

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. Asen Nikolov, MD, PhD
Head of Maternity Clinic, SBALAG - Sofia
President of the Bulgarian Society of Obstetrics and Gynecology**

Regarding the dissertation on the topic: "Invasion of the lymph and blood vessels in endometrial endometroid carcinoma - stage I by FIGO" with author Assoc. Prof. Dr. Elis Hudaim Ismail, MD for Doctor of Science Degree in Higher Education 7.0 Health and Sports, Professional 7.1 Medicine; Obstetrics and Gynecology
Scientific Degree 03.01.45

By order No. P-109-237 / 26.07.2019 of the Rector of the Medical University of Varna, pursuant to Part 4, Paragraph 2 of the Law for the Development of the Academic Staff in the Republic of Bulgaria, I was appointed to prepare a review under the procedure for obtaining a Scientific Degree Doctor of Science Assoc. Prof. Elis Ismail, MD, PhD from MU-Varna on the topic: "Invasion of the lymph and blood vessels in endometrial endometroid carcinoma - stage I by FIGO".

I. Curriculum vitae

Assoc. Prof. Dr. Elis Hudaim Ismail, MD was born in 1983 in Shumen. In 2008 she graduated in medicine from the Medical University of Varna. She is started working as a doctor at the Emergency Center in Varna. Since February 2011 until to this day she works as an obstetrician-gynecologist at the Gynecology Clinic of St. Anna-Varna Hospital. Since September 2011 she is a full-time assistant at the Department of Obstetrics and Gynecology.

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

In 2015, she is completed her second Master's Degree in Health Management. September 2015 - Becomes the Chief Assistant in the Department of Health Care - Branch of Shumen of MU – Varna. Since 2017 she is an Associate 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 forums in Bulgaria and abroad. She has conducted specializations in oncogynecology in Macedonia, Germany and Hungary.

She holds certificates for endoscopic surgery, hysteroscopy, ultrasound and colposcopy.

She is a member of BDAG, BAOG, BAMIGH, SEERS, ESGO, ENYGO.

Since 2013 and currently she is the national representative for Bulgaria of the European Community of Young Oncogynecologists (ENYGO).

II. Relevance of the dissertation.

The topic of the dissertation is up-to-date. The prognosis and treatment of cancer are dependent on a number of factors, with increasing attention being paid to the biology of the tumor. Endometrial cancer is the most common oncogynecologic localization in both Bulgaria and developed countries. The endometrioid type is more favorable than the non-endometrioid type. In recent years, there has been an increasing interest in tumor factors (histologic factors) that cause recurrence and

different survival rates in patients with a favorable prognosis (FIGO stage I endometrial carcinoma). On the other hand, there are ongoing discussions and controversies about the indications for lymphoid dissection, as well as for postoperative therapy in such patients. One of the factors related to the biology of the tumor is lympho-vascular invasion.

III. Structure of the thesis.

The dissertation presented by Assoc. Prof. Ismail is structured correctly, with the proportions observed between the different sections. It is written on 165 pages, its contents are illustrated with 20 figures and 33 tables. The author cited 211 literary sources, which were cited correctly and as required in the text. The literature review analyzes and monitors current state of the art on a range of issues regarding tumor biology, indications for lymph node dissection and postoperative radiotherapy, as well as methods for metastasis. Particular attention is paid to tumor invasion of the blood and lymphatic tract (lymphovascular invasion) as a prognostic factor.

The review concludes with several conclusions that underlie the clearly stated and stated goal of the thesis: "To determine the prognostic significance of tumor invasion in lymphatic and blood vessels in patients with endometrial endometroid carcinoma stage I by FIGO." In order to achieve this goal, Assoc. Ismail has set herself 10 tasks. The clinical contingent includes 117 patients with stage I endometrial carcinoma under FIGO who underwent surgery at the Gynecology Clinic of the MHAT"St. Anna " for a period of 6 years (2009 - 2014). The study is retrospective, but with a long enough follow-up period to account for the major oncological parameters: 5 year overall and disease - free survival. The methods used are described as: surgical method, radiotherapy, histological examination and data processing. Various statistical methods have been used, and the Kaplan-Mayer method is particularly valuable for assessing overall and disease - free survival. These statistical methods are at the heart of the results obtained,

which give the author grounds for interpretations and analyzes.

The Results and Discussion section is a step-by-step solution to the ten assignments of the dissertation, brings the contributions of the dissertation and is written on 42 pages. The author found that patients with tumor invasion of the lymphatic and blood vessels had a 28-month lower survival rate than recurrence compared to other patients. On the basis of the obtained results and their discussion, Assoc. Prof. Ismail comes to 14 conclusions and makes 4 recommendations for the practice.

