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## **ABSTRACT OF THE DOCTORAL THESIS**

**RISK FACTORS' SIGNIFICANCE, CLINICAL  
AND HISTOPATHOLOGICAL ASPECTS AND BIOLOGICAL  
MARKERS WITH PREDICTIVE  
ROLE IN ENDOMETRIAL CANCER**

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## THE GENERAL PART

Endometrial cancer is the most common neoplastic pathology of the uterus and the sixth most diagnosed cancer in women. The incidence of endometrial cancer increases with age, being the greatest between 45-65 years [1]. The most present are endometrioid endometrial cancers, which are estrogen dependent, being always preceded by endometrial hyperplasia. Estrogen exposure without progesterone counterbalance (as in obesity, nulliparity, early menarche, late menopause, postmenopausal replacement therapy) are important determinants of endometrial cancer; generically endometrioid endometrial cancers are low-grade tumors (G1 or G2), easily diagnosed, with Five-year survival rate above 90% [1].

Papillary serous and clear cell endometrial carcinoma however, have a high histological grade, are estrogen independent and occur in the atrophic endometrium of postmenopausal women, although cases have been described in patients without endometrial atrophy [1]. Risk factors for these cancers cannot be identified apart of ageing, although precancerous lesions could have existed in the presence of tumor protein p53 ("guardian of the genome") [2], endometrial glandular dysplasia or endometrial intraepithelial carcinoma (EIC) [3]; Five-year survival rate is below 45% [4]. The genetic determinism of these cancers is the subject matter of many research groups, but genetic studies have focused mainly on endometrioid endometrial carcinomas, leaving the other two relatively poorly defined.

All of the above led me to choose this research topic, the neoplastic endometrial pathology being important due to its large number of involved patients and to the complexity of diagnosis and treatment. I think that by deepening this topic I can contribute to improving algorithms for detecting people at risk and for an early diagnosis of endometrial tumor disease, which would lead to successful management, demonstrated by high survival rates.

Although preventable and unpredictable risk factors are largely well-known, although FIGO staging and endometrial cancer grading have reached a consensus, controversy over histological subclassification persists; markers used by clinicians for immunophenotypic characterization of endometrial lesions are not always validated, and perspectives in researching methods for an early diagnosis and for assessment of intravaginal ultrasound accuracy, as well as consensus statement on IETA terminology, remain under discussion for their role both in early and differential endometrial cancer diagnosis.

### Statistical data in endometrial cancer

Globocan 2018 data points out that the age standardized incidence has the highest values for North America (20.5 per 100,000 women, with 3.0 per 100,000 deaths) in second place being Central and Eastern Europe with 19.0 per 100,000, with 3, 9 per 100,000 deaths [5]. In Romania in 2018 there were 2,470 cases of endometrial cancer, meaning 6.4% of all cancers in women [6], ranking 11th on newly diagnosed cancers [6]; with mortality rate

ranked 21st in Europe. Five-year prevalence, regardless of age, shows that there are 8,478 women living with endometrial cancer in Romania in 2018, which means a proportion of 83.98‰.

## **Risk factors and protective factors in endometrial cancer**

**Obesity.** Compared to the normal-weight woman, the obese woman (BMI over 30) has twice the risk of endometrial cancer [7].

**Hormonal factors.** In menopause, the balanced production of estrogen and progesterone by the ovary ceases, but small amounts of estrogen arise from fatty tissue deposits, with postmenopausal estrogen having a much greater impact than before menopause [8].

**Estrogen therapy and contraceptive treatment** must be assessed for risks versus benefits [9] and the pregnancy protects the woman due to progesterone production [10].

**Diet and exercise.** Fat-free diet and exercise reduce the risk of endometrial cancer in women who exercise for 150 minutes a week [11].

**High blood pressure and diabetes** are common in obese or sedentary people, without determining whether their effect on the risk of endometrial cancer is direct or associated with other conditions [12].

**Family history.** In families with Lynch syndrome, there is an increased risk of colon cancer, women with this syndrome can develop endometrial cancer at a rate 70% higher. Breast cancer or ovarian cancer are significant risks while endometrial hyperplasia is a minor risk for endometrial cancer.

