoms (abdominal pain, abdominal distension, enlarged abdominal circumference, difficulty in eating or fast reading fullness more than 12 times a month) [21], and multiple markers (CA125, CA72-4, CA15-3, M-CSF) combined with artificial neural network [22] have been reported to improve the accuracy of diagnosis of CA125. Multiple strategies of combining CA125 with other biomarkers can improve the ability to screen for OC, but the cost and economic benefits of CA125 in postmenopausal women are still better than most new tumor markers.

3. CA125 with the Primary Treatment of Ovarian Cancer

There were differences in the expression of CA125 in different histopathological subtypes of OC. The expression of CA125 was higher in serous tumors and lower in mucinous tumors [23]. Compared with other subtypes, CA125 expression is higher in high-grade serous carcinoma (HGSC) and endometrioid carcinoma [24]. According to the different developmental characteristics and prognosis of different subtypes of EOC, the theory of the dualistic mechanism of OC [25] [26] has been gradually accepted. Type I of OC develops gradually from borderline tumors, and patients are usually younger and often at an early stage (FIGO I and II). The level of CA125 in patients with type II of OC was significantly higher than that in patients with type I, and the fluctuation of CA125 in type II was more severe than that in type I [27]. LU measured 14 biomarkers of OC in serum. CA125 had the highest recognition in type II patients when compared with

the healthy control group [27].

In recent years, the use of mathematical modeling in the initial stage of disease in CA125 to guide treatment decisions and predict survival has become a hot spot in the field of OC. Through Logistic regression and Cox regression analysis, multiple prediction indicators were integrated into the Nomogram which represented that a scale chart was used to visualize the prediction model. Peng collected the clinical data of 2465 patients with HGSC to construct a line chart to predict overall survival (OS) and cancer-specific survival (CSS) [28]. Clinicians can use this model to evaluate the prognosis of patients. Another mathematical model directly uses CA125 kinetic parameters to calculate the extent of CA125 decline, which has another name—CA125 elimination rate constant K (KELIM score). Colomban reviewed and evaluated the data of 2868 patients with OC in three randomized trials [29]. The predictive index of the KELIM score for PFS and OS was higher than that of the GCIG response [29]. KELIM can be used as an early sensitive marker for the initial treatment of OC. You proposed that the KELIM score calculated during neoadjuvant chemotherapy (NACT) can predict the probability of satisfactory tumor reduction during interval debulking surgery (IDS), which is an important parameter for IDS decision-making [30]. KELIM is strongly associated with the likelihood of complete IDS, subsequent platinum-free interval, progression-free survival, and overall survival, along with the efficacy of maintenance treatment with bevacizumab or veliparib [31]. Moreover, it could be used to identify the patients with poorly chemosensitive diseases, who will be the best candidates for innovative treatments meant to reverse chemoresistance, such as cell cycle inhibitors or immunotherapy [31]. At present, there are retrospective studies related to KELIM, and there is still a lack of large-scale prospective random studies to confirm the value of KELIM. Clinicians can get patients' KELIM scores through online access and calculators, which can provide help with surgical feasibility and chemotherapy strategies.

4. CA125 with Recurrent Ovarian Cancer

25% of patients with early stage and more than 80% of patients with advanced ovarian cancer would relapse [32]. The 5-year and 12-year survival rates of recurrent OC were lower than 30% and 5%, respectively [33]. The patients were followed up after the initial treatment, the follow-up including physical examination, imaging examination, and tumor marker monitoring. About 80% to 90% of relapses can be diagnosed by physical examination and serum CA125 [34]. CA125 indicates the remission and recurrence of the disease. The postoperative serum CA125 concentration higher than 35 U/ml may indicate that there are residual lesions or are not sensitive to chemotherapeutic drugs after tumor reduction. During the actual follow-up, in the absence of imaging evidence and clinical recurrence evidence, most patients with EOC would have a simple increase in tumor markers. Some scholars call this "Biochemical Relapse". The average interval between the end of initial treatment and the occurrence of Biochemical

Relapse in EOC patients was 10.8 months [35], and the progression of Biochemical Relapse to clinical relapse was about 2 to 5 months [32]. In 2011, The International Group of Gynecological Oncology Cooperation (GCIG) defined the standard of CA125 recurrence: CA125 increased to 2 times the lowest value with persistently elevated levels ≥35 U/ml after primary treatment, or CA 125 increased to 2 times that of 35 U/ml with CA125 levels fell to 35 U/ml after primary treatment [36]. It is also pointed out that both RECISTI 1.1 and CA125 criteria should be used to evaluate the progression or recurrence of OC [36].

