Original Paper

Clinicopathological Prognostic Parameters of Endometrioid Endometrial Carcinomas

ILEANA DROCAȘ[1], ȘTEFANIA CRĂIȚOIU[2], ALEX EMILIAN STEPAN[3], IOAN ANDREI DROCAȘ[4], MIOARA DESDEMONA STEPAN[5]

[1]PhD Student, Department of Histology, University of Medicine and Pharmacy of Craiova, Romania

[2]Department of Histology, University of Medicine and Pharmacy of Craiova, Romania

[3]Department of Pathology, University of Medicine and Pharmacy of Craiova, Romania

[4]Department of Urology, University of Medicine and Pharmacy of Craiova, Romania

[5]Department of Infant Care-Pediatrics-Neonatology, University of Medicine and Pharmacy of Craiova, Romania

ABSTRACT: Endometrioid endometrial carcinomas (EEC) are common malignant lesions of the female genital tract, with incidence and risk factors that raise issues to improve histopathological prognostic factors. The study included 50 EEC cases, for which the clinicopathological parameters represented by age, risk factors, tumor grade, histological differences, invasion pattern, tumor stage and association of endometrial hyperplasia were analyzed statistically. The results indicated the predominance of EEC in the 7th decade of life, with associated risk factors (78%), more frequently well differentiated (52%), with no other specifications related to differentiation (NOS, 60%), with irregular invasion pattern (66%) in<50% of the myometrial wall (48%). Irregular pattern, microcystic, elongated, and fragmented (MELF) pattern and myoinvasion associated with vascular invasion (MVI) pattern were significantly associated with high grade and advanced stage tumors. With the exception of EEC-NOS and squamous differentiation, all other tumors were associated with low grade (G1). In this study there was a tendency to associate the age group of 60-69 years with the presence of endometrial hyperplasia and with high grade and advanced stage. Apart from the high grade and advanced stage, in the aggressive profile of the EEC can be included as the clinicopathological parameters the 7th decade of life and the irregular, MELF and MVI invasion patterns.

KEYWORDS: *Endometrial endometrioid carcinoma, prognostic parameters, invasion pattern.*

Introduction

Uterine corpus cancer is one of the most common human malignancies, which raises many issues in clinical practice, both due to the incidence and associated risk factors and the difficulty of improving the prognosis of patients.

With over 300,000 new cases diagnosed each year, it is estimated that the incidence rate of uterine cancer will increase worldwide by more than 50% until 2040, mainly due to obesity and increased life expectancy, as well as hormone therapies used incorrectly or in excess [1,2].

In our day, with nearly 90,000 deaths annually worldwide, uterine cancer ranks 14th among the causes of cancer deaths [3].

Endometrial carcinomas account for over 90% of cancers with this location, of which over 75% are endometrioid endometrial carcinomas (EEC) [4,5].

According to the dualistic pathogenic model of the endometrium, EECs are carcinomas associated with persistent estogenism, not unopposed by progesterone, and which respond to hormone therapy [4].

Estrogen exposure increases the risk of developing EEC by 3-4 times, and after 10 years of continuous exposure the risk increases by 10 times [6].

Factors that induce endometrial exposure to high estrogen levels include obesity, early menarche, late menopause, tamoxifen therapy, nulliparity, the presence of estrogen-secreting ovarian tumors, and polycystic ovary [3,7].

Although the EEC mortality rate has fallen in Europe, it has remained high in patients without access to the latest oncological therapies [8].

Also, although both diagnostic and surgical and oncological treatment methods have been improved, including for different types of endometrial carcinoma in relation to molecular subtype, the biological behavior of EEC remains difficult to predict, and there is a continuing concern for improvement of the criteria for assessing of tumor aggressiveness [9].

The most important clinicopathological prognostic factors for EEC are considered to be the age group, body mass index (BMI), tumor grade and stage, and lymphovascular invasion. [10].

The study followed the existing relations between the prognostic clinicopathological parameters of the EECs, in order to identify tumor profiles associated with their aggressiveness.

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Material and Methods

The study included 50 endometrioid endometrial carcinomas (EEC), which were operated in the Gynecology and General Surgery Clinics of the County Emergency Clinical Hospital of Craiova, during 2017-2020.

