The Ability Pre-operative Serum (Cancer Antigen-125, Fatty Acid Synthase, and Glucose Transporter) to Predict Primary Suboptimal Cytoreduction in Epithelial Ovarian Cancer

Gatot Nyarumenteng Adhipumawan Winarno1*, Yudi Mulyana Hidayat1, Setiawan Soetopo2, Sofie Rifayani Krisnadi1, Maringan Diapari Lumban Tobing1, Syahrul Rauf1

1Department of Obstetrics and Gynecology, Faculty of Medicine, Padjadjaran University, Bandung, Indonesia; 2Department of Radiology, Faculty of Medicine, Padjadjaran University, Bandung, Indonesia; 3Department of Obstetrics and Gynecology, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia

ABSTRACT

BACKGROUND: The incidence of ovarian cancer ranks 8th in the world, with 295,414 cases and 184,799 death in 2018. Management in ovarian cancer is surgery and chemotherapy. Some studies state that patients who underwent optimal cytoreduction surgery have better survival rates than suboptimal cytoreduction surgery. The pre-operative serum assessed in this study was Cancer Antigen-125 (CA-125), Fatty Acid Synthase (FASN), and Glucose Transporter (GLUT) to predict suboptimal cytoreduction in epithelial ovarian cancer (EOC).

AIM: We aimed to use FASN and GLUT as other biomarkers, besides CA-125, to predict suboptimal cytoreduction surgery in epithelial ovarian cancer.

METHODS: This observational-analytic cross-sectional study included 109 women diagnosed with epithelial ovarian cancer (EOC) between 2017 and 2019, who had serum CA-125, FASN, and GLUT measured preoperatively and underwent cytoreductive surgery.

RESULTS: The results of the statistical analysis test in this study obtained p values at CA-125 (p = 0.0001), FASN (p = 0.017), and at GLUT (p = 0.013). While the cutoff point (COP) on CA-125 was 248.55, FASN was 0.445, and GLUT was 0.1980. The value of area under curve (AUC) obtained by the ROC method at CA-125 76.7%, FASN 65.3%, and GLUT 63.8%. The combination of CA-125 and FASN shows AUC value 76.9%, the combination of CA-125 and GLUT shows AUC value 72.2%, and the combination of the three shows AUC value 75.2%.

CONCLUSION: The use of CA-125 as a predictor of cytoreduction surgery is still considered to be the best predictor compared to serum biomarkers in this study.

Introduction

The number of new cases of ovarian cancer in 2018 is 295,414. When compared to 2012, this number has increased by 56414 new cases [1], [2]. Likewise, the mortality rate in ovarian cancer has increased from 152,000 in 2012 cases to 184,799 in 2018 [1], [2].

The standard of management of epithelial ovarian cancer is surgical staging in cases of early-stage (Stage 1) and cytoreduction surgery in cases of advanced stages (Stages 2, 3, and 4), which will be followed by adjuvant therapy of platinum-takasuran class chemotherapy [3]. Cytoreduction surgery has aimed to remove all tumors. If this surgery leaves a tumor >1 cm called suboptimal cytoreduction surgery, if the remaining tumor <1 cm called optimal cytoreduction surgery [3], [4].

The success rate varies in cytoreduction surgery depending on many things, including the oncologist, completeness of the operating equipment in a hospital, degree of cancer based on the International Federation of Gynecology and Obstetrics (FIGO), the histopathological type of ovarian cancer, and body mass index [5], [6], [7]. A study assessed ovarian cancer patients, and 30% of samples underwent optimal cytoreduction surgery. In contrast, the others (70%) underwent suboptimal cytoreduction surgery. The high rate of suboptimal cytoreduction surgery makes management of ovarian cancer which has a low survival rate. The high rate of suboptimal cytoreduction surgery is due to the inability to predict the results of cytoreduction surgery well.

Cytoreduction surgery can be predicted in various ways; one of them is pre-operative assessment. The pre-operative assessment consists of clinical examinations, supporting examinations such as routine blood laboratory examinations, ultrasound examination (USG), X-rays, computed tomography scans (CT Scan), magnetic resonance imaging (MRI), positron emission tomography scan (PET Scan), and assessment of tumor markers [8], [9], [10], [11].
Tumor markers that have been investigated as predictors of cytoreduction surgery are Cancer Antigen-125 (CA-125), human epididymis 4 protein (HE4), caspase 3, neutrophil to lymphocyte ratio (NLR), lymphocyte to monocyte ratio (LMR), vascular endothelial growth factor (VEGF) levels, and a combination of CA-125 with HE4, YKL 40, BCL 2, cathepsin L [12], [13], [14], [15], [16], [17].