For many years, many clinicians have regarded only the increase of CA125 as the basis for starting secondary recurrence treatment in the absence of imaging recurrence and clinical recurrence evidence. In the study of Rustin, patients with elevated CA125 and no evidence of clinical recurrence were included in the "early treatment group", and patients with elevated CA125 and clinical evidence of recurrence were included in the "delayed treatment group" [35]. It was found that the early treatment group had no obvious survival advantage but decreased the quality of life of the patients [35]. As available data show that chemotherapy does not benefit from survival immediately after Biochemical Recurrence, the NCCN guidelines recommend that treatment be postponed until clinical recurrence [37].

However, there were still some patients with asymptomatic recurrence of CA125 within the normal range (<35 U/ml). Unpublished data from the first affiliated Hospital of Chongqing Medical University show that 19.8% of patients with platinum-sensitive recurrent (PSR) serous ovarian cancer had imaging recurrence when the CA125 level was lower than 35 U/ml. In an Italian retrospective study, only 23.3% of the 331 patients with asymptomatic recurrence were diagnosed with CA125 alone [38]. Persistent CA125 levels lower than 35 U/ml can not completely rule out the risk of recurrence, because the critical value of 35 U/ml is not sensitive enough. The critical value of CA125 to define OC recurrence has been questioned. With the continuous development of precision medicine, imaging examination can find smaller lesions, which represents that relapse lesions can be found at lower CA125 levels than 35 U/ml. To overcome this defect, many studies have begun to adjust the threshold of CA125 to monitor the recurrence of OC. Wang found that the increase of CA125 to 1.68 times the lowest value can be used as an indicator of recurrence in patients with complete release of OC after initial treatment [39]. Levy proposed that the elevation of CA125 to 20 U/ml was an important predictor of recurrence [40]. Qin Xue suggested that the lowest value of CA125 ≥ 15 kU/L after initial treatment predicted early recurrence of OC [41]. Although there have been many studies to explore the relationship between CA125 and recurrence in recent years, the conclusions were still inconsistent. The critical value of OC recurrence defined by CA125 is still a prospective large sample trial to verify.

In addition to exploring the relationship between CA125 and Biochemical Recurrence, CA125 levels could also determine when to conduct imaging evalu-

ation, improve the possibility of optimal secondary tumor reduction, and predict survival time. Giuliani suggested that a CT examination should be performed in time to evaluate recurrent lesions when the level of CA125 was higher than 10.5% [42]. Qin Xue found that when CA125 increased 3 times in a row within the normal range (within 35 kU/L) after initial treatment, an early recurrence should be confirmed by timely imaging examination [41]. A French multicenter study suggested that a minimum value of CA125 lower than 20 kU/L was closely associated with longer OS and disease-free survival (DFS) [43]. Fleming suggested that twice the lowest value of CA125 appeared for the first time during follow-up after initial treatment, and that every week delay resulted in a 3% increase in the probability that secondary cytoreduction surgery did not reach R0 [44]. Local micro-recurrence, local micrometastasis, micro-lymph node metastasis, and isolated tumor cells may cause fluctuations in serum CA125 levels. However, the tumor size is too small to be detected by imaging or physical examination. The degree of CA125 fluctuation provides substantial evidence for imaging evaluation and secondary tumor reduction and provides the possibility of finding potential recurrence and appropriate timing of operation for patients with OC.

5. Conclusion

CA125 plays an important role in the screening, initial treatment, and recurrence prediction of OC. It is the most concerned and widely used biomarker in clinical practice. However, due to the high false positive rate and false negative rate of CA125, many researchers have proposed a reliable strategy for screening OC with multiple markers combined with CA125. Such strategies with low maneuverability, poor economic applicability, and other factors, are limited with a lack of clinical application value. 35 U/ml should not be regarded as the absolute critical value of recurrence estimated by CA125. There is still a risk of recurrence when it is lower than 35 U/ml. At present, the conclusion of the researchers is still not unified, and a large sample prospective trial is still needed to define the recurrence threshold of CA125. In addition, CA125 can be used as a predictor of treatment strategy and prognosis. The decreasing rate and trend of CA125 after surgery and chemotherapy the mathematical model was used to calculate the score to provide help for the feasibility of treatment and survival prognosis. To sum up, as a representative biomarker of OC to benefit most patients with OC, CA125 still has great scientific research and clinical potential, which needs more attention and energy to explore.

