UNIVERSITY OF MEDICINE AND PHARMACY
CRAIOVA

DOCTORAL THESIS

SUMMARY

Clinical, histopathological and immunohistochemical study of endometrial carcinomas

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KEYWORDS: endometrial carcinoma, histopathology, immunohistochemistry, statistical analysis, prognostic factors


Introduction

The thematic is very important in the current context in which endometrial carcinoma is considered to be the most common invasive malignancy of the female genital tract. Investigation of endometrial immunomarkers involved in carcinogenesis may influence early detection and treatment, with direct impact on prognosis by increasing life expectancy.

Study Objectives

The purpose of this doctoral thesis is that of extending knowledge about the clinical, histological and immunohistochemical factors involved in endometrial carcinogenesis. The major objective pursued by me in this personal study is to determine the most significant statistical correlation between clinical, histopathological and immunohistochemical markers involved in tumor invasion and aggression.

MATERIAL AND METHODS

A. Investigated material

The study analyzed clinical, morphological and biomolecular features of endometrial carcinomas diagnosed in the Pathology Laboratory of Clinical Emergency County Hospital Craiova, over a period of five years, between 2005-2009. The study included a total of 74 tumors from patients hospitalized in the Gynecology Clinics of the same hospital, the biological material being represented by pieces of hysterectomy or biopsy fragments.

B. Methods

The biological material was processed by the classical method by paraffin-embedded and Hemalaum-Eosin staining. Histopathological analysis was performed for all 74 endometrial carcinomas and included the following criteria: architectural type, tumor grade, histology type, tumor invasion and staging. Immunohistochemical analysis was performed on a group of 42
selected cases of endometrial carcinomas, using simple and doubles techniques. Statistical analysis use correlation coefficients like chi-square, Pearson.

**RESULTS**

**A. Clinical analysis of endometrial carcinomas**

Patients studied were characterized by low fertility, with early menarche and late menopause. Overweight patients diagnosed with endometrial carcinoma were found to have the pathology associated with diabetes mellitus. Anamnesis made to the 64 patients described the use of postmenopausal hormone replacement therapy in 13 cases, lasting over six months. In postmenopausal patients, the main symptom was metrorrhagia and leucorrhea. In women between 40 and 49 years, so sexually active the disease manifested as abnormal uterine bleeding, intermenstrual bleeding and dyspareunia.

**B. Histopathological analysis of endometrial carcinomas**

Of the 74 endometrial carcinomas studied, the vast majority was represented by endometroide carcinomas, 66 cases, representing 89.2%. Nonendometroide tumors were only 10.8% of them, being represented by mucinous carcinoma with 2.71% of cases, papillary serous carcinoma 5.38%, and clear cell carcinoma 2.71% of cases.

I noticed the predominance of G1 endometrial carcinoma found in 39 cases, followed by 19 cases of carcinoma G2 and G3 in 16 cases. Statistical analysis showed that the degree of differentiation was significantly correlated (VHS) with histology.

In terms of tumor progression, of the 47 cases of endometroide adenocarcinomas, in 36 cases the tumors were confined to the uterine corpus and in 4 cases have spread to the cervix. Local expansion and metastasis were present in 7 cases: two cases of periaortic limph nodes invasion, 3 cases of fallopian tubes, ovaries and pelvic nodes invasion, 2 cases of invasive carcinoma with liver metastases. Statistical analysis determined that tumor stage was significantly correlated (VHS) with myometrial invasion.
C. Immunohistochemical analysis of endometrial carcinomas

Were investigated immunohistochemically 42 cases represented by a number of endometroide carcinomas with varying degrees of differentiation and nonendometroide carcinomas (4 cases of serous carcinoma and 2 cases of clear cell carcinoma). ER imunoexpression showed a positive response in 32 cases, representing 76.19% of them. The expression of these receptors decreased parallel with increasing histological differentiation, having the lowest values for G3 carcinomas and for nonendometroide types. Pearson index showed a linear distribution, but negative between ER and Ki67 values.

p53 immunoassay was positive in 16 of the 42 cases analyzed, constituting 39.10% of all carcinomas investigated immunohistochemically.

Ki67 immunoassay showed positivity in all cases examined, at both stromal and epithelial level. I noticed that the average index for Ki67 proliferation has reached the highest values in nonendometroide carcinomas, in 68% of cases. For endometroide carcinomas there was a progressive increase in Ki67 with the tumoral grade of the carcinoma. p16 immunoassay showed positivity in 19.05% of the analyzed carcinomas. Negative tumors corresponded both endometroide and nonendometroide carcinomas. Endometroide carcinomas were p16 positive tumor grade G1 (1 / 18) and G3 (3 / 8), while nonendometroide p16 positive carcinomas (4 / 6) were serous and clear cell tumors.