Uncontrolled proliferation is one of the main characteristics of cancer. Proliferating cancer cells require much energy. The sources of energy come from glucose and the glucose metabolism needs a transporter called GLUT (Glucose Transport). It was happened because of the increasing glycolysis process up to 30 times faster in cancer cells [18]. One of the sources of energy is Glucose. Increased glucose metabolism increases glucose transport (GLUT). Previous studies had assessed that GLUT increased 20 times compared to healthy cells [19], [20], [21], [22], [23]. Glucose transporters typically found in ovarian cancer are GLUT1 (98.7%), GLUT3 (92.8%), and GLUT4 (84.4%) [24]. GLUT1 is the essential transporter in the absorption of glucose in tumor cells. The increase of GLUT1 levels has a relationship in worsening survival rates in ovarian cancer patients [24], [25]. Various studies have been conducted further to analyze the role of GLUT as a cancer predictor. Patients with advanced tumors are considered to have excessive GLUT1 expression, which will result in the possibility of suboptimal cytoreduction surgery [26]. This reason has led researchers to make GLUT1 one of the tumor markers assessed in this study.

Besides requiring glucose, cancer cells also need fatty acids. In cancer cells, the fatty acids needed come from food consumed (exogenous) or from the metabolism of fatty acids in the body (lipogenesis de novo) [27]. The primary source of fatty acids is from food consumed or exogenous, but the cancer cells will increase the production of fatty acids in the body or de novo lipogenesis. The synthesis of these fatty acids requires the activation of several enzymes; one of them is fatty acid synthase (FASN). FASN contributes to the process of fatty acid oxidation and biogenesis in cell membranes, which can thus divide rapidly [28]. Studies conducted by Cai et al. found that an increase of FASN was associated with the degree of cancer and the stage of cancer [28]. In stage IV, ovarian cancer has a higher FASN 94.1% compared to stage I ovarian cancer 1.25% [29], [30].

Due to the perceived strong relationship between FASN and GLUT1, the researchers will use FASN and GLUT1 as other biomarkers assessed in this study besides CA-125 to predict suboptimal cytoreduction surgery in epithelial ovarian cancer.

Results

There were 304 patients for the population in this study for the period 2017–2019. A total of 195 patients did not meet the inclusion criteria, so there were 109 patients sampled in this study. There were 56 patients underwent suboptimal cytoreduction surgery, while 53 others underwent optimal cytoreduction surgery (Table 1). The youngest sample is 17 years old, while the oldest is 75 years old (Table 1). There were 28 (25.7%) samples with parity 0, 16 (14.7%) samples with parity 1, 23 (21.1%) samples with parity 2, and 42 (38.5%) samples with parity > 3 (Table 1).

A total of 57 samples were patients with Stage III malignancy, 42 samples were patients with Stage II malignancy, and 10 samples were patients with Stage IV malignancy. The most histopathological types in this
study were the mucinous type with 38 patients (34.9%), the serous with 27 patients (24.8%), the endometroid with 21 patients (19.3%), the clear cell with 16 patients (14.7%), and others with 7 patients (6.4%) (Table 1). There were no differences between the variables of age, parity, BMI (Body Mass Index), stage and histopathology with p values greater than 0.05 (p = 0.001), so there is a difference between the suboptimal and optimal cytoreduction groups (Table 1).

Table 1: Background characteristics of the study population

| Variable          | N=109 | Group | p value |
|-------------------|-------|-------|---------|
| Age (years)       |       |       |         |
| Mean ± Std        | 14.70 ± 11.36 | 14.70 ± 11.36 | 14.70 ± 11.36 | 0.269 |
| Median            | 14.70 | 14.70 | 14.70 |
| Range (min-max)   | 0 - 57 | 0 - 57 | 0 - 57 |
| Parity            |       |       |         |
| Mean ± Std        | 0.559 | 0.559 | 0.559 |
| Median            | 0.559 | 0.559 | 0.559 |
| Range (min-max)   | 0.00 - 0.99 | 0.00 - 0.99 | 0.00 - 0.99 |
| Histopathology    |       |       |         |
| Mean ± Std        | 0.593 | 0.593 | 0.593 |
| Median            | 0.593 | 0.593 | 0.593 |
| Range (min-max)   | 0.00 - 0.38 | 0.00 - 0.38 | 0.00 - 0.38 |