Surgical specimens were represented by total hysterectomy samples, which were fixed in 10% formaldehyde and processed classically by paraffin inclusion and Hematoxylin-Eosin staining, within the Pathology Department of the indicated hospital.

The histopathological diagnosis was made in accordance with the latest indications of WHO (World Health Organization) specialists for uterine tumors [3].

For the investigated tumors, the EEC clinicopathological parameters were followed, respectively the diagnostic age, the associated risk factors, the association with precursor lesions, the tumor differentiations and the invasion pattern and their relation with the main prognostic histopathological parameters of the lesions represented by the tumor grade and stage.

Statistical analysis was performed using the chi-squared ($\chi 2$) comparison test within IBM SPSS (Statistical Package for the Social Sciences) Statistics 10 software, the values of $p<0.05$ being considered significant.

In this study, the ethical rules of scientific research were respected, being approved by the Local Ethics Committee.

Results

The analysis of the investigated clinicopathological parameters indicated the predominance of EEC after the age of 50 years (48 cases, 96%), with a maximum incidence in the 7th decade of life (31 cases, 62%), and with an average age of diagnosis of 62.3±6.9.

In most cases, associated risk factors were identified, namely hormonal status disturbance, obesity, family history (inherited factors) or their associations, an aspect observed for 39 cases (78%) (Table 1).

Histopathological analysis indicated the association of EECs with endometrial hyperplasia without atypia in 3 cases (6%), with atypia in 9 cases (18%) or mixed in 5 cases (10%), the hyperplastic areas being observed in the adjacent EEC areas (Table 1).

Depending on the architecture and nuclear atypia, the analyzed EECs were more frequently well differentiated (G1), an aspect observed in 26 cases (52%), and were characterized by relatively uniform, visible glands, sometimes with papillary projections with stratified atypical columnar epithelia and relatively low mitotic activity (Figure 1A).

Moderately differentiated EEC (G2) were identified in 32% of cases, with less visible glandular structures and sometimes solid tumor areas, with atypical cellularity including superior mitotic activity EEC G1 (Figure 1B).

In the case of poorly differentiated EEC (G3), identified in 16% of cases, glandular structures were virtually absent and replaced by compact tumor islands with atypia and high mitotic activity and frequently with the presence of necrosis areas (Figure 1C, Table 1)

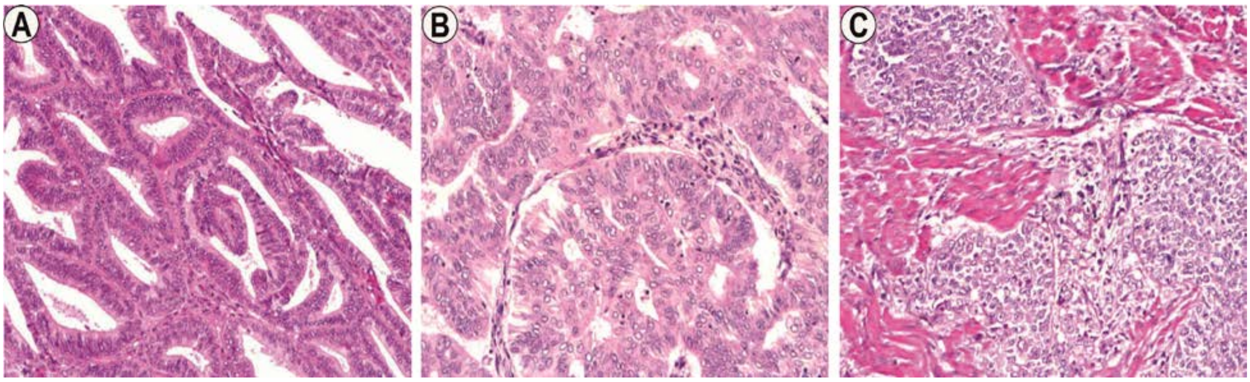

Figure 1. Endometrial endometrioid carcinoma (EEC), HE staining, x100.
A. Well differentiated (G1) EEC; B. Moderate differentiated (G2) EEC; Poorly differentiated (G3) EEC.

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Table 1. Distribution of cases in relation to the investigated clinicopathological parameters.