Conflicts of Interest

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

References

[1] Title of Cancer Stat Facts: Ovarian Cancer.

https://seer.cancer.gov/statfacts/html/ovary.html

[2] Sung, H., Ferlay, J., Siegel, R.L., Laversanne, M., Soerjomataram, I., Jemal, A. and Bray, F. (2021) Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Morta lity Worldwide for 36 Cancers in 185 Countries. *CA*: *A Cancer Journal for Clinicians*, **71**, 209-249. https://doi.org/10.3322/caac.21660

[3] Siegel, R.L., Miller, K.D. and Jemal, A. (2019) Cancer Statistics, 2019. *CA: A Cancer Journal for Clinicians*, **69**, 7-34. https://doi.org/10.3322/caac.21551

[4] Bast Jr., R.C., Feeney, M., Lazarus, H., Nadler, L.M., Colvin, R.B. and Knapp, R.C. (1981) Reactivity of a Monoclonal Antibody with Human Ovarian Carcinoma. *The Journal of Clinical Investigation*, **68**, 1331-1337. https://doi.org/10.1172/JCI110380

[5] Bast Jr., R.C., Klug, T.L., St John, E., Jenison, E., Niloff, J.M., Lazarus, H., Berkowitz, R.S., Leavitt, T., Griffiths, C.T., Parker, L., Zurawski Jr., V.R., and Knapp, R.C. (1983) A Radioimmunoassay Using a Monoclonal Antibody to Monitor the Course of Epithelial Ovarian Cancer. *The New England Journal of Medicine*, **309**, 883-887. https://doi.org/10.1056/NEJM198310133091503

[6] Van Haaften-Day, C., Shen, Y., Xu, F., Yu, Y., Berchuck, A., Havrilesky, L.J., Hacker, N.F., *et al.* (2001) OVX1, Macrophage-Colony Stimulating Factor, and CA-125-II as Tumor Markers for Epithelial Ovarian Carcinoma: A Critical Appraisal. *Cancer*, **92**, 2837-2844. https://doi.org/10.1002/1097-0142(20011201)92:11<2837::AID-CNCR10093>3.0.CO;2-5

[7] Jelovac, D. and Armstrong, D.K. (2011) Recent Progress in the Diagnosis and Treatment of Ovarian Cancer. *CA*: *A Cancer Journal for Clinicians*, **61**, 183-203. https://doi.org/10.3322/caac.20113

[8] Van Gorp, T., Cadron, I., Despierre, E., Daemen, A., Leunen, K., Amant, F., Timmerman, D., De Moor, B. and Vergote, I. (2011) HE4 and CA125 as a Diagnostic Test in Ovarian Cancer: Prospective Validation of the Risk of Ovarian Malignancy Algorithm. *British Journal of Cancer*, **104**, 863-870. https://doi.org/10.1038/sj.bjc.6606092

[9] Chan, K.K., Chen, C.A., Nam, J.H., Ochiai, K., Wilailak, S., Choon, A.T., *et al.* (2013) The Use of HE4 in the Prediction of Ovarian Cancer in Asian Women with a Pelvic Mass. *Gynecologic Oncology*, **128**, 239-244. https://doi.org/10.1016/j.ygyno.2012.09.034

[10] Pauler, D.K., Menon, U., McIntosh, M., Symecko, H.L., Skates, S.J. and Jacobs, I.J. (2001) Factors Influencing Serum CA125II Levels in Healthy Postmenopausal Women. *Cancer Epidemiology, Biomarkers & Prevention*, **10**, 489-493.

[11] Hirsch, M., Duffy, J., Davis, C.J., Nieves Plana, M., Khan, K.S. and International Collaboration to Harmonise Outcomes and Measures for Endometriosis (2016) Diagnostic Accuracy of Cancer Antigen 125 for Endometriosis: A Systematic Review and Meta-Analysis. *BJOG*: *An International Journal of Obstetrics & Gynaecology*, **123**, 1761-1768. https://doi.org/10.1111/1471-0528.14055

[12] Morshed, G. and Fathy, S.M. (2016) Impact of Post-Laparoscopic Sleeve Gastrectomy Weight Loss on C-Reactive Protein, Lipid Profile and CA-125 in Morbidly Obese Women. *Videosurgery and Other Miniinvasive Techniques*, **10**, 521-526. https://doi.org/10.5114/wiitm.2015.56480