Serum CA-125 values in the suboptimal cytoreduction group (1157.62 ± 2105.195) were higher than those of the optimal cytoreduction group (237.52 ± 319.431), as well as the values of the FASN, GLUT, FASN + CA-125 combination, GLUT + CA-125 combination, and the combination of GLUT + FASN + CA-125 have higher values in patients with suboptimal cytoreduction group than patients with optimal cytoreduction group (Table 2). Based on P-value analysis of CA-125 (p = 0.0001), FASN (p = 0.006), GLUT (p = 0.013), FASN + CA-125 combination (p = 0.0001), GLUT + CA-125 combination (p = 0.0001), and GLUT + FASN + CA-125 combination (p = 0.0001), p values in serum biomarkers have a value of less than 0.05 which means that there are significant differences in the suboptimal and optimal cytoreduction group patient variables (Table 2).

Table 2: Comparison between CA-125, FASN, and GLS

| Variable          | Suboptimal cytoreduction | Optimal cytoreduction | p value |
|-------------------|--------------------------|-----------------------|---------|
| CA-125 Mean ± Std | 1157.62 ± 2105.195       | 237.52 ± 319.431      | 0.0001  |
| Median            | 1157.62 ± 2105.195       | 237.52 ± 319.431      | 0.0001  |
| Range (min-max)   | 630.00 ± 1203.30         | 42.99-9934.00         | 5.10-1941.90 |
| FASN Mean ± Std   | 0.58 ± 0.27               | 0.45 ± 0.28           | 0.006   |
| Median            | 0.58 ± 0.27               | 0.45 ± 0.28           | 0.006   |
| Range (min-max)   | 0.11-1.59                | 0.03-1.19             | 0.0001**|
| GLUT Mean ± Std   | 0.41 ± 0.337              | 0.33 ± 0.298          | 0.0001**|
| Median            | 0.41 ± 0.337              | 0.33 ± 0.298          | 0.0001**|
| Range (min-max)   | 0.11-1.59                | 0.03-1.19             | 0.0001**|

In addition to using biomarker values as a single predictor, this study is also using a combination of biomarker values as predictors of suboptimal cytoreduction surgery. This combination value uses CA-125 as a categorical value where if the patient has a value > 248.55 is 2, and if the patient has a value < 248.55 is 1. The formula for three combination biomarker used two variables CA-125 and FASN as the categorical value based on each cut off point, where the value of CA-125 was > 248.55 = 2 and <248.55 = 1, while for the combination of CA-125 + FASN and CA-125 + GLUT used CA-125 as categorical value. This categorical value will then be multiplied by the value of each pair of combinations.

The combination value of CA-125 and FASN has a cutoff value of 0.69 (p = 0.0001) with a sensitivity value of 71.4%, specificity of 71.7%, and an accuracy value of 71.6% (Table 3). While the combination of CA-125 and GLUT has a cutoff point of 0.3793 (p = 0.0001) with a sensitivity of 67.9%, specificity 66%, and an accuracy value of 67% (Table 3). The combination of CA-125 + FASN + GLUT with a cutoff value of 0.5150 has sensitivity 71.4%, a specificity 71.7%, and an accuracy value of 71.6% (Table 3). Furthermore, each biomarker will be analyzed using ROC curve 23 analysis to illustrate in what direction the curve will move from the 50% line. The CA-125 is depicted in Figure 1. The curves in the ROC analysis move away from the 50% line and approach 100%, with a value of 76.7% (p = 0.000), which can illustrate that the CA-125 can predict 84 patients correctly from a total of 109 patient (Figure 1). Figure 2 illustrates FASN as a predictor of cytoreduction surgery with an area under
Table 3: Sensitivity and specificity of predictor cytoreduction scoring of epithelial ovarian cancer

| Variable              | Cutoff | Sensitivity % | Specificity % | AC % | PPV % | NPV % | p Value |
|-----------------------|--------|---------------|---------------|------|-------|-------|---------|
| CA-125                | 248.55 | 73.2          | 73.6          | 73.3 | 74.5  | 72.2  | 0.0001  |
| FASN                  | 0.445  | 62.5          | 60.4          | 61.4 | 62.5  | 60.4  | 0.017   |
| GLUT                  | 0.1980 | 75            | 56.6          | 68.1 | 64.6  | 68.2  | 0.001   |
| Combination CA-125 and FASN | 0.69   | 71.4          | 71.7          | 71.6 | 72.7  | 70.4  | 0.0001  |
| Combination CA-125 and GLUT | 0.3793 | 67.9          | 66            | 67   | 71.7  | 66    | 0.0001  |
| Combination CA-125, FASN, and GLUT | 0.5150 | 71.4          | 71.7          | 71.6 | 72.7  | 70.4  | 0.0001  |

