

The Influence of Cytokine Profile and Choice of Surgical Intervention in Patients with Obesity

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Abstract: *Endometrial carcinoma is the most common type of gynecological carcinomas. Several biological mechanisms trace the relationship between obesity and endometrial neoplastic risk. In surgical practice, there has been increasing interest concerning a group of cytokines as an independent prognostic factor for aggression and the possible therapeutic impact on the neoplastic process. The high-tech surgical capabilities of minimally invasive surgery and the immunological changes at cytokine level in level I endometrial carcinoma enabled the increasingly successful treatment of this neoplastic disease and its prevention. The cytokine profile can be used as an assessment factor of primary neoplastic immune damage, as well as for the selection of a surgical intervention.*

Keywords: stage I endometrial carcinoma, cytokine profile, obesity, robotic surgery.

1. Introduction

Endometrial carcinoma is the most common type of gynecological carcinomas. Optimistically, 53 % of all diagnosed cases of endometrial carcinoma are in stage I, when the therapeutic options are the most successful. The complex assessment at an immunological level, the irregularities and the intracellular metabolism form the basis of individual differences, neoplastic aggression, impact of anesthesia and surgical intervention, and postoperative recovery and prognosis.

Several biological mechanisms trace the connection between obesity and endometrial neoplastic risk (Cancer Risk). In women in the postmenopausal period, obesity leads to the conversion of androgens and to a rise in serum bioavailability of estrogens that are not balanced by progesterone, which in turn enhances the mitogenic activity of endometrial cells. Overweight women have a tenfold higher level of estrogens, as compared to women of normal weight [1]. Adipose tissue raises insulin, IGF-1 (insulin-like growth factor – 1 (IGF-1) playing a key role for the initiation and development of insulin resistance /obesity-linked hyperinsulinemia/ [2], which closes the circle increased estradiol bioavailability → lowered testosterone production → increased estrogen neoplastic sensitivity and possible neoplastic proliferation, i.e., obesity → angiogenesis → tumor development (Stromal Adipose Neoplasia) [3].

According to research studies in Europe and the USA, women who are overweight (BMI > 30 kg/m²) run a three times higher risk of developing endometrial carcinoma in comparison with women having normal weight. (Agency for Research on Cancer (IARC), World Cancer Research Fund, American Institute for Cancer Research). Obesity is also associated with maintaining a continuously high level of inflammatory processes, with increases in pro-inflammatory cytokines and acute phase inflammatory proteins, which in turn degrade cellular DNA and trigger and assist the tumor process.

Obesity in various degrees, especially disease-related (BMI > 40 kg/m²), is closely related to the pathogenesis of endometrial carcinoma, but it is also a "bottleneck" in the selection of surgical procedure due to difficulties with pulmonary ventilation, a steep position and postoperative complications [4]. Despite the possibility of early clinical diagnosis, and modern anaesthesiological, pharmacological and technological possibilities for surgical intervention, such as minimally invasive surgery, the mortality of women diagnosed with endometrial carcinoma still remains high, which necessitate a complex immunological assessment. Therefore, in surgical practice the interest is increasingly higher regarding a group of cytokines as independent prognostic factors, aggression and a possibility of influencing therapeutically the neoplastic process. Cytokines are among the first mediators of inflammation and stress responses to operational trauma. Many experimental and clinical studies have demonstrated that surgical trauma leads to a change in the immunological response, progressing to the production of pro-inflammatory cytokines, as well as to the suppression of the cell-mediated immunity.

Cytokines [5] are essentially necessary for the specific immune response to trauma, neoplastic processes, etc. The cytokine profile can be used as a factor of assessment of the primary neoplastic immune damage and for selecting a surgical intervention for overweight patients. The functional classification divides cytokines into three types, as follows. Type 1 – increase the cellular immune response TNF- α , INF- γ , as the tumor necrosis factor alfa (TNF- α) plays a fundamental role in the progress of inflammatory immune processes, cell apoptosis, and malignancy [6]. Type 2 – improve the antigenic immune response – IL-10, IL-13, IL-4. Interleukin 10 (IL-10) – a cytokine synthesis inhibitory factor (CSIF) – is increased in serum, peritoneal fluid and saliva malignancies, viral infections and advanced autoimmune processes [7, 8]. Type 3 – with a proinflammatory function (proinflammatory cytokines) – IL-1, IL-6, IL-12, INF- α . Interleukin 6 (IL-6) plays a significant role in the acute phase

