

The difference in histological grades of endometrial carcinoma in curettage and hysterectomy – cross-sectional study

Razlika histološkog gradusa karcinoma endometrija u kiretaži i histerektomiji – presječna studija

Barbara Sabrine Franjić¹, Iva Milić Vranješ³, Jakov Milić^{2*}, Milanka Mrčela⁴

¹Department of Physical Medicine and Rehabilitation, Osijek University Hospital, Osijek

²Faculty of Medicine Osijek, Josip Juraj Strossmayer University of Osijek, Osijek

³Clinic for Gynecology and Obstetrics, Osijek University Hospital, Osijek

⁴Department of Pathology, Osijek University Hospital, Osijek

Abstract. Objectives: To determine the compatibility rate between histological grades of endometrial carcinoma in curettage and hysterectomy and to determine how quantity of material, given by the method of fractional hysterectomy, affects the compatibility between histological grades in the two methods. **Material and methods:** The study included 102 patients with endometrioid endometrial cancer who underwent methods of fractional curettage and hysterectomy. Data regarding the pathohistological status of uterine tissue was obtained from the available medical records. Information on age and clinical diagnoses were obtained from referrals for pathohistological tissue examination. The age of the subjects was determined at the time when the tissue samples were taken for analysis. Data on the amount of material was obtained from the description of macroscopic evaluation of the given material. **Results:** Most subjects had grade II endometrioid endometrial cancer (47.1 % and 50 %). Most of the respondents had a medium deficient material obtained by fractional curettage (40.2 %). There was no statistically significant difference between the histological grade determined after the fractional curettage and hysterectomy. There were no statistically significant differences in histological grade in the sample obtained by fractional curettage and hysterectomy depending on the amount of material in fractional curettage. **Conclusions:** There was no statistically significant differences in the grade of endometrial cancer in samples obtained by the fractional curettage and hysterectomy. The correspondence is higher in higher tumor grade (III), and lower in lower tumor grades (I, II). The amount of material did not affect the grade deviation in the sample obtained by fractional curettage and hysterectomy.

Key words: endometrioid endometrial cancer; fractional curettage; hysterectomy; histological grade

Sažetak. Cilj: Ispitati podudarnost histološkog gradusa endometrioidnog karcinoma endometrija u uzorcima dobivenim frakcioniranom kiretažom i histerektomijom te ispitati utječe li količina materijala dobivenog frakcioniranom kiretažom na podudarnost histoloških gradusa. **Materijal i metode:** U istraživanju su bile uključene 102 pacijentice oboljele od endometrioidnog karcinoma endometrija. Iz dostupne medicinske dokumentacije prikupljeni su arhivski podatci o patohistološkom nalazu tkiva maternice dobivenog metodom frakcionirane kiretaže i histerektomijom. Iz uputnice za patohistološki pregled tkiva dobiveni su podatci o dobi i uputnim kliničkim dijagnozama. Podatci o količini materijala dobiveni su iz opisa makroskopske procjene prikupljenog materijala. **Rezultati:** Najveći broj ispitanica imao je gradus II endometrioidnog karcinoma endometrija (47,1 % i 50 %). Najveći dio ispitanica imao je srednje obilan materijal dobiven frakcioniranom kiretažom (40,2 %). Nije uočena statistički značajna razlika između histološkog gradusa utvrđenog nakon frakcionirane kiretaže i nakon histerektomije, kao ni u histološkom gradusu između uzoraka dobivenih frakcioniranom kiretažom i histerektomijom s obzirom na količinu kiretiranog materijala. **Zaključci:** Nije bilo statistički značajne razlike u određenim gradusima karcinoma endometrija u uzorcima dobivenima metodom frakcionirane kiretaže i histerektomije. Podudarnost je veća u višem gradusu tumora (III), a manja u nižem

***Corresponding author:**

Jakov Milić, MD

Faculty of Medicine Osijek,

Josip Juraj Strossmayer University of Osijek

Cara Hadrijana 10E, 31 000 Osijek, Croatia

E-mail: milic.jakov@gmail.com

<http://hrcak.srce.hr/medicina>

gradusu tumora (I, II). Količina materijala nije utjecala na odstupanje gradusa u uzorku dobivenom frakcioniranom kiretažom i histerektomijom.