AC: Accuracy classification, PPV: Positive predictive value, NPV: Negative predictive value

curve (AUC) value of 65.3% (p = 0.006). This AUC FASN value was described as being able to predict 71 patients correctly from a total of 109 patients. Not much different from GLUT can only predict 70 patients correctly from 109 patients (AUC value 63.8% p = 0.0013) (Figure 3). AUC value of a combination of FASN + GLUT + CA-125 is 75.2% (p = 0.000), this value can correctly predict 82 patients out of 109 patients (Figure 4).

Discussion

Cytoreduction surgery plays an essential role in the management of epithelial ovarian cancer. Tumor residues are considered to be a prognostic factor of the survival rate of patients. The standard management of epithelial ovarian cancer management is surgical therapy and followed by platinum therapy and taksan for advanced stage [31]. Based on the GOG Guideline, the main goal for cytoreduction procedures is to take all parts of the tumor or leave the tumor part with size <1 cm (optimal cytoreduction) [32]. Based on research conducted by Bacalbasa in 2014, he collected 338 patients who were willing to be the subjects in his study. He found that 242 patients who underwent optimal cytoreduction had an increase in survival compared to patients who underwent suboptimal cytoreduction [33].
An appropriate predictor tool is needed to assess whether the patient can do optimal cytoreduction or not. Several methods have been used to predict the results of cytoreduction surgery such as physical examination, ultrasound examination, CT scan, and laboratory examination. However, it seems that the predictor tool still has many shortcomings. Tumor markers that have been investigated as predictors of cytoreduction surgery are CA-125, human epididymis 4 protein (HE4), Caspase 3, neutrophil to lymphocyte ratio (NLR), lymphocyte to monocyte ratio (LMR), vascular endothelial growth factor (VEGF) levels serum-peritoneum-VEGF load, and a combination of CA 125 with HE4, YKL 40, BCL 2, and cathepsin L [12], [13], [14], [15], [16], [17]. Therefore, in this study researchers are trying to find alternative examinations that are expected to be other predictors than CA-125, namely, FASN and GLUT.

CA-125 or commonly referred to as CA-125 is the most studied serum biomarker as a predictor of cytoreduction surgery. Vorgias et al. in their study entitled “Can the pre-operative Ca-125 predict optimal levels of cytoreduction in patients with advanced ovarian carcinoma? A single institution cohort study” examining 426 patients with stage III/IV ovarian cancer stated that CA-125 is a good predictor for predicting optimal cytoreduction. Furthermore, Vorgias said that the cutoff point of CA-125 is 500 IU/mL with the sensitivity 78.5%, the specificity 89.6%, positive predictive value 84.2%, negative predictive value 85.4%, and the accuracy rate 85% [34]. Based on the recommendations of The Society of Gynecologic Oncology and the American Society of Clinical Oncology Clinical Practice Guideline that every patient who has a low likelihood of optimal cytoreduction, then it is better to receive NACT therapy first [35]. Even the study from Canada stated that the reduction in CA-125 during chemotherapy was related to the success rate of cytoreduction surgery [36].

In this study was found that there were significant differences in CA-125 as a predictor of cytoreduction surgery (p = 0.0001). The cutoff point of CA-125 as a predictor was 248.55 U/mL, with a sensitivity 76.92%, a specificity 73.6%, and an accuracy rate 73.3% (Table 3). Figure 1 shows ROC curve of CA-125 with cytoreduction with AUC value that was 76.7% CI 67.8%-85.6% (p = 0.000), implicating that CA-125 can predict cytoreduction correctly in 84 patients out of a total of 109 patients.

In normal biological systems, levels of CA-125 or Mucin 16 (MUC-16) are expressed in several epithelial layers of organs such as the mouth, esophagus, lung, breast, large intestine, ovary, and cervix. CA-125 has the function of hydration and lubrication to maintain the mucosal layer of epithelial cells and protect the cell surface from pathogen attack [37]. Regulatory errors in CA-125 play a role in cancer pathogenesis [13], [37]. In ovarian cancer, MUC16 will interact with NK cells through the Siglec receptor-9 and cause immunosuppression. This MUC16 will interact with galectin 1 and 3 in cancer cells, which will cause an increase in cancer progressivity [37].