**Early menarche and late menopause.** Early menarche increases the risk for all cardiovascular diseases [13]. Late menopause is related to breast and liver cancer but the relationship to endometrial cancer is controversial.

**Polycystic ovary syndrome (PCOS)** is an increased risk for endometrial cancer, but does not present any risk for ovarian or breast cancer [14].

**Intrauterine device (IUD)** seems to induce a low risk for endometrial cancer, but the data are poor and limited to those that do not contain hormones.

**Age** is a risk factor for all cancers [15].

**Radiation therapy.** Radiation-induced bystander effect (RIBE) has recently been identified, through which non-irradiated cells placed in the vicinity or at a distance show similar responses to irradiated ones. Understanding the response of targeted and neighboring cancer cells to irradiation will lead to an improved therapeutic efficacy [16].

## **Endometrial cancer prevention**

Behavioral risk factors should be eliminated by maintaining optimal weight, controlling blood glucose and metabolic syndrome, avoiding sedentary lifestyle, dieting, regular gynecological examination, follow-up and treatment of endometrial hyperplasia, genetic counseling and hormone therapy as needed.

## **FIGO staging and grading in endometrial cancer**

FIGO staging in endometrial cancer is surgical, and the degree of histological differentiation describes the appearance of cancer cells compared to normal ones, microscopically evaluated, being at Low Risk: Stage IA (G1 and G2) of endometrioid type; at Intermediate Risk: Stage IA G3 of endometrioid type and Stage IB (G1 and G2) of endometrioid type; at High risk: Stage IB G3 of endometrioid type at all stages and of non-endometrioid type. According to current standards of FIGO-grading in endometrioid endometrial cancer (EEC) [17], the assessment is based on the degree of glandular differentiation: grade 1 display a solid, non-glandular structure, with scaly growth, in less than 5% of tumor volume; grade 2 has a solid, non-glandular structure, with scaly growth, in between 6% - 50% of the tumor volume; grade 3 has a solid, non-glandular structure, with scaly growth, for over 50% of the tumor volume.

## **Immunohistochemical markers in endometrial cancer**

D2-40 (podoplanin) may indicate the risk of lymph node metastasis [18]. Pancytokeratin PANCK (AE1-AE3) is useful as a screening for most human carcinomas. Cytokeratin 7 (CK7, K7) if present in the absence of CK20 is a good indicator for endometrial cancer [19]. Nephrilysin/CD10, can help definind the diagnosis [20] along with Chromogranin A and Ki67, which has a predictive value in oncology in term of disease's evolution [21]. Vimentin, in association with estrogen and progesterone receptors, is the standard for the typical immunophenotype [22]. Inhibins/activins are not yet clearly certified as important neither for the prognosis nor for clinical implications in endometrioid adenocarcinomas, although some studies indicate their presence correlated with histological grade, surgical staging, and myometrial invasion [23].

## **Therapeutic approaches in endometrial cancer**

The treatment of choice in EC is surgical, by hysterectomy, often accompanied by salpingo-oophorectomy and lymph nodes removal, followed or not by peritoneal lavage, omentectomy and peritoneal biopsy. Sentinel lymph node mapping is useful in the early stages of endometrial cancer and if cancer dissemination cannot be concluded by available imaging tests [24].

Radiotherapy is decided in relation to the stage, tumor grading, opting for external, internal radiotherapy (brachytherapy) or their combination. Hormone therapy is used in stages III-IV and in the recurrent ones and is frequently associated with chemotherapy [25].

Targeted therapies with angiogenesis inhibitors (Bevacizumab), mTOR inhibitors (Everolimus, Temsirolimus, Ridaforolimus) and BMI1 inhibitors (PTC-028) uses molecules that strictly address to the changes in the cancer cell [26]. In the therapy of endometrial cancer-for rare forms, a phase II clinical study showed that Trastuzumab in combination with other chemotherapeutics were effective [27].

## **New perspectives for early diagnosis: risk assessment for endometrial cancer (REC) by transvaginal ultrasonography (TVS)**

There is no screening method dedicated to endometrial cancer (except in relation to Lynch syndrome); in addition, there is no consensus on the cut-off value for the endometrium thickness (ET) from which to consider the abnormality. Many studies consider the value of ET  $\geq 5$  mm in menopausal women with bleeding a border that must require investigation [28].

