

**ATTN: The Chairman of the Scientific jury appointed by an order
No R-109-237/26-Jul-2019 of the Rector of the Medical University of
Varna**

Peer Review

**by Prof. Dr. Slavcho Tomov, MD, PhD, DSc
Rector of Medical University – Pleven**

About the dissertation on:

**"INVASION IN THE LYMPH AND VESSELS IN ENDOMETRIAL
ENDOMETROID CARCINOMA - I STAGE BY FIGO"**

with author Assoc. Prof. Dr. Elis Hudaim Ismail, MD, PhD for Doctor of Science
Degree in Higher Education 7.0 Health and Sports, Professional 7.1 Medicine;
Specialty "Obstetrics and Gynecology" 03.01.45

Career path and career development

Assoc. Prof. Dr. Elis Hudaim Ismail, MD, PhD was born in 1983 in Shumen. In 2008 she graduated in medicine from the Medical University of Varna. She started working as a physician at the Emergency Center in Varna at the Hospital of "St. Anna" (2009-2011). From February 2011 until now she has been working as an obstetrician-gynecologist at the Gynecology Clinic of the Hospital "St. Anna - Varna". Since September 2011 she is a full-time assistant at the Department of Obstetrics and Gynecology, Medical University - Varna.

In 2013 she defended her dissertation on the topic: "Prognostic factors in the combined treatment of invasive cervical cancer IB1 stage" and acquired the educational and scientific degree "Doctor".

In 2015, she completed a second Master's Degree in Health Management.

Since September 2015 she has acquired the scientific degree of Chief Assistant at the Department of Health Care – Shumen Branch of MU-Varna. From 2017 she holds the academic position of Assistant Professor in Obstetrics and Gynecology at the Department of Health Care - Shumen Branch of Medical University - Varna. She is active in the field of oncology, operative gynecology and minimally invasive surgery. She has participated in numerous scientific forums in Bulgaria and abroad. She has conducted specializations in oncogynecology in Macedonia, Germany and Hungary. She holds certificates for qualifications in endoscopic surgery, hysteroscopy, ultrasound and colposcopy.

She is a member of BSAG, BAOG, BAMIGS, SEERS, ESGO, ENYGO.

From 2013 until now she is national representative for Bulgaria of the European Community of Young Oncologists (ENYGO).

The relevance of the dissertation

Endometrial cancer is the most common malignant disease of the female genital organs in the developed countries of Europe and North America. According to data from the National Cancer Registry, published in 2017 for 2014, there are 1,225 newly diagnosed cases of endometrial cancer in Bulgaria (33/100.000 women). In 2015, uterine cancer is the second most common after breast cancer in women in Bulgaria.

Surgical treatment of this disease is primary and fundamental. It achieves healing, staging, resp. prognosis of the disease. In recent years, so-called minimally invasive laparoscopic and robotic techniques have been increasingly applied.

Discussion as a part of the surgical treatment is still the performance of lymph node dissection (pelvic and paraaortic) and its impact on quality of life, early and late postoperative complications and survival. No less relevant and debatable topics are the indications for postoperative radiation therapy. The decision on whether to perform lymph node dissection or radiation therapy is determined by the study of various prognostic factors. In recent years, in addition to the established classical prognostic factors, more and more attention is being paid to new ones. One is lympho-vascular invasion of the tumor. Endometrioid carcinoma (type 1) has a better prognosis than nonendometrioid carcinoma (type 2). Factors such as tumor invasion in the blood and lymph vessels are thought to underlie the different survival rates of patients with the same stage and histologic type. This model of study, as well as some genetic studies, pave the way for so-called personalized medicine. In this regard, the topic of Assoc. Prof. Ismail's dissertation is very topical and such a scientific development would lead to improved therapeutic results and would help to individualize the approach in patients with endometrial endometrioid carcinoma.

Structure of the dissertation

The dissertation submitted for review is written on 165 pages. The results are illustrated with 20 figures and 33 tables. 211 literary sources were used and were cited correctly in the text. The structure of the dissertation work meets the requirements of the legal framework.

The dissertation begins with an Introduction, which outlines the morbidity and major challenges in EC diagnosis and treatment. The literature review is very comprehensive, has been written on 52 pages and includes 16 subsections in which the current state of research on the problem has been synthesized. At the end of the review, the author draws 5 conclusions, on the basis of which she formulates the

purpose of the dissertation: “To determine the prognostic significance of tumor invasion in lymphatic and blood vessels in patients with endometrial endometroid carcinoma in stage I according to FIGO. To this end, 10 tasks have been set.

The Material and Methods section covers 11 pages. The clinical contingent includes 117 patients in Stage I endometrial endometroid carcinoma who underwent surgery for a period of 6 years (2009 - 2014) at the Gynecology Clinic of St. Anna Hospital in Varna. They meet the criteria of the study and are followed for a period of 5 years. The methods used (surgical, histopathological, radiation, staging, monitoring and data processing) are described in detail and correctly. Statistical processing includes descriptive, variational, and graphical analysis, Log-Rank, Breslow, Tarone-Ware tests, Cox regression analysis, and the Kaplan-Meier survival method.

The Results and Discussion section covers 42 pages and essentially looks at the 10 tasks.

The highlights of this section are 6:

1. Overall survival of the studied contingent;
2. Determining the role of lymph node dissection on overall survival;
3. Role of postoperative radiation therapy on overall survival;
4. The disease-free survival of the studied contingent;
5. Survival of patients with relapses after treatment;
6. Role of adverse histopathological factors on disease-free survival:

lymphovascular invasion, myometrial invasion, tumor grade.

As a result of the analysis and discussion of the survey data, Assoc. Prof. Ismail formulates 14 conclusions that answer 10 tasks. However, I will pay particular attention to some of the conclusions that I consider to be of the utmost importance:

- Lymph node dissection in Stage I in endometroid endometrial carcinoma is relevant only for metastatic lymph nodes of the imaging diagnostic methods and

enlarged ones. Lymph node dissection (pelvic and / or paraaortic) **does not increase overall and disease-free survival.**

- Lymph node metastases have a **poor prognostic value**, regardless of the radiation therapy used. In these cases, chemotherapy takes place.
- Patients with **positive LVSI have a 28-month lower disease-free survival** rate compared to patients without LVSI.
- **Postoperative radiotherapy in the studied contingent has no protective effect on overall and disease-free survival.** Patients at increased risk (MI > 1/2 - IB stage, G3, LVSI (+), LNM) should be combined with brachytherapy and / or chemotherapy.
- **LVSI (+) and G3 are independent prognostic factors that reduce both overall and disease-free survival**, whereas deep myometrial invasion alone does not affect these indicators.

Based on the results obtained and the conclusions drawn, Assoc. Prof. Ismail proposes 4 recommendations for the behavior of diagnosed "endometrial carcinoma", which would contribute to better therapeutic results and individualization of the approach in daily clinical practice. Assoc. Prof. Ismail's dissertation has a scientific and practical contribution, 6 of which are original and 7 - of confirmatory nature.

Publications related to the dissertation

The author presents 12 publications related to the topic of the dissertation - 10 in Bulgarian scientific publications and 2 - in international ones. In 9 of the publications Assoc. prof. Elis Ismail is the first author.

In conclusion, the dissertation presented is original and up-to-date. It contains significant scientific contributions and meets the criteria for awarding the Doctor of Science degree to Dr. Elis Ismail, which gives me reason to

recommend that the members of the Scientific Jury support it with a positive vote.

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