Various evidence has been found about changes in several branches of metabolism that support the transformation of malignancy. Changes in metabolism that occurs in cancer are associated with activation of proto-oncogenes and inactivation of tumor suppressor genes. Various oncogenic signaling pathways are needed in tumor cell metabolism to support cell growth and resistance. Various cellular metabolic changes to support the three basic need of cells that are dividing; the formation of adenosine triphosphate (ATP) increase macromolecular biosynthesis and monitor redox conditions. Cancer cells require changes in all significant macromolecular metabolic pathways: Carbohydrates, proteins, lipids, and nucleic acids [27].

FASN and GLUT play an essential role in the metabolic changes that exist in cancer cells. FASN plays a role in lipogenesis de novo, a mechanism of synthesis of fatty acids in the body. The rapid proliferation of cancer cells requires large amounts of fatty acids [38]. The lipogenesis de novo process will produce saturated fatty acids and monounsaturated fatty acids. These types of fatty acids make cancer cells survive from oxidative stress, which will cause cell death. Besides, fatty acids in large quantities can also reduce the absorption of drugs by cancer cells which will cause resistance to therapy [39].

Increased synthesis of fatty acids in tumor cells will increase the activation of several enzymes in the lipogenic pathway. Increased FASN activity found
in early oncogenesis, which would correlate with the pathogenesis of cancer. Therefore, an increase in FASN expression can indicate a more aggressive type of cancer cell [28].

Until now, there have been no studies using serum FASN as a predictor of suboptimal surgery in ovarian cancer. Stefanie et al. said in their study that benign ovarian tumors have low FASN numbers when compared to malignant ovarian tumors. In FASN staining, high-grade serous carcinoma has a higher score compared to low-grade serous carcinoma [29].

There was a significant difference in FASN as a predictor of cytoreduction surgery (p = 0.006). The cutoff point of FASN as a predictor was 0.445, with a sensitivity 62.5%, a specificity 60.4%, and an accuracy rate 61.4% (Table 3). Figure 2 shows ROC curve of FASN with cytoreduction with AUC value was 65.3% CI 54.8%-75.8% (p = 0.006), implicating that FASN can predict cytoreduction correctly in 71 patients out of a total of 109 patients.

The next biomarker serum is GLUT, one of the proteins that play a role in transporting glucose. Glucose is a source of fuel for almost all body cells, including cancer cells. Glucose will go through processes glycolysis, the Krebs cycle, and oxidative phosphorylation to supply energy in the form of ATP. Malignant cells will tend to metabolize through the process of glycolysis, and it will require faster glucose absorption [18]. The glucose demand will increase GLUT expression.

Based on Table 2, GLUT has a significant difference as a predictor of cytoreduction surgery (p = 0.013). The use of GLUT as a predictor of cytoreduction surgery resulted in a sensitivity of 75% and specificity of 56.6%, with a cutoff point of 0.1980 (Table 2). Figure 2 shows the ROC curve of GLUT with cytoreduction with AUC value that was 63.8% CI 53.2–74.4% (p = 0.0013), implicating that GLUT can predict cytoreduction correctly in 70 patients out of a total of 109 patients.

The combination of CA-125 + FASN produces a cutoff point of 0.69 with CA-125 as a categorical group (1; ≦ 248.55, 2> 248.55). The use of this combination has a sensitivity rate of 71.4%, a specificity of 71.7%, and an accuracy rate of 71.6% (p = 0.0001). While the combination of CA-125 + GLUT produces a cutoff point of 0.3793 with CA-125 as a categorical group (1; ≦ 248.55, 2> 248.55). The use of this combination has a sensitivity rate of 67.9%, a specificity of 66%, and an accuracy value of 67% (p = 0.0001).

The combination of the three namely CA-125 + FASN + GLUT can correctly predict 82 patients out of 109 patients (Figure 6) using CA-125 (1; ≦ 248.55, 2> 248.55) and FASN (1; ≦ 0.445, 2 > 0.445) as a categorical group. All three have a cutoff point of 0.5150 (Table 3) with a sensitivity value of 71.4%, specificity of 71.7%, and an accuracy value of 71.6%.