[13] Monteiro, S., Franco, F., Costa, S., Monteiro, P., Vieira, H., Coelho, L., Oliveira, L. and Providência, L.A. (2010) Prognostic Value of CA125 in Advanced Heart Failure Patients. *International Journal of Cardiology*, **140**, 115-118. https://doi.org/10.1016/j.ijcard.2008.11.023

[14] Moss, E.L., Hollingworth, J. and Reynolds, T.M. (2005) The Role of CA125 in Clinical Practice. *Journal of Clinical Pathology*, **58**, 308-312. https://doi.org/10.1136/jcp.2004.018077

[15] Yu, S., Yang, H.J., Xie, S.Q. and Bao, Y.X. (2012) Diagnostic Value of HE4 for Ovarian Cancer: A Meta-Analysis. *Clinical Chemistry and Laboratory Medicine*, **50**, 1439-1446. https://doi.org/10.1515/cclm-2011-0477

[16] Ferraro, S., Braga, F., Lanzoni, M., Boracchi, P., Biganzoli, E.M. and Panteghini, M. (2013) Serum Human Epididymis Protein 4 vs Carbohydrate Antigen 125 for Ovarian Cancer Diagnosis: A Systematic Review. *Journal of Clinical Pathology*, **66**, 273-281. https://doi.org/10.1136/jclinpath-2012-201031

[17] Zhang, M., Cheng, S., Jin, Y., Zhao, Y. and Wang, Y. (2021) Roles of CA125 in Diagnosis, Prediction, and Oncogenesis of Ovarian Cancer. *Biochimica et Biophysica Acta. Reviews on Cancer*, **1875**, Article 188503. https://doi.org/10.1016/j.bbcan.2021.188503

[18] Dochez, V., Caillon, H., Vaucel, E., Dimet, J., Winer, N. and Ducarme, G. (2019) Biomarkers and Algorithms for Diagnosis of Ovarian Cancer: CA125, HE4, RMI and ROMA, a Review. *Journal of Ovarian Research*, **12**, Article No. 28. https://doi.org/10.1186/s13048-019-0503-7

[19] Ueland, F.R., Desimone, C.P., Seamon, L.G., Miller, R.A., Goodrich, S., Podzielinski, I., Sokoll, L., Smith, A., van Nagell Jr., J.R., and Zhang, Z. (2011) Effectiveness of a Multivariate Index Assay in the Preoperative Assessment of Ovarian Tumors. *Obstetrics and Gynecology*, **117**, 1289-1297. https://doi.org/10.1097/AOG.0b013e31821b5118

[20] Coleman, R.L., Herzog, T.J., Chan, D.W., Munroe, D.G., Pappas, T.C., Smith, A., Zhang, Z. and Wolf, J. (2016) Validation of a Second-Generation Multivariate Index Assay for Malignancy Risk of Adnexal Masses. *American Journal of Obstetrics and Gynecology*, **215**, 82.e1-82. e11. https://doi.org/10.1016/j.ajog.2016.03.003

[21] Andersen, M.R., Goff, B.A., Lowe, K.A., Scholler, N., Bergan, L., Drescher, C.W., Paley, P. and Urban, N. (2010) Use of a Symptom Index, CA125, and HE4 to Predict Ovarian Cancer. *Gynecologic Oncology*, **116**, 378-383. https://doi.org/10.1016/j.ygyno.2009.10.087

[22] Zhang, Z., Yu, Y., Xu, F., Berchuck, A., van Haaften-Day, C., Havrilesky, L.J., de Bruijn, H.W., van der Zee, A.G., Woolas, R.P., Jacobs, I.J., Skates, S., Chan, D.W. and Bast Jr., R.C. (2007) Combining Multiple Serum Tumor Markers Improves Detection of Stage I Epithelial Ovarian Cancer. *Gynecologic Oncology*, **107**, 526-531. https://doi.org/10.1016/j.ygyno.2007.08.009

[23] Cramer, D.W., Fichorova, R.N., Terry, K.L., Yamamoto, H., Vitonis, A.F., Ardanaz, E., Aune, D., Boeing, H., Brändstedt, J., Boutron-Ruault, M.C., Chirlaque, M.D., Dorronsoro, M., Dossus, L., Duell, E.J., Gram, I.T., Gunter, M., Hansen, L., Idahl, A., Johnson, T., Khaw, K.T., Kaaks, R., *et al.* (2018) Anti-CA15.3 and Anti-CA125 Antibodies and Ovarian Cancer Risk: Results from the EPIC Cohort. *Cancer Epidemiology, Biomarkers & Prevention*, **27**, 790-804. https://doi.org/10.1158/1055-9965.EPI-17-0744