TVS is included in a number of endometrial cancer risk assessment algorithms, and in 2008 an international group for the analysis of endometrial tumors have established IETA terminology based on definitions and measurements necessary for sonographic description of the endometrium and uterine lesions [29].

Mathematical models have been developed that include ultrasound variables in grayscale and color Doppler, such as endometrial echogenicity, endometrial midline appearance, endometrial–myometrial junction, vascular pattern, which helps to calculate the risk for malignancy in postmenopausal bleeding and in endometrial thickness ET over 4.5 mm [30].

The IETA criteria are: a) Endometrium morphology: 1. homogeneous (without cystic areas) and 2. inhomogeneous (with cystic areas); b) Endometrial–myometrial junction: 1 regular, 2.irregular, 3. Interrupted, 4. not defined; c) Intracavitary fluid: 1. pure liquid collection, 2. ground glass, 3. mixed; d) Doppler color score (1. no color; 2. minimal color; 3. moderate amount of color; 4. abundant color); e) Vascular pattern (1. single dominant vessel without branching; 2. single dominant vessel with branching; 3. multiple vessels with focal origin; 4. multiple vessels with multifocal origin; 5. circular flow; 6. scattered vessels).

## THE SPECIAL PART

### Endometrial cancer in relation to the analyzed cases

We analyzed 594 cases with uterine bleeding, hospitalized between 2015 - 2019, of which 153 were endometrial cancers, with a mean age of 56.41 years. This average cannot be compared with those of other studies, because by calculating standardized rates by age groups in different regions of Europe the average age can be below 40 years in northern and southern Europe, around 45 years in Eastern Europe and below 40 years in Western Europe, 9 in the USA being globally appreciated at 60 years; identically, atypical endometrial hyperplasias constantly appear after 40 years, being equally present over this age, the average age being 54 years. This study confirms the results of other studies estimating that 50-54 years old women are the most affected by atypical endometrial hyperplasia [31]. The mean age at detection of typical endometrial hyperplasia is 54.53 years.

The inequity between the addressability to medical services and the level of education of women in urban areas compared to rural ones is obvious, the latter being present in obstetrics-gynecology hospitals at a rate lower than 50%, while having a level of education that stops especially at the primary, secondary and vocational studies.

Family history or personal history of neoplasms reaches 100% in adenomyosis/endometriosis, 69.23% in cervicitis, 35.33% in typical endometrial hyperplasias, 30% in ovarian cysts, 25% in cervical dysplasias, 22.91% in endometrial polyps, 16.54% in leiomyomas, 9.09% in endometritis, 7.18% in endometrial cancer, the empirically attributable genetic risk being recognized in the scientific community [32].

Menarche was declared on average at 12 years and menopause at 49 years. Compared to other studies, it seems that menarche settles faster in our area, the average in other countries being 13.53 years, while the average for installed menopause is 49 years in general [33].

Histologically, the aggressive and rare forms of mucinous endometrioid adenocarcinomas, with clear and squamous cells, moderately differentiated and undifferentiated endometrioid carcinomas, mixed or serous, secretory ones and uterine carcinosarcoma are not exceptional. The associations between endometrial lesions, benign or malignant, are superior to other communications [34]. The diagnostic accuracy of immunohistochemical markers in endometrial adenocarcinomas and endometrioid serous carcinomas stands up the use of immunohistochemical diagnosis in routine practices, immunohistochemistry being used on daily basis in medical systems that rely on evidence-based medicine [35]. The risk of recurrence in stage I was high for 15.09% of cases, intermediate for a quarter of them (25.47%) and low for more than half of cases (59.43%), these figures being increased in the context in which other studies reports high risk in up to 14% of cases, intermediate in around 7% and low in 4% of cases [36].