Conclusion

Although the use of CA-125 has not been proven to be specific as a predictor of cytoreduction surgery, it seems that GLS and FASN are no better than the use of CA-125. Neither the combination nor the value of the biomarker singly does not have better
results than the use of CA-125. It is hoped that this research can provide an overview of other biomarkers for their use as predictors of cytoreduction surgery.

Acknowledgments

I would like to thank the Head of Department of Obstetrics and Gynecology, Head of Gynecology Division of Department of Obstetrics and Gynecology, Dr. Hasan Sadikin Hospital/Faculty of Medicine, Head of Dr. Hasan Sadikin, Dean of Faculty of Medicine Padjadjaran University Bandung, and my PhD advisors during the study.

Ethical approval and consent to participate

The study was approved by Research Ethics Committee, Faculty of Medicine Padjadjaran University/Dr. Hasan Sadikin Hospital Bandung, Indonesia, No. Ref 0518010184. “The Research Ethics Committee Universitas Padjadjaran Bandung, to protect the rights and welfare of the research subject, and to guaranty that the research using survey questionnaire/registry/surveillance/epidemiology/humaniora/social-cultural/archived biological materials/stem cell/other non-clinical material, will carried out according to ethical, legal, social implications, and other applicable regulations, has been thoroughly reviewed the proposal entitled The Ability Pre-operative Serum (CA-125, FASN, and GLUT) to Predict Primary Suboptimal Cytoreduction in Epithelial Ovarian Cancer”.

The suspected ovarian cancer patient was invited to participate this study. The patient who was willing to be participants in this study will be asked to fill and sign an informed consent form. They were told that all data concerning of self-sample would be handled with full confidentiality.

Declarations

The datasets used and/or analyzed during the current study are available from the corresponding author on request.

References

1. World Health Organization. GLOBOCAN 2012: Estimated Cancer Incidence, Mortality, and Prevalence Worldwide in 2012. World Health Organization2012. Available from: http://www.globocan.iarc.fr/Pages/fact_sheets_population.aspx. [Last accessed on 2017 Apr 25].
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424. https://doi.org/10.3322/caac.21492
PMid:30207593
3. Morgan RJ, Armstrong DK, Alvarez RD, Bakkum-Gamez JN, Bebbakhit K, Chen LM, et al. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Ovarian Cancer, Including Fallopian Tube Cancer and Primary Peritoneal Cancer; 2015. Available from: http://www.nccn.orgprofessionals/physician- gls/pdf/ovarian.pdf. [Last accessed on 2015 Jun 22]. https://doi. org/10.1097/01.cot.0000397914.46574.8b
4. Prat J. The International Federation of Gynecologists and Obstetricians. New FIGO Ovarian Cancer Staging Guidelines; 2014. Available from: https://www.sgo.orgclinical-practice/ guidelines/new-figo-ovarian-cancer-staging-guidelines. [Last accessed on 2017 Jan 01]. https://doi.org/10.1016j. bsgyn.2015.03.006
5. Obeidat B, Latimer J, Crawford R. Can optimal primary cytoreduction be predicted in advanced stage epithelial ovarian cancer? Role of preoperative serum CA-125 level. Gynecol Obst Invest. 2004;57(3):153-6. https://doi.org/10.1159/000076236
PMid:14726621
6. Eltabbakh GH, Mount SL, Beatly B, Simmons-Arnold L, Cooper K, Morgan A. Factors associated with cytoreducibility among women with ovarian carcinoma. Gynecol Oncol. 2004;95(2):377-83. https://doi.org/10.1016j.ygyno.2004.07.045
PMid:15491760
7. Rodriguez N, Rauh-Hain JA, Shoni M, Berkowitz RS, Muto MG, Feltmate C, et al. Changes in serum CA-125 can predict optimal cytoreduction to no gross residual disease in patients with advanced stage ovarian cancer treated with neoadjuvant chemotherapy. Gynecol Oncol. 2012;125(2):362-6. https://doi.org/10.1016j.ygyno.2012.02.006
PMid:22333992
8. Martínez-Saíd H, Rincon D, De Oca MM, Ruiz G, Ponce J, López-Granziel C. Predictive factors for irresectability in advanced ovarian cancer. Int J Gynecol Cancer. 2004;14(3):423-30. https://doi.org/10.1002/jgyn.2004.07.045
PMid:15661212
10. Testa AC, Ludovisi M, Mascilini F, Di Legge A, Malaggesse M, Fagotti A, et al. Ultrasound evaluation of intra-abdominal sites of disease to predict likelihood of suboptimal cytoreduction in advanced ovarian cancer: A prospective study. Ultrasound Obstet Gynecol. 2012;39(1):99-105. https://doi.org/10.1002/uog.10100
PMid:21913276
11. Bristow RE, del Carmen MG, Pannu HK, Cohade C, Zahurak ML, Fishman EK, et al. Clinically occult recurrent ovarian cancer: Patient selection for secondary cytoreductive surgery using combined PET/CT. Gynecol Oncol. 2003;90(3):519-28. https://doi.org/10.1016/s0090-8258(03)00336-6
PMid:13678719
12. Tang Z, Chang X, Ye X, Li Y, Cheng H, Cui H. Cui H. Usefulness of human epithidymis protein 4 in predicting cytoreductive surgical outcomes for advanced ovarian tubal and peritoneal carcinoma. Chin J Cancer Res. 2015;27(3):309-17. https://doi.org/10.1007/s10545-014-0710-3
PMid:26157328
13. Bottini P, Scatena R. The role of CA 125 as tumor marker: Biochemical and clinical aspects. AdvExpMedBiol.2015;867:229- 44. https://doi.org/10.1007/978-94-017-7215-0_14