of inflammation, blood formation, bone metabolism and evolution of malignant processes [9, 10]. Interleukin 8 (IL-8 – CXCL8) influences the motion of leucocytes and macrophages (chemotaxis, migration, respiratory burst) by enhancing the antimicrobial activity and cell survival [11-15], and is related to obesity, especially to the higher grade ones having higher baseline values of cytokines IL-6, IL-10 and to the possibility of postoperative complications. The purpose of this research was to study and compare the serum level of IL-6 and IL-10 cytokines in women with stage I endometrial carcinoma in the two approaches to surgery, namely, minimally invasive /robotic (R) and conventional (O).

2. Material and Methodology

In order to attain the objective set above, 97 women diagnosed with stage I endometrial carcinoma between the ages of 46 years and 81 were subjected to research. In the pre-surgery clinical study, it was found that 68 out of them had an exceptionally high body mass index (BMI > 40 kg/m²). Figure 1 illustrates the number of patients operated by conventional (O) surgery (O, n = 35) and by robotic (R) minimally invasive surgery (R, n = 62), divided into groups depending on their body mass index. The appropriate surgical intervention was performed at the Clinic of Gynecological Oncology of the Dr. G. Stransky Multiprofile University Hospital for Active Treatment, city of Pleven.

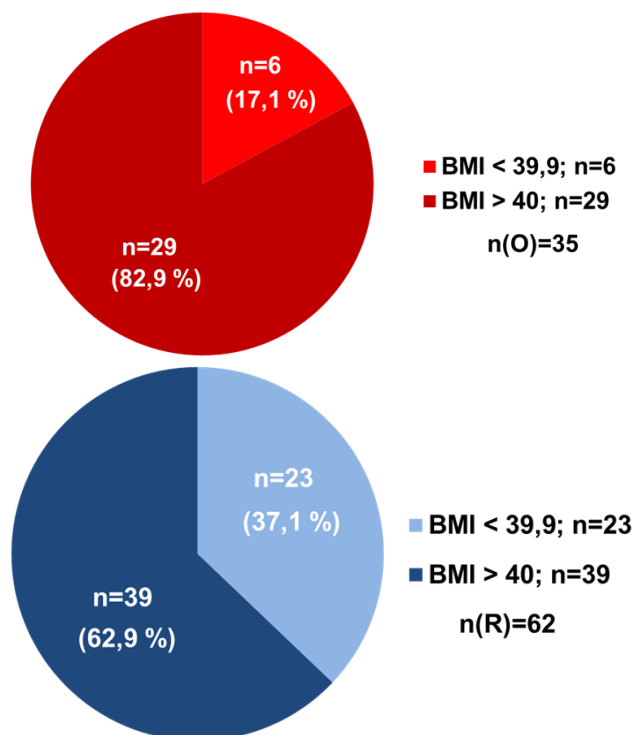


Figure 1: Body mass index (BMI in kg/m²) in women with stage I endometrial carcinoma operated by conventional (O, n = 35) and minimally invasive (R, n = 62) surgical technique.

The immunological parameters IL-6 and IL-10 were studied by Human ELISA tests by Diaclone according to the methodological instructions. Blood samples were collected at

the third hour after surgery; separated serum was stored at T ≤ 200 °C. A dynamic follow-up of the listed parameters was performed – before surgery, at the third hour and on the third day, respectively, in both intervention methods that were applied with robotic (R) and conventional (O) operating techniques. The serum levels of IL-6 and IL-10 were tested in 15 clinically healthy women aged 45 years to 67 years old, used as a control group.

The samples were read for optical density at 450 nm by a Model 2100 Stat Fax ELISA Reader, produced by Awareness Technology Inc. /Petrunka Petrova Immunodiagnostics Medical Diagnostics Laboratory, Pleven [16].