## **Charlson Comorbidity Index in endometrial lesions**

The Charlson Comorbidity Index classifies comorbidities based on the International Classification of Diseases with which hospitals operate administratively. For each comorbidity category is assigned a value between 1-6, depending on the adjusted mortality risk, the sum of these values creating a unique score for each patient; the zero value of the score indicates the absence of a comorbidity, and the higher the score, the higher the probability of death is. In endometrial cancer, the Charlson Comorbidity Index analyzes patients' secondary diagnoses and can predict mortality by assigning a weight to each comorbidity, a procedure used by medical research to assess the burden of the disease and especially the characteristics of Case mix. After cohorting the 594 patients by decades of age, in order to calculate the chances of survival at 10 years, for identifying the most common involved comorbidities the results were: hypertension (62.28%), obesity (35.01%) and diabetes (22.89%), on the first three ranked, all of which being risk factors for tumor disease in general, and cardiovascular disease fourth-highest ranked. These results are similar with the literature [37]. The study in this dissertation highlights the need for extensive screening for diabetes (for every woman with diabetes there are at least 9 who may develop endometrial cancer or atypical endometrial hyperplasia), obesity (there are at least 8 obese women who may develop endometrial cancer or atypical endometrial hyperplasia), and high blood pressure (for every woman with high blood pressure there may be at least 3 other women with high blood pressure who may develop endometrial cancer or atypical endometrial hyperplasia). High blood pressure increases the risk of endometrial cancer compared to typical endometrial hyperplasia (for every hypertensive woman there may be at least 3 women who may develop endometrial cancer or atypical endometrial hyperplasia), which demonstrates the role of hypertension in endometrial cancer, as highlighted by other research [38].

The ten-year survival rate is 95.85% for women under 50 years old decrease to 82.31% for the decade 50-59, decrease to 62.90% for the decade 60-69, decrease to 35.98% for the decade 70-79 and is 1.38 % over 80 years old. This study also documents that the prevalence of diabetes among 594 women exceeds the prevalence of diabetes among general population by at least 10 percent (22.39%) and confirms the working hypothesis that the presence of comorbidities (hypertension and obesity) is strongly positive correlated with endometrial cancer.

## **The role of ultrasound in endometrial cancer**

Transvaginal sonography remains an integral part of a complete gynecological examination, endometrial thickness values over 5.15 mm appear to be the cut-off for endometrial hyperplasia or endometrial cancer, according to the largest study [39, 40], performed on 48,230 women in postmenopause, which were investigated by transvaginal ultrasonographic screening.



The objective of this study was to create an imaging atlas in order to exemplify the salutary role of transvaginal ultrasound in identifying and discriminating malignant endometrial lesions from premalignant and benign ones. We analyzed 420 cases out of 594 assisted for endometrial lesions with bleeding in the two clinics between 2015-2019, IETA statistics demonstrating statistically significant differences in endometrial echogenicity, endometrial junction vascular patterns, presence and character of intrauterine fluid and IETA Doppler score, in malignant versus benign endometrial lesions. The ultrasound classification of the examined lesions was compared with the histopathological results; the correctness of the method and the statistical significance of the IETA validation was assessed using the area under the ROC curve (AUC-ROC) [41].

The results showed that it is possible to discriminate, by the inhomogeneous endometrial morphology, between endometrial cancer and atypical endometrial hyperplasia versus other lesions. Likewise, the endometrial junctions is linear in benign versus premalignant or malignant endometrial lesions (which exhibit an indefinite or irregular junction), which means that in the presence of an indefinite or irregular endometrial junction the neoplasia must be the first suspect.

The vascular pattern presents statistically significant differences, the benign diseases having vascular aspect without vascular branches (81.57%) while in endometrial cancer the circular vascularization is dominant, with multiple vessels with focal origin or multifocal origin, which demonstrates that the sonographic evaluation has its confirmation in the establishment of endometrial angiogenesis. Also the aspect of intracavitary fluid shows statistically significant differences in relation to the diagnosis, the presence of mixed aspect in endometrioid endometrial cancers being confirmed.

IETA scores of 3 or 4 in endometrial cancer are present twice as frequently compared to other endometrial lesions, which supports the value of sonography in establishing the neoplastic etiology.