Ključne riječi: endometrioidni karcinom endometrija; frakcionirana kiretaža; histerektomija; histološki gradus

INTRODUCTION

Endometrial carcinoma is a malignant tumor arising from malignantly altered endometrial mucosa cells.

Endometrial carcinoma is the most common cancer of the female genital organs. According to the report of the Cancer Registry of the Republic of Croatia, endometrial cancer is in fourth place among cancers in general. It accounts for 6-7 % of all cancers in women¹. The proportion of histologically confirmed cases is 79 %, the proportion registered only from death data is 1 %, while the mortality-incidence ratio is 0.37 %^{1,2}. The incidence rate in 2013 was 26.9 /100 000. In 2015 there were 597 newly diagnosed women¹. The average age of patients diagnosed with endometrial cancer is 55 to 65 years. It is rarely found in women under 40, while more than 85 % of cases are in women over 50 years³. Increased incidence of endometrial cancer has been expressed in countries with better socioeconomic status⁵.

The cause of endometrial cancer is not fully known, but certain risk factors have been determined³. An important factor is hormonal imbalance, especially given the fact that most endometrial cancer cells contain estrogen and/or progesterone receptors. The risk factors are: obesity, which is at the forefront and increases the risk of disease 10 fold, then polycystic ovary syndrome and anovulation, late menopause, early menarche, nulliparity, estrogen gonad tumors, replacement treatment with selective estrogen receptor modulators like tamoxifen, hormone estrogen treatment, family predisposition, and diabetes mellitus^{2,6,7}. In all these cases, we find states of hyperestrinism, that is, chronic exposure to unpaired estrogen, exogenous or endogenous. Protective factors reduce the risk of endometrial cancer, including multiparity, the use of oral hormonal contraception, and early menopause^{2,8}.

The estrogenic effect on the uterine mucosa is promitotic, while progesterone does the opposite by suppressing mitoses, reducing the number of estrogen receptors, stimulating the conversion of estradiol to estrone and thus reducing the effect of estrogen². With prolonged influence of estrogen, without the influence of progesterone proliferative changes will occur that can result in typical or atypical hyperplasia or progress to cancer^{9,10}. Endometrial carcinoma is divided into two types: estrogen-dependent type I and estrogen-inde-

Fractional curettage is the gold standard diagnostic method for endometrioid endometrial carcinoma. The aim of this study was to examine concordance in histological grade between samples obtained by fractional curettage and hysterectomy.

pendent type II. Estrogen-dependent tumors occur in 80 % of cases, occurring more frequently in perimenopause and premenopause associated with stated risk factors. These are often well-differentiated tumors, mostly adenocarcinomas with estrogen and progesterone receptors (ER, PR)⁴. Microscopically, these are subtypes with a more favorable prognosis (endometrioid), minimal invasion, infrequent metastasis and relapses. The estrogen-independent carcinoma lacks estrogen and progesterone receptors. It mainly occurs in women in late menopause. Microscopically, these are subtypes with poorer prognosis (serous, clear cell), deep myometrial infiltration, frequent metastases, and relapses³.

Endometrial carcinomas macroscopically grow focally in the form of a polypoid mass or diffuse throughout the cavum surface. Tumor tissue is soft and fragile, partly necrotic. The uterus is usually enlarged, although it can be atrophic. Numerous nodules in the wall or limited white areas extending from the tumor into the myometrium are invasion³.

The first symptoms that appear in patients are abnormal and irregular bleeding and enlargement of the uterus³. Bleeding may be accompanied by lower abdominal pain, pyometra, endometrial cell finding in Pap smear, and premenopausal anovulation. Endometrial cancer accounts for 25 % of

postmenopausal bleeding. The most common cause of bleeding is endometrial hyperplasia. It indicates changes in endometrial glands and stroma as a result of prolonged non-repressed estrogen stimulation². According to the World Health Organization, they are classified as *Hyperplasia simplex* with a 1% chance of developing cancer, *Hyperplasia simplex atipica* with an 8% chance of developing cancer, *Hyperplasia complex* i *Hyperplasia complex atipica* with a 2% or 29% chance of developing cancer¹¹.