1. The overall and disease-free survival for stage I EEC is 89.3% and 93.75%, respectively. This histological appearance has a favorable prognosis.
2. The recurrence rate (local and distant) of the studied contingent is 6.25%.
3. Distant recurrences in parenchymal organs (liver, lung) account for 71% of the recurrence of the disease.
4. Over 50% of recurrence cases occur within the first 2 years and this should increase alertness in the follow-up of patients within the first 24 months after treatment.
5. Thorough staging with precision imaging (CT with contrast, MRI, or PET / CT) of the abdomen and lung before surgery is essential, especially in cases with poor histological data (G3, LVSI).
6. Revision of the histological preparations (second opinion) by an experienced pathologist of the material from the diagnostic test abrasion will lead to the selection of patients for more accurate staging and therapeutic tactics.
7. Treatment of recurrence (local and distant) is unsuccessful, regardless of the therapeutic agents used (TGT, CT, hormone therapy) and efforts should be directed towards prevention of their occurrence.
8. Stage I lymph node dissection does not have a staging role, except for increased palpation (clinical) and imaging methods. Lymph node dissection (pelvic and / or para-aortic) does not increase overall and disease-free survival.
9. Lymph node metastases have a poor prognostic significance, regardless of the applied TGT. The use of chemotherapy in these cases is appropriate.
10. LVSI positive patients have a 28-month lower average median survival to recurrence compared to other patients.
11. A case of MI equal to or greater than 1/2 of the myometrium has a 12-month less median survival to recurrence.

12. The high grade of the tumor (G3) has a strong negative effect on the median survival to recurrence. Patients with this histological parameter experience 40 months less (10 times) than others.
13. Post-operative TGT in the study 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.
14. LVSI positive and G3 tumor are independent factors that reduce both overall and disease-free survival, whereas deep myometrial invasion alone does not affect these indicators.

RECOMMENDATIONS FOR THE PRACTICE

1. Revision of histological preparations from the curettage material: is it carcinoma, sarcoma, mixed tumor, hyperplasia, EIN; histologic type (endometrioid, various components; nonendometrioid-serous, clear-cell, adenosquamous), G3, LVSI.
2. All cases with the exception of pure endometrioid carcinoma, G1-2 without LVSI, are subject to expert imaging of the abdomen and lung (PET / CT).
3. In the absence of distant or lymph node metastases from imaging, the volume of surgical treatment is total hysterectomy with bilateral salpingo-oophorectomy and exploration of the abdominal cavity, and palpation of the retroperitoneal space (pelvic and paraaortic lymph nodes). Lymph node dissection is recommended only for increased lymph nodes.
4. Chemotherapy and brachytherapy are recommended postoperatively in the presence of LNM, positive LVSI, G3. In the presence of MI > 1/2, TGT and brachytherapy are recommended, and in the absence of the aforementioned adverse factors, observation or vaginal brachytherapy alone.

IV. Contributions.

The contributions of the dissertation are 12 and are mainly scientific and practical. Six of the contributions are original in nature, the rest are confirmatory.
Contributions (scientific and practical)

1. An input document was created to build a database for women with stage I

endometrial cancer by FIGO.

2. A retrospective clinical and epidemiological study was performed, covering 112 patients with endometroid endometrial carcinoma - stage I, diagnosed, treated and monitored at the Gynecology Clinic of the Hospital of St. Anna - Varna AD and Oncology Hospital - Varna for the period 2009 - 2014 (for the first time in Bulgaria).

3. Frequency distribution of demographic and clinical characteristics of the sampled patients is presented.

4. The peculiarities of the overall survival of the studied contingent are analyzed.

5. Factors affecting overall survival have been identified.

6. A ranked quantitative assessment of the risk factors for overall survival (for the first time in Bulgaria).

7. The features of disease-free survival are analyzed. 8. The localization of the recurrence occurred (for the first time in Bulgaria).

9. The peculiarities of survival after relapse (for the first time in Bulgaria) are analyzed.

10. Frequency distribution of adverse histological parameters was performed in patients in Stage I EEC (for the first time in Bulgaria).

11. Poor histological factors for affecting disease-free survival were investigated (for the first time in Bulgaria).

12. Recommendations for behavior in primary diagnosis of endometrial carcinoma have been made.

V. Dissertation-related publications.

The scientific articles related to the dissertation are 12, 3 of which have been published in foreign journals. Dr. Ismail is the first author of 9 and the second - 3 of them.

VI. Conclusion

The dissertation work of Assoc. Prof. Dr. Elis Ismail, MD, PhD represents an excellent study on an important and relevant clinical oncogynecology problem associated with the establishment of optimal diagnostic and treatment approach based on established histopathological parameters in patients with endometrial endometrioid carcinoma in the first stage of FIGO. Through the obtained results, the dissertation has made contributions of original and applied character, enriching the existing knowledge and experience in our country. By relevance, scale and originality, the work has all the merits of a dissertation work for the acquisition of the Doctor of Science for the National Academy of Sciences. All this gives me the absolute conviction to vote positively for the award of the Doctor of Science in the of Obstetrics and Gynecology to Assoc. Prof. Dr. Elis Ismail, MD, PhD.

09 Sep 2019

Prof. Asen Nikolov, MD, PhD

Sofia