Parameters		No. cases
Age groups	40-49	2
	50-59	12
	60-69	31
	70-79	5
Risk facors	Absent	11
	Obesity	3
	Hormonal status	20
	Inherited	3
	Mixed	13
Hyperplasia	Absent	33
	Without atypia	3
	With atypia	9
	Mixed	5
Tumor Grade	Well differentiated (G1)	26
	Moderate differentiated (G2)	16
	Poorly differentiated (G1)	8
Tumor differentiation	NOS	30
	Squamous	10
	Secretory	4
	Villoglandular	2
	Ciliated	2
	Non-villous small papillae	1
	Microglandular	1
Invasion pattern	Irregular	33
	Pushing	7
	Diffuse infiltrative	4
	Microcystic, elongated, and fragmented (MELF)	3
	Myoinvasion associated with vascular invasion (MVI)	3
Tumor Stage	IA	24
	IB	19
	II	4
	IIIA	1
	IIIC1	2

Most EECs were undifferentiated-no other specifications NOS (60%), in which the aspects were classical glandular malignant, with the presence of glands of variable size, generally medium, sometimes complex with anastomosed or cribriform appearance, with variable mitotic activity and sometimes with desmoplastic response (Table 1).

In the EEC-NOS group, 76.7% of tumors were G1/G2.

EEC-NOS were followed in the order of frequency by EEC with squamous differentiations (20%), observed in G1-G3 EEC with glandular focal distribution or mixed with glandular structures, with the presence of keratin lamellae or morules or as tumor masses with different degrees of differentiation (Figure 2A).

Secretory differentiations of EEC were observed in 8% of cases, all tumors being G1, with a confleunt glandular pattern, with supra-and subnuclear epithelial cellular vacuolations. (Figure 2B).

At the same time, each of villoglandular and ciliated differentiations were identified in 4% of cases, associated with G1 EEC, the tumor architecture being in the form of thin papillae with delicate fibrovascular cores, respectively glands covered by ciliated epithelia (Figure 2C).

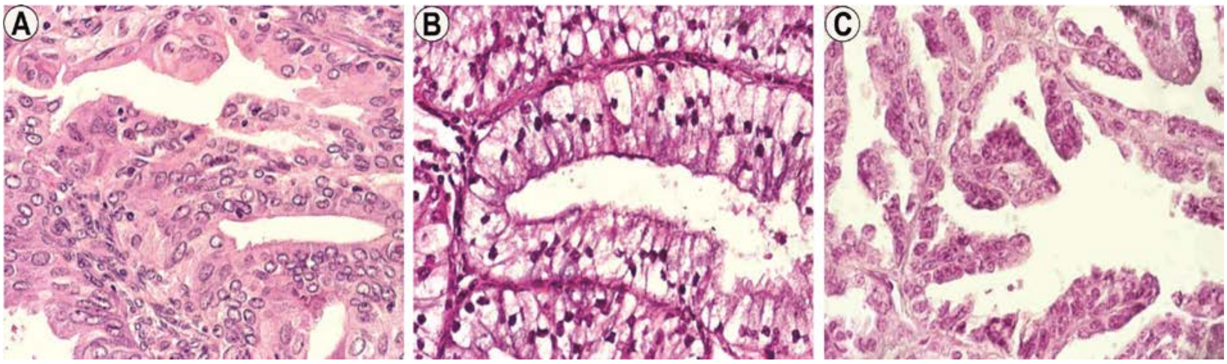

Figure 2. Endometrial endometrioid carcinoma (EEC), HE staining, x200. A. Squamous differentiation. B. Secretory differentiation. C. Villoglandular differentiation.

The rarest differentiations, observed in each 2% of cases, were those with small non-villous small papillae and microglandular, which were associated with EEC G1 and respectively G2, and which were characterized by the presence of small papillae without fibrovascular cores and the presence of confluent acinar glandular structures with small lumen.

Numerous patterns of tumor invasion have been identified in this study.

The most common was observed irregular pattern identified in 33 cases (66%), which was characterized by heterogeneous tumor groups that invaded desordered the stroma, sometimes with inflammatory reaction and desmoplastic response, the appearance being more common in G1/G2 EEC (Figure 3A).

The pushing pattern was identified in 7 cases (14%) and associated with G1 EEC, presented tumor masses that induced pressure on the adjacent structures (Figure 3B).