### **Study of population groups at risk, by assessing the knowledge and perception of endometrial cancer, in Arad and Timiș counties**

In order to assess the perception regarding endometrial cancer, the questionnaire "Significance of risk factors and endometrial cancer" was designed, in which were present: dropdown question (age), dichotomous questions with imposed, predefined answers (yes/no type, rural/urban); closed questions with answers to choice, semi-open (how many partners, how often have you been gynecological examined) filter questions (talk to your doctor or partner); direct questions (smoking, drinking alcohol); indirect questions (fear of neoplasia) etc. The first part of the questionnaire contains the identification elements, being followed by the fields containing the sociodemographic data, later questions were added that go from simple to complex and Cronbach's alpha was validated. The completion of the

questionnaire was done face-to-face, in a confidential interview, the participants assuming, under their signature, the desire to answer, the time allocated to each respondent being on average 30 minutes. The sample size (318 women) was calculated for a 95% confidence level, a 50% confidence level and a confidence interval level (margin of error) of 4, which ensures a relevance of 50+ responses. /- 4.

The results show that the female population is becoming more concerned about their reproductive system health, the fear of tumor disease being perceived in a wide range of opinions, from the impossibility of its presence to the extreme fatalism asserted as a relentless fact. Preventive methods are generally known, partially applied, but sanogenic behavior, even if it is in principle known, is not widely applied [42]. Thus, regarding the behavioral risk factors for endometrial cancer, there are the early onset of sexual life, the increased number of sexual partners, lack of protection during sexual intercourse, absence of basic notions of reproductive health, fear or embarrassment in the open approach to these problems etc.

Our study shows that women, regardless of their residence, begin to become sexually active around the age of 18, but a third of them start just before adulthood. Monogamy is not a rule, on average there are 2-3 sexual partners, the use of condom protection being more common in those with more than 2 partners. Regarding the behavioral risk factors characterized by alcohol and tobacco use, almost half of the respondents admit alcohol in their lives while a quarter are smokers.

PAP testing has already entered the culture of women in Romania, at least in those under 60 years of age. Visits to the gynecologist are generally infrequently, once every 5 years, which should be corrected. Genetic factors are still incompletely evaluated, although our data show that people carrying genes involved in oncogenesis can reach a rate of 23%. Respondents are aware of the link between endometrial cancer and hypertension, diabetes, increased body mass index, sexually transmitted infections, family history, sedentary lifestyle and they are eager to discuss genital health issues.

The questionnaire method is valuable in research on population groups at risk, and this questionnaire was internally validated with a coefficient of  $\alpha$  over 0.8.

## CONCLUSIONS AND PERSONAL CONTRIBUTIONS

**These four studies contained in this doctoral thesis have achieved the proposed objectives, because:**

- They demonstrated that both endometrial cancer and other endometrial lesions, are mainly due to genetic or behavioral impairment factors that affect carcinogenesis,
- They showed that the interception of patients occurs at the right time to ensure the diagnosis and treatment of endometrial lesions, in order to achieve Ten-year survival in the highest rates,
- They have provided evidence that the histopathological profile and immunophenotype of malignant lesions are generally common to those reported by other studies, but rare and aggressive forms of endometrial cancer occur in high rates,
- They demonstrated that immunophenotyping is relevant for the differential diagnosis of benign and malignant endometrial lesions, being positive in most investigated malignancies,
- They emphasized that using IETA (International Endometrial Tumor Analysis) terminology on daily basis significantly contributes to the detection of premalignant or malignant endometrial lesions, being a tool that can be used as a preferred safety substitute to other more invasive investigative techniques,
- The impact of comorbidities on survival was emphasized,
- The relative risks or chances of disease of the female reproductive system in relation to age, comorbidities, family history, education, marital status, were supported, with statistical validation,
- They reiterated that the low level of education, the rural environment and the isolation of the housewife aggravate the manifestations of endometrial diseases,
- They presented that, in general, the interviewed women perceive correctly the presence of risk factors for tumor disease, genetic input, living environment and behavioral slippage echoed by tumor disease,
- They found that, in close connection with the balanced perception of risk factors, preventive gestures are known by the female population that can partially avoid the risks of tumor disease, but there is still no culture of regular medical examinations or capitalization of available screening tests,
- They emphasized that the addressability of women to the medical specialist is not a routine, appearing especially under the pressure of the already installed disease's signs and symptoms,
- They demonstrated that there are still inequities in the access to specialized medical services, which can dangerously delay the correct management of early detection of tumor disease,

- The risk factors for endometrial cancer were presented from the perspective of the female population, also showing their sources of medical information,
- There were identified behavioral elements that could be modified in order to prevent increased morbidity due to endometrial cancer,
- They recorded the main present comorbidities in women with and without endometrial lesions, in terms of obesity, family history or personal history
- They established the internal consistency of the designed questionnaire which was applied specifically for this study and which has not been used before.