According to a classification known as the 2009 FIGO (*The International Federation of Gynecology and Obstetrics*) classification, endometrial cancers are divided into several degrees.

Expansion stage is the most important predictive factor together with the degree of tissue differentiation (grade). The grade is determined by the ratio of the solid and glandular component in the

tumor, the appearance and size of the nuclei, the number and size of nucleoli and the appearance of chromatin in the pathohistological image. According to the relationship between the solid and glandular components, we distinguish three degrees of tumor differentiation.

Grade I (G1) has up to 5% non-squamous solid tissue, grade II (G2) has 6-50% non-squamous solid tissue and grade III (G3) has more than 50% of non-squamous solid tissue. Given the appearance of the nuclei, we also distinguish three degrees of tumor differentiation. Grade I (G1) has cells with oval or elongated nuclei, finely dispersed chromatin with measurable nucleoli and late mitosis, in grade II (G2) cells nuclei have characteristics between grades I and III and in grade III (G3) cells have irregular, polymorphic nuclei, coarse-grained chromatin with large eosinophilic nucleoli with numerous mitoses (Figure 1, Figure 2)^{12,13}.

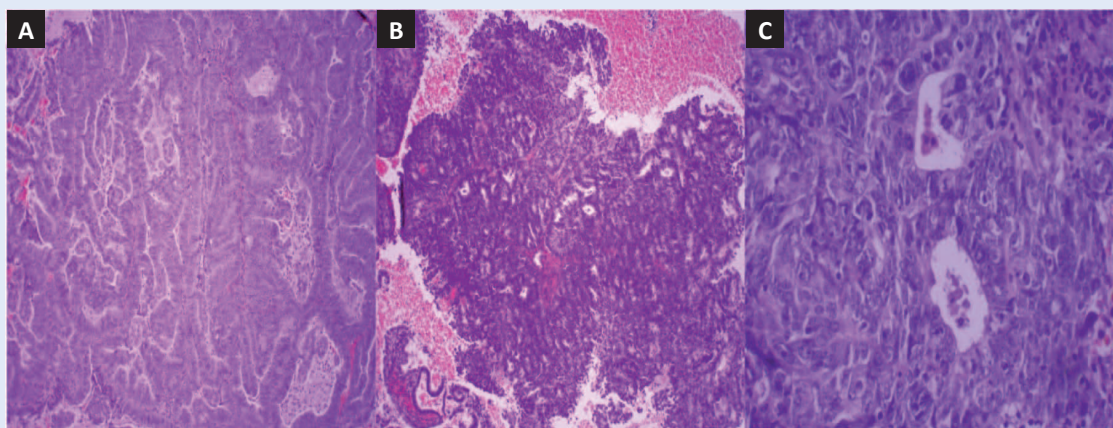


Figure 1. *Adenocarcinoma endometrioides endometrii*, sample acquired by curettage, hemalaun eosin staining (HE). A – grade I, 100x; B – grade II, 40x; C – grade III, 400x