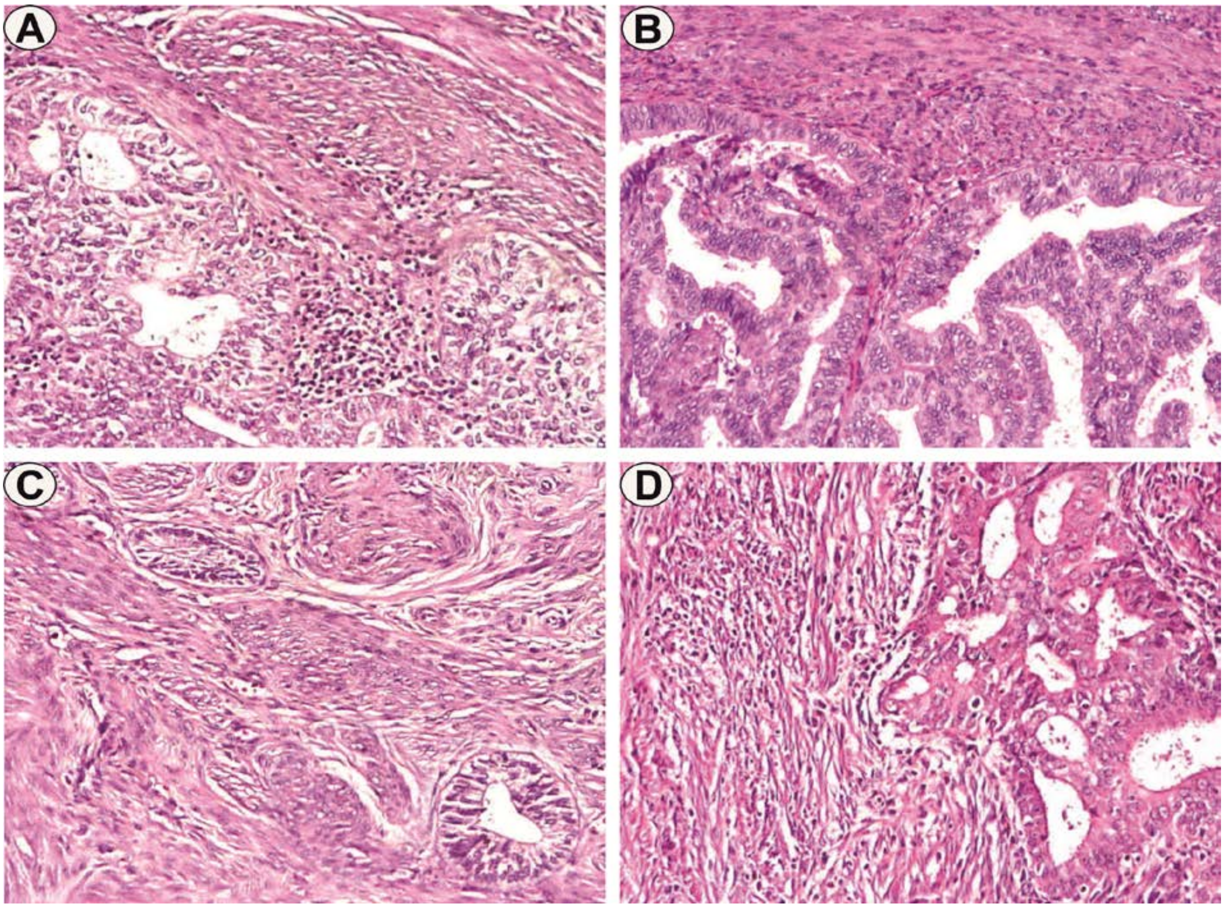

Figure 3. Endometrial endometrioid carcinoma (EEC), invasion patterns, HE staining, x100. A. Irregular. B. Pushing. C. Diffuse infiltrative. D. Microcystic, elongated, and fragmented (MELF).

The diffuse infiltrative pattern was observed in 4 cases (8%), exclusively in G1 EEC and was characterized by the presence of isolated and infiltrative tumor glands in the myometrium (Figure 3C).

At the same time, the microcystic, elongated, and fragmented (MELF) pattern and myoinvasion associated with vascular invasion (MVI) pattern were identified in each of 3 cases (6%), especially in G2/G3 EEC and were characterized by the presence of invasive complex tumor islands associated with vascular invasion, which in the case of MVI was represented by groups of sinus histiocyte-like cells (Figure 3D).