E-cadherine immunoassay showed positivity for 80.95% of endometrial carcinomas studied. We found that the G1 and G2 endometroide carcinomas were all positive for E-cadherine while G3 carcinomas showed positivity only in 4 cases. Nonendometroide carcinomas were positive only in two cases.
CONCLUSIONS

• The analyzed tumors belonged to patients within a large spectrum of ages, between the IVth and VIIIth decades of age, the maximum incidence being mostly within the perimenopause (50-69 years).

• The study of personal physiological history allowed obtaining interesting conclusions on reproductive factors which may influence the risk of endometrial cancer: low fertility, with early menarche and late menopause.

• Pathological history confirmed the high incidence of endometrial carcinoma in obese patients (56.75%) who had the disease associated with diabetes mellitus, while the polycystic ovary syndrome was present in only 10.81% of patients and the replacement therapy in 17.56% of patients.

• The histopathological study revealed the clear predominance of endometroide carcinomas (89.2%) rather than nonendometroide ones (10.8%).

• Endometroide carcinomas showed maximum incidence around the age of 65 while the histological assessment degree indicated predominant well differentiated forms, with the following frequency incidence: G1 tumors, 57%, G2 - 27.98%, G3 - 14.70%

• Out of the 59 diagnosed cases of endometroide carcinomas, a total of 34 cases were typical endometroide adenocarcinomas, representing 51.53%, the other 25 cases (48.47%) being represented by variants (with squamous differentiation - 15.15%, viloglandulare - 13.62%, with ciliated and secretory cells - 10.60%).

• The immunohistochemical study comparing the two types of endometrial carcinomas, the endometroide and the nonendometroide ones, aimed at the appreciation of the hormonal receptors expression (ER and PR), as well as at some of their markers of aggressiveness (p53, p16, Ki67, E-cadherine).

• We noticed the decrease of the hormonal receptors expression, ER and PR, in parallel with the increased histological degree of differentiation, the lowest values occurring in the case of endometroide G3 carcinomas and their absence in nonendometroide carcinomas; this finding may be of a particular clinical importance because almost half of poorly differentiated endometrial carcinomas contain estrogen / progesterone receptors and they might benefit from a progesterone therapy.
• The study of the oncoproteine immunoexpression p53 was positive in 39.10% of the analyzed cases, corresponding mostly to the nonendometroide and endometroide G3 carcinomas (intense and diffuse positive), G1 and G2 endometroide tumors being rarely positive (weak and focal positive); one may sustain that for endometroide carcinomas the number of positive cases decreased proportionally with the increasing degree of differentiation, thus defining a subset of endometrial carcinomas with a highly aggressive behavior.

• The analysis of p53 expression and of hormonal receptors (ER and PR) showed an inverse relationship. Thus, in the case of endometroide tumors of low level (G1 and G2) the ER and PR expression was the highest, while p53 expression was low compared with the endometroide tumors of high-level (G3) and with the nonendometroide ones where the expression ER and PR was the lowest and p53 expression very high (level 3); as a result, the immunohistochemical determination of ER, PR and p53 on curettage fragments at patients with endometrial tumors G1 and G2 allows the recognition of patients with favorable prognosis who should not undergo radical surgery.

• The analysis of Ki67 proliferation index showed progressively increasing values of the IP along with the degree of differentiation and carcinomas type; the lowest values were recorded in the group of endometroide carcinomas where the IP values presented progressive increase with their degree of differentiation; the immunohistochemical determination of proliferative activity using Ki67 index might contribute in addition to conventional histological parameters, to identify the subgroup of endometrial carcinomas with a high-risk.

• The Ki67 index may be useful in identifying those serous carcinomas which do not express p53; in these cases, the intense and diffuse positivity (more than 75% of cells) represents an argument in favor of serous carcinomas.

• The statistical analysis outlined a high negative linear distribution between PR and Ki67 values, with a 0.93 Pearson index.

• The analysis of p53 and Ki67 expression indicates a proportional relationship, p53 having the highest level within the tumors group with the largest IP-Ki67, respectively within the endometroide level 3 carcinomas and within the squamous nonendometroide ones.
• The analysis of the expression for p16 showed positivity in endometroide G3 and nonendometroide carcinomas; the immunomarker was intense and diffuse in the nonendometroide carcinomas unlike the endometroide G3 carcinomas which showed a focal immunomarker of weak intensity.

• On curettage fragments from patients with endometrial cancer, p16 expression is useful to identify high-risk patients and provides important information regarding the traditional prognostic markers.

• Endometroide carcinomas indicate progressively higher percentages of the absence of E-cadherine expression, proportional with the decrease of the histological differentiation level, which might explain the more aggressive behavior of nonendometrioide carcinomas than that of endometroide ones.
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**Abstracts**