[24] Köbel, M., Kalloger, S.E., Boyd, N., McKinney, S., Mehl, E., Palmer, C., Leung, S., Bowen, N.J., Ionescu, D.N., Rajput, A., Prentice, L.M., Miller, D., Santos, J., Swenerton, K., Gilks, C.B. and Huntsman, D. (2008) Ovarian Carcinoma Subtypes Are Different Diseases: Implications for Biomarker Studies. *PLOS Medicine*, **5**, e232. https://doi.org/10.1371/journal.pmed.0050232

[25] Charkhchi, P., Cybulski, C., Gronwald, J., Wong, F.O., Narod, S.A. and Akbari, M.R. (2020) CA125 and Ovarian Cancer: A Comprehensive Review. *Cancers*, **12**,

Article 3730. https://doi.org/10.3390/cancers12123730

[26] Nezhat, F.R., Apostol, R., Nezhat, C. and Pejovic, T. (2015) New Insights in the Pathophysiology of Ovarian Cancer and Implications for Screening and Prevention. *American Journal of Obstetrics and Gynecology*, **213**, 262-267. https://doi.org/10.1016/j.ajog.2015.03.044

[27] Lu, D., Kuhn, E., Bristow, R.E., Giuntoli 2nd., R.L., Kjær, S.K., Shih, I.M. and Roden, R.B. (2011) Comparison of Candidate Serologic Markers for Type I and Type II Ovarian Cancer. *Gynecologic Oncology*, **122**, 560-566. https://doi.org/10.1016/j.ygyno.2011.05.039

[28] Peng, X. and Liu, J. (2023) 791P Development and Validation of Nomograms to Predict Survival in Patients with High-Grade Serous Ovarian Cancer. *Annals of Oncology*, **34**, S531. https://doi.org/10.1016/j.annonc.2023.09.1969

[29] Colomban, O., Tod, M., Leary, A., Ray-Coquard, I., Lortholary, A., Hardy-Bessard, A.C., Pfisterer, J., Du Bois, A., Kurzeder, C., Burges, A., Péron, J., Freyer, G. and You, B. (2019) Early Modeled Longitudinal CA-125 Kinetics and Survival of Ovarian Cancer Patients: A GINECO AGO MRC CTU Study. *Clinical Cancer Research*, **25**, 5342-5350. https://doi.org/10.1158/1078-0432.CCR-18-3335

[30] You, B., Robelin, P., Tod, M., Louvet, C., Lotz, J.-P., Abadie-Lacourtoisie, S., Colomban, O., *et al.* (2020) CA-125 ELIMination Rate Constant K (KELIM) Is a Marker of Chemosensitivity in Patients with Ovarian Cancer: Results from the Phase II CHIVA Trial. *Clinical Cancer Research*, **26**, 4625-4632. https://doi.org/10.1158/1078-0432.CCR-20-0054

[31] Lauby, A., Colomban, O., Corbaux, P., Peron, J., Van Wagensveld, L., Gertych, W., Bakrin, N., Descargues, P., Lopez, J., Kepenekian, V., Glehen, O., Philip, C.A., Devouassoux-Shisheboran, M., Tod, M., Freyer, G. and You, B. (2021) The Increasing Prognostic and Predictive Roles of the Tumor Primary Chemosensitivity Assessed by CA-125 Elimination Rate Constant K (KELIM) in Ovarian Cancer: A Narrative Review. *Cancers*, **14**, Article 98. https://doi.org/10.3390/cancers14010098

[32] Salani, R., Backes, F.J., Fung, M.F., Holschneider, C.H., Parker, L.P., Bristow, R.E. and Goff, B.A. (2011) Posttreatment Surveillance and Diagnosis of Recurrence in Women with Gynecologic Malignancies: Society of Gynecologic Oncologists Recommendations. *American Journal of Obstetrics and Gynecology*, **204**, 466-478. https://doi.org/10.1016/j.ajog.2011.03.008

[33] Colombo, N., Lorusso, D. and Scollo, P. (2017) Impact of Recurrence of Ovarian Cancer on Quality of Life and Outlook for the Future. *International Journal of Gynecological Cancer*, **27**, 1134-1140. https://doi.org/10.1097/IGC.0000000000001023

[34] Marcus, C.S., Maxwell, G.L., Darcy, K.M., Hamilton, C.A. and McGuire, W.P. (2014) Current Approaches and Challenges in Managing and Monitoring Treatment Response in Ovarian Cancer. *Journal of Cancer*, **5**, 25-30. https://doi.org/10.7150/jca.7810