Tumor stage analysis indicated that most EECs were classified in stage IA (48%) or IB (38%), followed by stage II (8%) and III (6%), with statistically significant associations of G1 EEC with stage I and G2/G3 EEC with stages II/III ($p=0.007$, $\chi 2$ test) (Figure 4A).

Irregular invasion patterns, MELF and MVI were more frequently associated with G2/G3 EEC ($p=0.008$, $\chi 2$ test) and advanced stages ($p=0.052$, $\chi 2$ test), where the aspect was at the border of statistical significance (Figure 4B-C).

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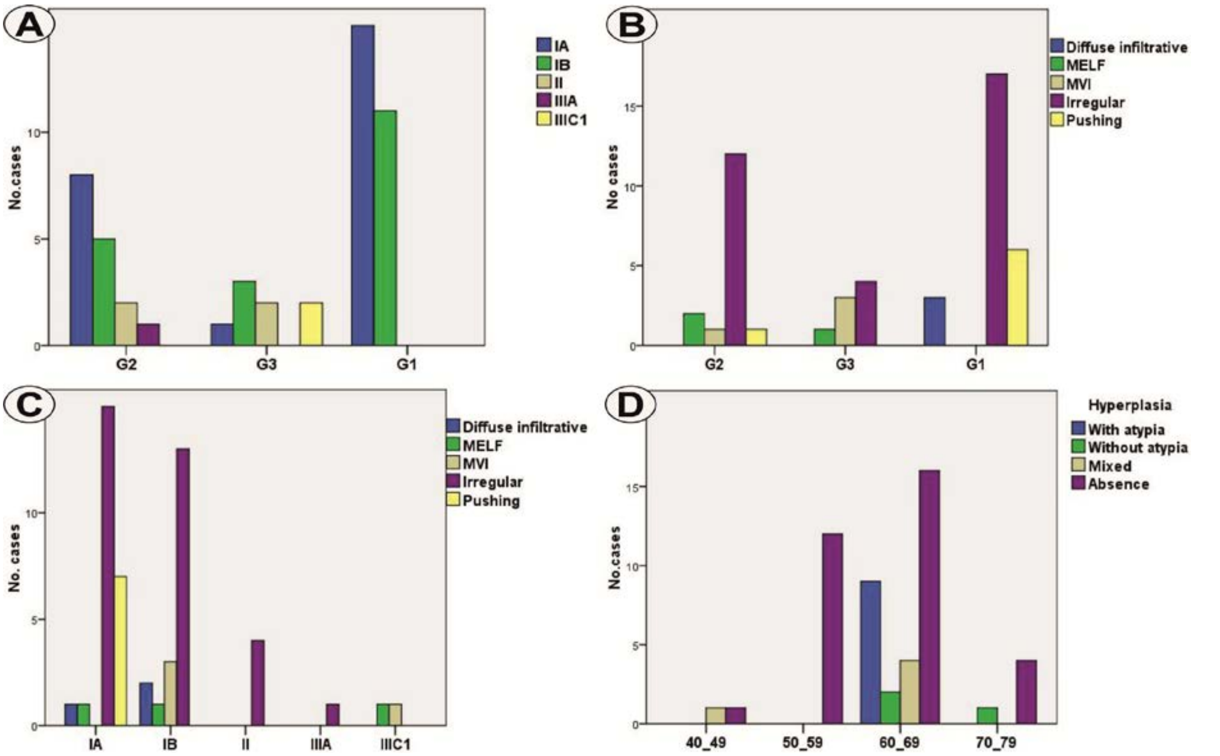

Figure 4. A. Distribution of cases depending on tumor stage and grade. B. Distribution of cases depending on tumor grade and invasion pattern. C. Distribution of cases depending on tumor stage and invasion pattern. D. Distribution of cases depending on age group and the presence of endometrial hyperplasia.

In this study, although apart from EEC-NOS and EEC with squamous differentiations that were associated with G1-G3 tumors, all other EECs with different differentiations were associated with G1 tumors, the aspects were not statistically significant ($p=0.346$, $\chi2$ test).

Also, most of the EEC in stages II/II were of the NOS type, the distribution of cases in relation to histological differences and the tumor stage indicating insignificant differences ($p=0.986$, $\chi2$ test).

We did not find statistical associations of age or risk factors with the analyzed histological parameters.