https://www.id-press.eu/mjms/index
PMid:26530369

14. Komura N, Mabuchi S, Yokoi E, Kozasa K, Kuroda H, Kodama M, et al. Prognostic significance of pretreatment leukocyte alterations in patients with epithelial ovarian cancer. J Obstet Gynaeco Res. 2017;43(S1):102-31.

15. Budiana IN, Suhatno, Hoesin F, Budiono. Profil ekspresi caspase-3 pada kanker ovarium tipe epithel. Indones J Cancer. 2013,7(3):85-91.

16. Chudeckaneta AM, Cymbaluk A, Menkiszak JL, Sompolska AM, Toloczko AI, Rzepka IA. Serum HE4, CA125, YKL-40, bcl-2, cathepsin-L, and prediction optimal debulking surgery, response to chemotherapy in ovarian cancer. J Ovarian Res. 2014;7(62):62. https://doi.org/10.1186/1757-2215-7-62

PMid:25018782

17. Eo W, Kim HB, Lee YJ, Suh DS, Kim KH, Kim H. Preoperative lymphocyte-monocyte ratio is a predictor of suboptimal cytoreduction in stage III-IV epithelial ovarian cancer. J Cancer. 2016;7(13):1772-9. https://doi.org/10.7150/jca.15724

PMid:27698915

18. Riedl CC, Akhurst T, Larson S, Stanziale SF, Tuorto S, PMid:11571727

19. Barron CC, Bilan PJ, Tsakiridis T, Tsiani E. Facilitative glucose transporters: Implications for cancer detection, prognosis and treatment. Metabolism. 2015;65(2):124-39. https://doi.org/10.1016/j.metabol.2015.10.007

PMid:26773935

20. Adekola K, Rosen ST, Shanmugam M. Glucose transporters in cancer metabolism. Curr Opin Oncol. 2012;24(6):650-4.

PMid:22913968

21. Augustin R. The protein family of glucose transport facilitators: It’s not only about glucose after all. IUBMB life. 2010;62(5):315-33. https://doi.org/10.1002/iub.315

PMid:20209635

22. Thorens B, Mueckler M. Glucose transporters in the 21st Century. Am J Physiol Endocrinol Metab. 2010;298(2):E141-E5.

PMid:20090031

23. Calvo MB, Figueroa A, Pulido EG, Campelo RG, Aparicio LA. Potential role of sugar transporters in cancer and their relationship with anticancer therapy. Int J Endocrinol. 2010;2010:205357.

https://doi.org/10.1155/2010/205357

PMid:20706540

24. Cantuaria G, Fagotti A, Ferrandina G, Magalhaes A, Nadji M, Angioli R, et al. GLUT-1 expression in ovarian carcinoma: Association with survival and response to chemotherapy. Cancer. 2001;92(5):1144-50. https://doi.org/10.1002/1097-0142(20010901)92:51144-;aid-cncr1432;3.0.co;2-t

PMid:11571277

25. Tsukioka M, Matsumoto Y, Noriyuki M, Yoshida C, Nobeyama H, Yoshida H, et al. Expression of glucose transporters in epithelial ovarian carcinoma: Correlation with clinical characteristics and tumor angiogenesis. Oncol Rep. 2007;18(2):361-8. https://doi.org/10.3892/or.18.2.361