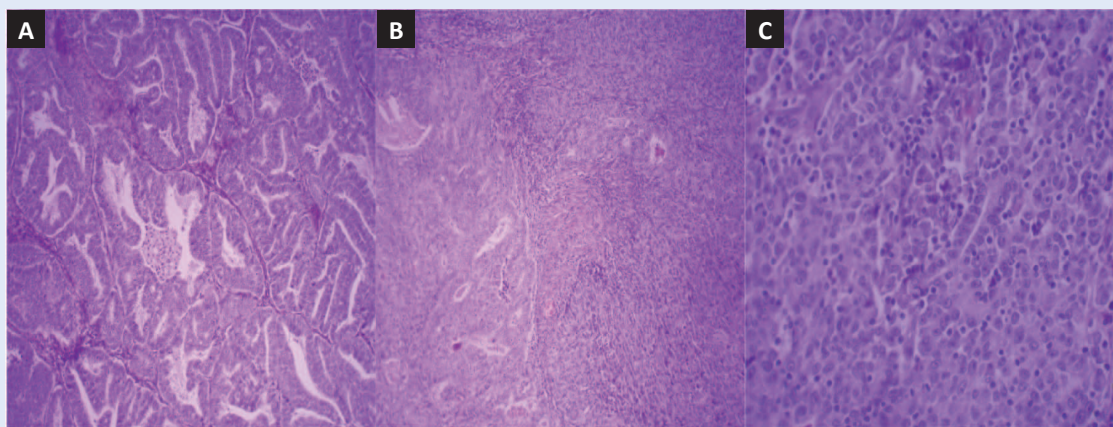


Figure 2. *Adenocarcinoma endometrioides endometrii*, sample acquired by hysterectomy, hemalaun eosin staining (HE). A – grade I, 40x; B – grade II, 100x; C – grade III, 200x

The appearance of the nucleic acid raises the level of the total histological grade by one value^{12,13}.

The basis of diagnosis is a good medical history. This is followed by gynecological vaginal and rectal bimanual examination. The Pap test can be used for diagnosis, although its reliability is 50 % due to endometrial cell degeneration, cervical canal stenosis in some women, poor G1 desquamation, and poor endocervical differentiation from endometrial cells².

Uterobrush, one of the forms of gynecological cytological diagnostics, has a sensitivity of 90 to 95 %, depending on the present tissue fragments¹⁴. Transvaginal ultrasound assesses the thickness and appearance of the endometrium, the presence of endometrial fluid or other changes. Suspicious endometrial thickness is above 5mm. In most patients, the endometrium is thicker than 10mm^{2,15}. The Color Doppler is used to differentiate hyperplasia from neoplasia by assessing changes in blood flow resistance. Fractional curettage is the gold standard for diagnosis. The sensitivity of this method is 95 %². Another method of histological diagnosis is hysteroscopy with biopsy^{2,16}. Tumor marker Ca 125 above 40U/ml indicates lymph node metastases with a sensitivity of 77.8 % and a specificity of 81.1 %¹⁷.

Prognostic factors are: stage of expansion, age, histologic type of tumor, grade, penetration into the myometrium, penetration into the vascular spaces, peritoneal cytology, involvement of cervix and lymph glands, intraperitoneal spread, steroid receptor status, increased expression of mutant p53, Her 2/neu, K-ras, PTEN, p21 and p16 genes^{2,4}. The depth of myometrial invasion is also an important prognostic factor as it has been shown that deeper penetration into the myometrium carries a greater risk of lymphatic space infiltration. Thus, 1 % of patients without myometrial invasion have metastases in the pelvic lymph nodes, while in patients with myometrial invasion up to 1/3 as many as 25 % of the lymph nodes are malignant¹⁸. In addition, tumor grade is important because poorer tumor differentiation carries a greater risk of penetrating the myometrium and the formation of distant metastases².

The aim of this study was to examine the concordance in histological grade of endometrioid

endometrial carcinoma on material obtained by fractional curettage with histological grade of carcinoma on material obtained by hysterectomy in the same patients.

This study also examined whether there are differences in the diagnosed tumor grade in relation to the amount of curetted material obtained by fractional curettage and hysterectomy.

We hypothesized that a significant difference in the tumor grade will be observed when comparing the two methods used, and that the amount of curetted material will play a role in the differences observed in the tumor grading.

SUBJECTS AND METHODS

The study was organized as a cross-sectional study¹⁹.

Subjects included in the study were patients with uterine carcinoma undergoing fractional curettage and hysterectomy at the Clinic for Gynecology and Obstetrics in Clinical Hospital Center Osijek from 1st January 2010 to 31st December 2015.

Inclusion criteria: women with uterine carcinoma who were examined histopathologically primarily using the tissue sampled by fractional curettage followed by hysterectomy, with uterine tissue re-examined microscopically.

Exclusion criteria: other forms of endometrial carcinoma other than the endometrioid type of endometrial carcinoma, women with carcinoma of the uterus who have a pathohistological diagnosis based solely on a sample obtained from one of these two methods.

Patients were classified according to age, histologic grade of the tumor, and the quantity of the material obtained by fractional curettage into groups.