3. Result and Discussions

In view of the current relevance of the issue of "cytokines", their significance to the outcome of a surgical intervention and a later healthy prospect, the serum levels of IL-6 and IL-10 were examined pre-surgically, at the third hour and on the third day after the completed interventions (Figure 2 and Figure 4). In the course of the dynamic monitoring of the serum level of IL-6 in ten women operated by robotic and open (conventional) surgery, an increase in the levels was recorded after the third hour. IL-6 is a pleiotropic cytokine providing information about the strength of the acute phase reaction to inflammation, the surgical trauma severity, the expected complications and the neoplastic progression. It is noteworthy that the IL-6 levels in patients operated by conventional surgery are up to ten times higher than in those operated by robotic method. Moreover, the serum levels remained higher also after the third day following the open surgery, as opposed to the reduced values recorded after the minimally invasive approach.

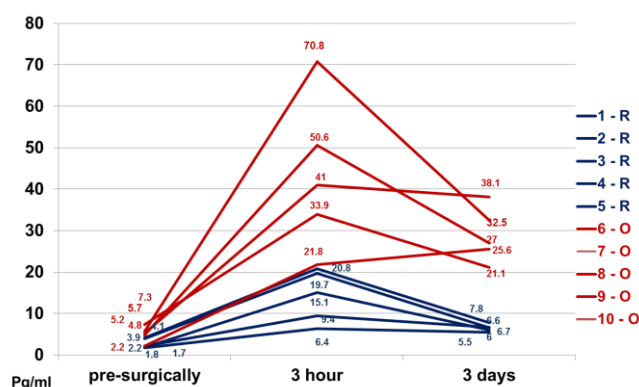


Figure 2: Recorded values of serum IL-6 in women with stage I endometrial carcinoma operated by minimal invasive surgery (R, n = 5) and conventional (O, n = 5) operating techniques.

A comparison of the serum level of IL-6 cytokine in both surgical approaches relative to the body mass index (BMI) of the operated women is presented in Figure 3. A significant difference is evident in the cytokine levels of IL-6 in the groups of operated patients having a body mass index BMI ≤

39.9 kg/m² (left) and BMI > 40 kg/m² (right). The deviations are again the most significant in women with BMI >40 kg/m² operated by the conventional technique.

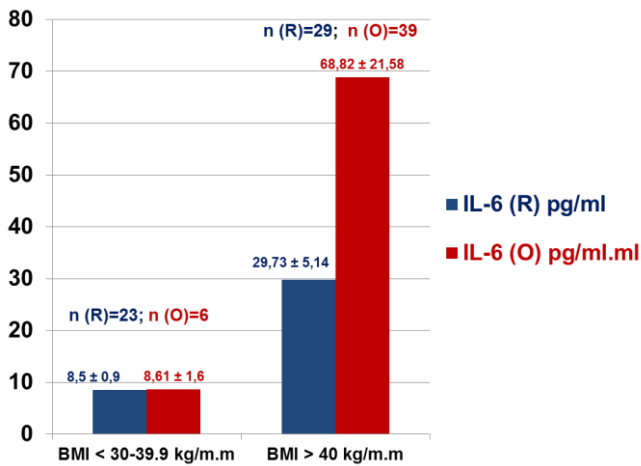


Figure 3: Correlation between body mass index (BMI) and measured levels of IL-6 during the third hour after the operating period in women with stage I endometrial carcinoma operated by minimally invasive surgery (R) and conventional (O) operating techniques.

Demanding attention is also the tracing of the cytokine profile of IL-10 (cytokine synthesis-inhibitory factor) that binds to the antigenic immune response of the organism. In this case IL-6, plays the role of a "trigger" factor for IL-10. The "inclusion" of IL-10 in the immune regulation has a dual effect. On the one hand, it promotes the phagocytic activity and T2-helper lymphocytes and, on the other, inhibits the proinflammatory response and function of T1-helper lymphocytes.

Notwithstanding the individual variations in cytokine levels, the results obtained by tracing the profile of IL-10 follow the previous trend, Figure 4. The cytokine level was increased at the third hour after the intervention, as in patients operated by the method of open surgery the level remained high even after the third day following the intervention.