PMid:17611657

26. Semaan A, Munkarah AR, Arabi H, Bandyopadhyay S, Seward S, Kumar S, et al. Expression of GLUT-1 in epithelial ovarian carcinoma: Correlation with tumor cell proliferation, angiogenesis, survival and ability to predict optimal cytoreduction. Gynecol Oncol. 2011;121(1):181-6. https://doi.org/10.1016/j.ygyno.2010.11.019

PMid:21167567

27. Cairns RA, Harris IS, Mak TW. Regulation of cancer cell metabolism. Nat Rev Cancer. 2011;11(2):85-95.

PMid:21258394

28. Ameer F, Scanduzzi L, Hasnain S, Kalbacher H, Zaidi N. De novo lipogenesis in health and disease. Metabolism. 2014;63(7):895-902. https://doi.org/10.1016/j.metabol.2014.04.003

PMid:24814684

29. Ueda SM, Yap KL, Davidson B, Tian Y, Murthy V, Wang TL, et al. Expression of fatty acid synthase depends on NAC1 and is associated with recurrent ovarian serous carcinomas. J Oncol. 2010;2010:285191. https://doi.org/10.1155/2010/285191

PMid:20508725

30. Cai J, Xu L, Tang H, Yang Q, Yi X, Fang Y, et al. The role of the PTEN/PISK/Akt pathway on prognosis in epithelial ovarian cancer: A meta-analysis. Oncologist. 2014;19(5):528-35. https://doi.org/10.1634/theoncologist.2013-0333

PMid:24718516

31. Romanidis K, Nagomi EA, Halkia E, Piliakoudis M. The role of cytoreductive surgery in advanced ovarian cancer: The general surgeon’s perspective. Management. 2014;7(9):12.

32. Chang SJ, Hodeib M, Chang J, Bristow RE. Survival impact of complete cytoreduction to no gross residual disease for advanced-stage ovarian cancer: A meta-analysis. Gynecol Oncol. 2013;130(3):493-8. https://doi.org/10.1016/j.gyno.2013.05.040

PMid:23747201

33. Bacalbasu N, Dimas S, Balescu I, David L, Brasoveanu V, Popescu I. Results of primary cytoreductive surgery in advanced-stage epithelial ovarian cancer: A single-center experience. Anticancer Res. 2015;35(7):4099-104. https://doi.org/10.1016/j.anticancer.2016.03.120

PMid:26124361

34. Vorgias G, Iavazzo C, Savvopoulos P, Myrokefalitaki E, Katsoulis M, Kalinoglu N, et al. Can the preoperative Ca-125 level predict optimal cytoreduction in patients with advanced ovarian carcinoma? A single institution cohort study. Gynecol Oncol. 2009;112(1):11-5. https://doi.org/10.1016/j.gyno.2008.09.020

PMid:19119502

35. Wright AA, Bohike K, Armstrong DK, Bookman MA, Cliby WA, Coleman RL, et al. Neoadjuvant chemotherapy for newly diagnosed, advanced ovarian cancer: Society of gynecologic oncology and american society of clinical oncology clinical practice guideline. Gynecol Oncol. 2016;143(1):3-15. https://doi.org/10.1016/j.gy neo.2016.05.022

36. Kessous R, Wissing MD, Piedimonte S, Abitol J, Kogan L, Laskov I, et al. CA-125 reduction during neoadjuvant chemotherapy is associated with success of cytoreductive surgery and outcome of patients with advanced high-grade ovarian cancer. Acta Obstet Gynecol Scand. 2020;99(7):933-40. https://doi.org/10.1111/aogs.13814

PMid:31954071

37. Haridas D, Ponnusamy MP, Chugh S, Lakshmanan I, Seshacharyulu P, Batra SK. MUC16: Molecular analysis and its clinical experience. Anticancer Res. 2015;35(7):4099-104. https://doi.org/10.1016/j.anticancer.2016.03.120

PMid:26124361

38. Menendez JA, Lupi R, Fatty acid synthase and the lipogenic phenotype in cancer pathogenesis. Nat Rev Cancer. 2007;7(10):763-77. https://doi.org/10.1038/nrc2222

PMid:17882277

39. Rysman E, Brusselans K, Scheyts K, Timmermans L, Derue R, Munck S, et al. De novo lipogenesis protects cancer cells from free radicals and chemotherapy by promoting membrane lipid saturation. Cancer Res. 2010;70(20):8117-26. https://doi.org/10.1158/0008-5472.can-09-3871

PMid:2087698