From the available medical documentation of the Clinical Institute of Pathology and Forensic Medicine of the Clinical Hospital Center Osijek, archival data were collected on the histopathological findings of uterine tissue obtained by the method of fractional curettage and hysterectomy, age, and the information on the clinical reference diagnoses.

Material quantity data were obtained from the description of the macroscopic evaluation of the material. All received material obtained by fractionated curettage, with no residues, was processed pathohistologically.

Uterine tissue material obtained from fractional curettage and hysterectomy was analyzed. The material used was processed by standard histochemical technique, embedded in paraffin blocks and stained with standard histochemical staining (hemalaun and eosin)²⁰. Considering the amount of material intended for histopathological diagnostics, the subjects were classified into three categories: subjects with scarce, moderately plentiful and plentiful material.

The study was approved by the Ethical committee of the Faculty of Medicine Osijek.

Statistical methods

Numerical data are described by arithmetic mean and standard deviation. The normality of the distribution of numerical variables was tested by the Kolmogorov-Smirnov and Shapiro-Wilks tests. The Chi square test and the McNemar-Bowker test were used to determine the differences in proportions between the independent and dependent samples, respectively. To determine the differences between the methods and in relation to the quantity of material, absolute differences in grades were calculated and used as separate variables. A *one-way* ANOVA was used to determine differences between groups with a post hoc Bonferroni test. Spearman's correlation was used

to determine the correlation between ordinal and scalar variables. The selected significance level was set at $\alpha = 0.05$. Statistical analysis was made using the SPSS statistical program (version 16.0, SPSS Inc., Chicago, IL, USA)^{21,22}.

RESULTS

The study was conducted on 102 subjects with endometrial carcinoma.

The mean age of the patients was 68,9 (SD 8,4).

The majority of subjects had grade II endometrioid endometrial carcinoma, 48 (47.1 %) patients with fractional curettage and 51 (50 %) with hysterectomy (Table 1).

The amount of material obtained by the fractional curettage method was defined as scarce, moderately plentiful and plentiful, and the subjects were therefore divided into three groups. In total, 29 samples were with scarce material, 41 with moderately plentiful and 41 with plentiful material. Most of the subjects had medium abundant material obtained by fractional curettage (40.2 %).

No significant differences in grade were found in the sample obtained by fractional curettage and hysterectomy depending on the amount of fractional curettage material, even though the total grade concordance was 66,7 % (66 of 102 patients) (Table 2).

Table 1. The proportion of individual tumor gradients in the sample obtained by fractional curettage and hysterectomy

| Tumor grade | Number (%) of subjects | |
|-----------------|-------------------------|---------------------|
| | Fractional curettage | Hysterectomy |
| 1 | 42 (41,2) | 34 (33,3) |
| 2 | 48 (47,1) | 51 (50) |
| 3 | 12 (11,8) | 17 (16,7) |
| In total | 102 (100,00) | 102 (100,00) |

Table 2. Absolute grade difference determined by analysis of the sample obtained by fractional curettage and hysterectomy depending on the amount of material

| Grade difference | Amount of material | | | In total | P* |
|------------------|--------------------|----------------------|-----------|------------|-------|
| | Scarce | Moderately plentiful | Plentiful | | |
| None | 16 | 27 | 23 | 66 | 0,370 |
| 1 grade | 11 | 14 | 8 | 33 | |
| 2 grade | 2 | 0 | 1 | 3 | |
| In total | 29 | 41 | 32 | 102 | |

*Chi-square test

Table 3. Congruence in histological grade of endometrial cancer diagnosed in samples obtained by fractional curettage versus samples obtained by hysterectomy

| Grade in curettage | Grade in hysterectomy | | | In total | <i>P</i> * |
|--------------------|-----------------------|----|----|----------|------------|
| | 1 | 2 | 3 | | |
| 1 | 24 | 16 | 2 | 42 | 0,231 |
| 2 | 9 | 33 | 6 | 48 | |
| 3 | 1 | 2 | 9 | 12 | |
| In total | 34 | 51 | 17 | 102 | |

* McNemar-Bowker test

No significant difference was found in the age of the subjects depending on the grade determined by analysis of the sample obtained by curettage ($P = 0.073$, ANOVA) or by hysterectomy ($P = 0.072$, ANOVA). There was a significant difference in age depending on the clinical diagnosis ($P = 0.024$, ANOVA). The post hoc Bonferroni test did not show between which groups there was a difference in mean age.