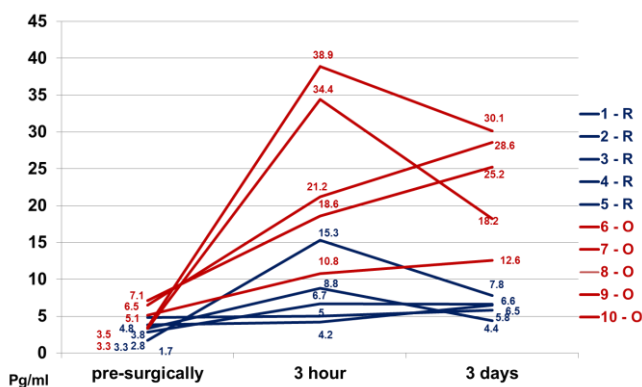


Figure 4: Recorded values of the serum level of IL-10 in women with stage I endometrial carcinoma operated with minimally invasive (R, n=5) and conventional (O, n=5) operating techniques.

A faster approach to the baseline cytokine levels was

observed only in women operated by the robotic surgery method. The profile established is correlated with the ratio between the body mass index (BMI) of the patient and the levels of IL-10 measured in both types of performed interventions, Figure 5.

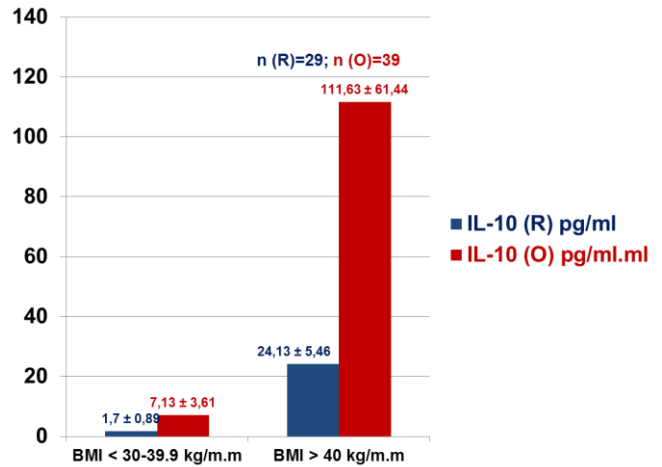


Figure 5: Correlation between body mass index (BMI) and measured levels of IL-10 during the third hour after the operating period in women with stage I endometrial carcinoma operated by minimally invasive (R) surgery and conventional (O) operating techniques.

The study performed was focused on the immunopathological changes in stage I endometrial carcinoma, when these changes are much smaller as compared to the advanced stages of the disease, but these observations open an opportunity for a basic complex immunological assessment of individual immunological deviations and the surgery's high technological capabilities. The minimally invasive surgery demonstrated a reduced acute-phase response as compared to open procedures and better preservation of the cellular immune mechanisms. Robotic operations of endometrial carcinoma entail less blood loss as compared to open surgical interventions, Table 1.

Table 1: Post-surgery characteristics in women with stage I endometrial carcinoma operated by minimally invasive (R) and conventional (O) operating techniques.

Parameters	R n=62	O n=35	P
Uterine size in SD/g	101,45 ± 24,96	121,48 ± 31,00	P<0,001
Blood loss in SD/ml	96,93 ± 26,86	435,71 ± 108,85	P<0,001
Surgical time in SD/min	95,96 ± 29,76	139,85 ± 30,13	P<0,001
Hospital stay in SD/d	3,37 ± 0,27	10,8 ± 0,26	P<0,001

4. Summary

The high-tech surgical capabilities of minimally invasive surgery and the immunological changes at cytokine level in level I endometrial carcinoma enable the increasingly successful treatment of this neoplastic disease and its prevention. Research confirms the view that minimally invasive surgery reduces the so-called "cytokine burst", which presupposes the decrease of postoperative risk and days of intensive care and hospitalizations. In this particular

case, it is important that we have an obese patient with neoplastic problem and possibilities for new angiogenesis and spreading of the neoplastic process.

The adoption and implementation of Da Vinci minimally invasive surgical system (Intuitive Surgical System, Inc., Sunnyvale, CA) in Bulgaria for treatment of endometrial carcinoma (stage I) reduces the so-called "cytokine burst", thus lowering the post-surgery risk and postoperative days of intensive care and hospitalizations. The findings listed as a result of our study are important for the pathogenetic clinical diagnostic thinking, for the selection of surgical approach, postoperative care, short-term and more distant prognosis.

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