[35] Rustin, G.J., van der Burg, M.E., Griffin, C.L., Guthrie, D., Lamont, A., Jayson, G.C., Kristensen, G., Mediola, C., Coens, C., Qian, W., Parmar, M.K., Swart, A.M. for the MRC OV05 and EORTC 55955 Investigators (2010) Early versus Delayed Treatment of Relapsed Ovarian Cancer (MRC OV05/EORTC 55955): A Randomised Trial. *The Lancet*, **376**, 1155-1163. https://doi.org/10.1016/S0140-6736(10)61268-8

[36] Rustin, G.J.S., Vergote, I., Eisenhauer, E., Pujade-Lauraine, E., Quinn, M., Thigpen, T., *et al.* (2011) Definitions for Response and Progression in Ovarian Cancer Clinical Trials Incorporating RECIST 1.1 and CA 125 Agreed by the Gynecological Cancer Intergroup (GCIG). *International Journal of Gynecological Cancer*, **21**, 419-423. https://doi.org/10.1097/IGC.0b013e3182070f17

[37] Lu, H.-W., Ye, D.-D., Wu, B., *et al.* (2023) Interpretation of NCCN Clinical Practice Guidelines for Ovary Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer in 2023 (1st Edition). *Chinese Journal of Practical Gynecology and Obstetrics*, **39**, 58-67.

[38] Gadducci, A., Fuso, L., Cosio, S., Landoni, F., Maggino, T., Perotto, S., Sartori, E., Testa, A., Galletto, L. and Zola, P. (2009) Are Surveillance Procedures of Clinical Benefit for Patients Treated for Ovarian Cancer? A Retrospective Italian Multicentric Study. *International Journal of Gynecological Cancer*, **19**, 367-374. https://doi.org/10.1111/IGC.0b013e3181a1cc02

[39] Wang, F., Ye, Y., Xu, X., Zhou, X., Wang, J. and Chen, X. (2013) CA-125-Indicated Asymptomatic Relapse Confers Survival Benefit to Ovarian Cancer Patients Who Underwent Secondary Cytoreduction Surgery. *Journal of Ovarian Research*, **6**, Article No. 14. https://doi.org/10.1186/1757-2215-6-14

[40] Levy, T., Weiser, R., Boaz, M., Shem, E.B., Golan, A. and Menczer, J. (2012) Prognostic Significance of Rising Serum CA-125 Levels within the Normal Range in Patients with Epithelial Ovarian, Primary Peritoneal, and Tubal Cancers, Who, after Initial Treatment, Had a Complete Clinical Response. *International Journal of Gynecological Cancer*, **22**, 1344-1348. https://doi.org/10.1097/IGC.0b013e3182691254

[41] Qin, X., Liu, X.-L., Wang, X.-Y., *et al.* (2016) Clinical Significance of Serum CA125 in Prognosis Evaluation and Recurrence Monitoring of Epithelial Ovarian Cancer. *Chinese Journal of Practical Gynecology and Obstetrics*, **32**, 473-476.

[42] Giuliani, M., Gui, B., Valentini, A.L., DI Giovanni, S.E., Miccò, M., Rodolfino, E., Falcione, M., de Waure, C., Palluzzi, E., Salutari, V., Scambia, G. and Manfredi, R. (2017) Early Detection of Recurrence or Progression Disease in Patients with Ovarian Cancer after Primary Debulking Surgery. Correlation between CT Findings and CA 125 Levels. *Minerva Ginecologica*, **69**, 538-547. https://doi.org/10.23736/S0026-4784.17.04062-X

[43] Riedinger, J.M., Wafflart, J., Ricolleau, G., Eche, N., Larbre, H., Basuyau, J.P., Dalifard, I., Hacene, K. and Pichon, M.F. (2006) CA 125 Half-Life and CA 125 Nadir during Induction Chemotherapy Are Independent Predictors of Epithelial Ovarian Cancer Outcome: Results of a French Multicentric Study. *Annals of Oncology*, **17**, 1234-1238. https://doi.org/10.1093/annonc/mdl120

[44] Fleming, N.D., Cass, I., Walsh, C.S., Karlan, B.Y. and Li, A.J. (2011) CA125 Surveillance Increases Optimal Resectability at Secondary Cytoreductive Surgery for Recurrent Epithelial Ovarian Cancer. *Gynecologic Oncology*, **121**, 249-252. https://doi.org/10.1016/j.ygyno.2011.01.014