Clinical diagnoses included postmenopausal metrorrhagia (68 women, 66.7 %), endometrial hyperplasia (17 women, 16.7 %), polyp (5, 4.9 %) and other causes (foreign body, tumor suspected, uterine prolapse, hematometra, 12 women, 11.8 %).

A positive correlation was found between tumor grade determined by fractional curettage and hysterectomy (Spearman $\rho = 0.515$, $P < 0.001$). Separate correlations between the groups were also calculated depending on the amount of material obtained via fractional curettage. All correlations were significant: Spearman's $\rho = 0.425$, $P = 0.021$ for scarce material, Spearman's $\rho = 0.454$, $P = 0.003$ for moderately plentiful material, and Spearman's $\rho = 0.671$, $P < 0.001$ for plentiful material.

The McNemar-Bowker test found that there was no significant difference in tumor grade depending on the method ($P = 0.231$) (Table 3).

Agreement between the two methods can also be calculated from table 3. The agreement was worse, the higher the grade determined by hysterectomy (24/34 [70,6 %] for grade I, 33/51 [64.7 %] for grade II, and 9/17 [52.9 %] for grade III).

DISCUSSION

The study examined data from patients with endometrioid endometrial carcinoma over a six-year period, from January 1st 2010, to December

31st, 2015. Materials obtained by the method of fractional curettage and hysterectomy of the subjects were analyzed. In the literature, the mean age of subjects (60-64 years) was on average lower than that in our sample^{23,24}.

The samples were divided into three groups depending on the determined histologic grade.

Grade I was described in the literature as the most common finding (55 %), while the proportion of grade I in this study was slightly lower. A higher percentage of grade I in the literature may be associated with better population health education and more regular gynecological examinations that allow early diagnosis of cancer. Grade III is rarer in both the samples tested and in the literature (18 %)¹³. The low incidence of grade III may be associated with the knowledge that a period of several years is required for the tumor to develop and progress to a high degree, especially if the person is in a state of unopposed hyperestrinism. Due to early manifestation of symptoms, such as irregular bleeding, tumors are more frequently diagnosed in the lower stages^{2,9}. The literature reports a discrepancy between histological grade in material obtained by fractional curettage and hysterectomy in 16 to 40 % of cases, which is partly explained by insufficient amount of material obtained by fractional curettage¹³. The difference in histological grade in the material of fractional curettage and hysterectomy can be a problem if the decision on the extent of surgery is based on the finding of fractional curettage²⁵. The finding of fractionated curettage is recommended to be used as one of the indicators of histological grade expected by hysterectomy. If the decision to extend surgery is based solely on the histologic grade of the tumor on the fractionated curettage material, some patients

will receive inappropriate treatment while others will be afforded unnecessary morbidity²⁶. According to the literature, fractional curettage is a reliable diagnostic method for the determination of endometrial carcinoma, but cannot accurately determine the exact histologic grade of the tumor²⁷. Our results seem to confirm these results. Even though we did not observe significant differences in tumor grade depending on the method, and there was also a statistically significant positive correlation between the gradients ob-

In our study it was shown that the concordance in the grade of endometrial cancer in samples obtained by the fractional curettage and hysterectomy is statistically significant. The correspondence is higher in higher tumor grade (III), and lower in lower tumor grades (I, II). The amount of material did not affect the grade deviation in the sample obtained by fractional curettage and hysterectomy.

tained by these two methods, the exact concordance between the tumor grades diagnosed with the two methods was less satisfactory. In the grade III sample obtained by fractional curettage, there was the highest concordance with the hysterectomy findings, which is in accordance with the literature data (90.4 %). It can be assumed that this is due to the higher atypia of the cells in the higher stage of the tumor, the more accurate and easier determination of the grade, as well as the larger tumor area, which makes the tumor tissue less likely to be absent in the curettage pattern²⁸. The similarity of the examined sample is slightly lower than in the literature, but it is assumed that the reason for this is the smaller number of women with grade III in this study. As was the case in literature, with data indicating a lower concordance in lower histologic tumor grades (grade I 74.0 %, grade II 75.3 % to 59 %, depending on the source), in our study the agreement between the grades determined by the two methods was lowest in the samples of grade I. Surgical grading is recommended for more accurate grading²⁹⁻³¹. The concordance in histology gradients of the examined samples was slightly lower than in the literature.