**These four studies contained in this doctoral thesis have achieved the proposed goals in that:**

- They identified the characteristics of endometrial pathology with hospitalization in women from Arad and Timis counties, signaling the areas with deficiencies that can be alleviated, in order to improve reproductive health, both from the point of view of the health system, which is not sufficiently accessible and prompt in the dispensation of chronic diseases and from the multidisciplinary evaluation of the patient's perspectives,.
- The inconsistent addressability of patients to available preventive health services has also been documented.
- Ten-year survival for endometrial lesions were calculated, using the Charlson Comorbidity Index [43].
- They successfully compared the fidelity of the immunohistochemical and sonographic diagnosis in endometrial lesions, using IETA terminology.
- They reported the perception, partially correct, of the health determinants and how these health factors are known or ignored by people at risk in a female population that is still anchored in a patriarchal society, where feelings are restrained, and embarrassment or prohibition may dominate discussion sexually related discussion.
- They managed to establish the level of knowledge related to the health of the female reproductive system, and that any intervention for reducing morbidity from endometrial cancers require a paradigm shift from both patients and health system authorities.

Through these research methods applied in these four studies, **the working hypotheses were confirmed:**

- Endometrial cancer is associated with age, diabetes, obesity;
- The presence of specific immunohistochemical markers to endometrial cancer is more common than in other endometrial lesions;

- ETA terminology contributes significantly to the distinction between ultrasound aspects of endometrial cancer versus endometrial hyperplasia;
- The most common comorbidities presented in women with endometrial lesions are cardiovascular disease, hypertension, diabetes, obesity, ie those common to the general population;
- There is an inversely proportional relationship between the number and weight of comorbidities (as established by the Charlson Comorbidity Index) and Ten-year survival;
- Transvaginal ultrasound using IETA terminology can detect malignant lesions from benign ones in endometrial pathology.

Research should be continued in the **following directions**:

- The management of the woman with a pathological family history indicating the risk of tumor disease, must provide adequate screening methods, by supplementing health programs with genetic testing.
- Development of medical services and correction of their deficiencies, as shown in the specific Ishikawa diagram.
- Intensification of health education and introduction of these elements in school curricula.
- Continuing education of gynecologists in order to include updated ultrasound courses, in the spirit of IETA terminology.

The paper provided **additional arguments** regarding the role of genetics, imaging, immunohistochemistry and different risk and prognosis indices, both at the individual and population level, for tumor disease, emphasizing the importance of evidence-based medicine and also pleading for an individual approach of each patient, depending on demographic criteria, own biology and lifestyle hazards..

In addition, **it highlights the inequities in the accessibility** of a part of the population to health services, services that must be supported by constant funding, for a real democratization of a complete and quality healthcare, in relation to the most effective and available methods of diagnosis and treatment.

**Summarizing**, contributions are:

- Structuring the imaging, anatomopathological and immunophenotyping elements of differential diagnosis (by IETA terminology, with an atlas of eloquent sonographic images for different types of uterine lesions, with the achievement of histological and immunohistological atlas of representative cases captured in this study).
- Associations of risk factors for endometrial lesions and their correlation with the sociodemographic characteristics of patients and responders to the questionnaire.

- Construction of Ishigawa cause-effect diagram, which highlighted the key aspects of the elements that lead to endometrial cancer, an useful tool in health policies dedicated to female pathology outside pregnancy.
- Observations regarding the cultural, educational, social, family and medical communication, with behavioral adjustment plan.
- Last but not least, highlighting the system factors that could be improved to ensure prevention, early diagnosis and appropriate treatment for every woman, aiming to reduce disease, increase quality of life and reduce costs to society caused by preventable gynecological morbidity.

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