However, EEC in the 60-69 age group was more frequently associated with the presence of endometrial hyperplasia ($p=0.058$, $\chi2$ test), with G2/G3 tumors ($p=0.258$, $\chi2$ test) in stages II/III ($p=0.605$, test2 test) (Figure 4D).

Discussion

The age of diagnosis for EEC varies widely, between 20-80 years, but over 90% of cases are identified in patients over 50 years, with an average diagnostic age of 63 years [3].

The number of reported cases under the age of 40 is below 10%, existing cases in which patients were 15-30 years old [11].

The age of the patients in our study is close to the data in the literature, most cases being in the seventh decade of life.

Also, the associated risk factors identified in 78% of cases are found in classic and recent studies that have indicated that obesity, hormonal status and family history have an effect in initiating EEC.

For postmenopausal women, increased body mass index (BMI) appears to be associated with a 4-fold higher risk of developing endometrial tumors, being resposablle for 5% of EEC cases [2].

Also, a BMI ≥ 30 presents a 2.28 higher risk of mortality from endometrial cancer, the aspect being important especially in the conditions in which the proportion of obese women becomes higher, especially in developed countries [2,12].

Some studies have indicated a risk related to the distribution of adipose tissue in obese women, the android distribution increasing the risk compared to the ginoid distribution [13].

Moreover, the increase of BMI in peri-and postmenopausal women seems to be the result of pathogenic mechanisms associated with increased levels of insulin-like growth factor (IGF-1) and adipose tissue cytokines (leptin, adiponectin) [14].

Risk factors related to hormonal status are mainly related to endogenous estrogen and progesterone levels.

Among them, nulliparity increases the risk of endometrial carcinoma by 3 times, as well as the risk of mortality, especially in older women, with tumors in advanced stages [15].

Thus, in an extended nine-year study, which included women aged 25-45 and diagnosed with EEC, two-thirds of them were nulliparous [16].

Also, in an extensive study that included over 1000 incidentally diagnosed endometrial carcinomas, the protective role of the short duration of reproductive life, given by the late age of menarche and early age of menopause, was demonstrated once again in relation with EEC [17].

The same group of hormonal risk factors includes estrogen-producing ovarian tumors, such as granulosa and thecal cell tumors, responsible for 5-15% of EECs [18].

Ovarian disorders associated with progesterone deficiency or endogenous estrogenism such as anovulatory cycles or polycystic ovary syndrome are incriminated in EEC initiation [19].

In the same context, the risk of EEC due to hormone replacement therapy is dependent on the dose and duration of treatment, in case of long use endometrial proliferative lesions such as hyperplasia being observed [20].

In the case of Tamoxifen, the risk seems to increase 7.5 times, an aspect reported in extensive studies that included thousands of patients [21].

Regarding genetic risk factors for EEC, they are involved in 10% of cases, the aspect being associated with mutations of K-ras, Her2/neu, p53, p16, PTEN (Phosphatase and tensin homolog) [22,23].

Also, genetic mutations in hereditary nonpolypoid colorectal cancer syndrome (HPNCC) have a variable risk of 22-60% to induce endometrial cancer, while mutations in the genes MLH1 (MutL protein homolog 1) and MSH2 (MutS protein homolog 2) increase the risk by 42% and 61%, respectively [24,25].

The intervention of genetic factors is also demonstrated by the association of EEC with primary malignant neoplasms with other locations in the genital tract, such as ovarian and breast cancer [26].

EEC precursor lesions are considered to be hyperplasia with or without atypia.

If in the case of atypical hyperplasia the progression to EEC is present in 1-3% of cases, in the case of atypical hyperplasia 25-30% of patients will present at the same time or in the first year an EEC diagnosis [3].

Endometrial hyperplasia is frequently diagnosed peri-or postperimenopausal, more frequently between 50-55 years [3].

In our study, hyperplasia was associated with EEC in 34% of cases.

EEC G1-G3 grading is done according to the percentage of solid areas of tumor growth with non-glandular, non-squamous pattern, respectively <5% for G1, 6-50% for G2, and>50% for G3 [3].

It is also recommended that if more than 50% of tumor cells have high cytological atypia, the degree to be increased by one level [27].

The current trend is to grade EEC in two stages, respectively low grade (which includes G1/G2 tumors) and high grade (which includes G3 tumors), an aspect that could increase the prognostic power of this histopathological parameter [28].