The amount of material obtained by fractional curettage was designated as scarce, moderately plentiful and plentiful, and patients were divided into three groups according to the amount of material. According to some literature reports, a smaller amount of material is thought to correlate with a lower concordance of histologic cancer gradients in materials obtained by fractional curettage and hysterectomy¹³. In this study, no statistically significant differences in the tumor grades in the samples obtained by fractional curettage and hysterectomy was found, depending on the amount of fractional curettage material. This finding can be attributed to the fact that the estimation of the amount of material does not have a strictly defined classification system, but is based on a subjective macroscopic evaluation of the material obtained. According to research to date, the problem of assessing the appropriateness of materials encountered by gynecologic pathology specialists is evident³². Some studies have linked endometrial atrophy to a scarce or inadequate amount of material obtained by fractional curettage, but no correlation of a smaller amount of curettage with the older age of patients and postmenopausal status has been established³³.

According to the literature, abnormal postmenopausal bleeding is the first symptom of endometrial cancer and the most common clinical diagnosis with which patients are referred to a physician for examination and referred for fractional curettage. As much as 66 % of endometrial cancers are detected due to this symptom^{34,35}. It should be emphasized that, although the most common first symptom of endometrial cancer is bleeding, the very occurrence of irregular bleeding may not necessarily indicate the existence of endometrial cancer, since endometrial hyperplasia and atrophy are more common causes of irregular bleeding³⁶.

The analysis of the data did not establish a statistically significant difference in the age of the subjects depending on the grade determined by the analysis of the sample obtained by curettage or hysterectomy. This can be explained by the literature citing postmenopausal women as being the target group for the detection of endometrial cancer²⁴.

This research bears importance because it shows that the statistical significance of the tumor histological grade concordance in materials obtained by fractional curettage and hysterectomy has been demonstrated to indicate the reliability of fractional curettage as a diagnostic method, especially in higher grade tumors. What is important to note is that the amount of material did not adversely affect the histological grade concordance, but it also puts into focus that a proper classification for determining the quantity of obtained material is necessary.

Sufficiently high concordance between the methods indicates the reliability of fractional curettage as a diagnostic procedure, especially in higher carcinoma grades. If there is a high concordance in histological grade, fractional curettage can be used as a reliable, but also as a less invasive method in determining the degree of cancer development. Given that it is a less invasive method, fractional curettage is more acceptable to patients.

The other advantage of fractional curettage lies in the fact that it can be performed on an outpatient basis, which reduces the cost of diagnosis and treatment compared to a hysterectomy that requires longer hospitalization and therefore has a higher cost.

Limitations of the study: The amount of material was determined subjectively, a standard method of precise determination should be developed. Even though all patients diagnosed in a five year period were included, the sample size is still rather small, especially among the patients with higher tumor grades, larger, multicentre studies are recommended in the future. To fully assess how quantity of material, given by the method of fractional hysterectomy, affects the compatibility between histological grades in the two methods can only be measured in randomized control trials.

CONCLUSION

Based on the conducted research and the results obtained, it can be concluded that fractional curettage is a good diagnostic method for determining the existence of endometrial cancer which significantly correlated with the grades of carcinoma diagnosed from the samples acquired

by hysterectomy, but it should not be considered as a definitive diagnosis for determining the exact endometrial cancer grades as the total agreement in the grades was less satisfactory.

No significant differences in concordance of endometrial cancer grades in the samples obtained by fractional curettage and hysterectomy were observed. The coincidence is higher in the higher tumor grade (III) and lower in the lower tumor grade (I, II).

No statistically significant difference in grade deviation was found depending on the amount of fractional curettage material in the sample obtained by fractional curettage and hysterectomy.

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