However, some specialists still consider the standard three-tier grading system, and so often both grading systems are used [28].

In this study we used the three-tier grading system and found some differences related to the relationship of G1/G2 and G3 tumors with the investigated parameters. Most of the tumors investigated were of low grade (G1/G2), an aspect observed in 84% of cases.

As early as two decades ago, Clement PB et al. indicated the existence of numerous tumor differentiations within the EEC, respectively squamous, secretory, villoglandular, non-villous small papillae, microglandular, sertoliform or with metaplastic changes, some of these aspects being identified in this study [29].

Squamous differentiations occur in 10-25% of cases and often follow the degree of the glandular component [3], in our study being present in 20% of cases.

Although the glandular component is the one that indicates the prognosis of tumors, and in some studies the squamous component did not appear to change the prognosis or was associated with an increase in survival, other authors indicate an increased resistance to treatment of EEC with squamous differences and a tendency for relapses [30,31].

In our EEC study with squamous differences belonged both to G1 and G2/G3 tumors.

EEC with villoglndular differences is present in various studies between 13-31%, or up to 40% mixed with typical EEC with a survival rate of over 90% at 3 years [32].

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In contrast, other authors indicate invasive villoglandular differentiations as being associated with a higher rate of lymph node metastases [33].

In this study EEC with villoglandular differentiations was present in only 4% of cases, all tumors being well differentiated.

Regarding non-villous small papillae differentiation, they can be identified in until 8% of EEC cases, usually G1/G2, and microscopic aspects can create confusion with serous carcinomas, but with a double survival compared to them at 5 years, respectively over 80% [34].

In this study the aspect was present in 2% of cases and the tumors were well differentiated. EECs with secretory and microglandular differentiations are generally well differentiated and have a favorable prognosis, usually without recurrences or metastases [35], aspects that were also identified in this study.

EECs with ciliated differences are relatively rare, and have an unpredictable but often favorable evolution, sometimes with myometrial and vascular invasion [36].

In our study, the aspect was present in 4% of cases, the tumors being well differentiated.

Literature data indicate the existence of numerous EEC invasion patterns, which were also identified in this study, respectively the irregular pattern, pushing pattern, diffuse infiltrative pattern, microcystic, elongated, and fragmented (MELF) pattern, and myoinvasion associated with vascular invasion (MVI) pattern [3,37,38].

Of these, in this study MELF and MVI patterns were associated with high-grade and advanced tumors. Some studies indicate the presence of MELF pattern in almost 16% of myoinvasive EECs, and along with MVI pattern it is frequently associated with the presence of regional lymph node metastases [37,38].

The tumor stage is one of the classic prognostic factors of the EEC, in present being important to measure as accurately as possible the depth of tumor invasion in the uterine wall, recognition of the involvement of the cervix, fallopian tube, ovary and description of the invasion pattern and stromal response [10].

In this study 86% of tumors were in stage I, with internal half myometrial invasion in 48% of cases.

Along with tumor stage and grade, the lymphovascular invasion seems to be the most important histopathological parameter for the EEC prognosis [3].

Lymphovascular invasion is present in 5-15% of EEC, being associated with different patterns of invasion, the focal or extensive patern being important, given that the presence of invasion in more than 5 vessels is associated with a poorly prognosis [39,40].

In our study, the aspect was frequently associated with MELF and MVI tumor invasion patterns.

Data from the literature indicate the usefulness of clinico-imaging correlations for assessing the EEC prognosis, and in this study we observed relations not only between histological parameters such as grade, tumor stage and invasion pattern but also trends of their association with clinical parameters such as the age group of patients.

Conclusions

The results of the study indicated associations between EEC invasion patterns and classical parameters such as tumor stage and grade, as well as the tendency to associate age groups with histopathological parameters.

The high degree, the advanced stage and the MELF and MVI invasion patterns present especially in the seventh decade of life indicate an aggressive clinicopathological profile of the EEC.

The clinicopathological parameters investigated in this study may contribute to the improvement of the criteria for assessing the advancement potential of EEC.

Conflict of interests

None to declare.

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Corresponding Author: Alex Emilian Stepan, Department of Pathology,
University of Medicine and Pharmacy of Craiova, 66 1 May Avenue, 200628 Craiova, Romania,
e-mail: astepan76@yahoo.com