COMPARISON OF PREOPERATIVE AND POSTOPERATIVE FINDINGS OF HISTOLOGIC TUMOR TYPES AND HISTOLOGIC GRADE IN PATIENTS WITH ENDOMETRIAL CARCINOMA

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Purpose: Our aim was to determine the degree of agreement between preoperative and postoperative histologic type/subtype and degree of tumor differentiation, and to determine the degree of upgrading and downgrading in relation to preoperative and postoperative histopathologic findings. *Methods:* We analyzed data on 393 patients. Data included age, preoperative and postoperative histologic type/subtype and histologic grade of tumor. Data on 317 patients were included in statistical processing. *Results:* Statistical analysis showed moderate agreement between preoperative and postoperative histologic type/subtype of endometrial carcinoma and low degree of agreement between preoperative and postoperative histologic grade of tumor. The lowest agreement in histologic grade was recorded in patients with histologic grade 1 (55.04%), while most accurate agreement was found in patients with grade 3 (73.33%). There was a low degree of agreement between preoperative and postoperative histologic grade in patients with endometrioid adenocarcinoma in both cases. The lowest accuracy in the agreement of histologic grade was in G1, while grades 2 and 3 were similar in the degree of agreement. *Conclusions:* There is moderate agreement of preoperative and postoperative histologic type/subtype and low agreement of preoperative and postoperative histologic grade of tumor. The lowest degree of agreement was recorded for preoperatively G1 tumors and highest for preoperatively G3 tumors, which is important because of the clinical significance of tumor histologic grade 3.

Key words: endometrial carcinoma, histologic type, histologic grade

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INTRODUCTION

Endometrial carcinoma is the sixth most common malignancy in the world. About 320,000 new cases of this malignancy are diagnosed annually, and 380,000 new cases were diagnosed in 2018. Highly developed countries have a higher incidence of 5.9%, compared to low-developed ones with a frequency of 4.0%, but mortality is higher in low-developed countries. North America and Europe have the highest incidence of endometrial carcinoma as the most common malignancy of the female genital tract and the fourth most common malignancy in general, after breast, lung and colorectal cancer. In Europe, it is ranked eighth in the number of deaths; 23,700 deaths were reported in 2012. In North America, it is the sixth most common cause of death in general, with about 55,000 new cases and 11,000 deaths as its consequence reported annually (1).

According to data from 2018, Serbia is ranked 11th according to the incidence of endometrial cancer in the world. It is the fifth most common malignancy in our country, with more than 700 new cases diagnosed annually. The incidence rate is around 26.7/100,000 according to the 2012 National Cancer Registry in central Serbia (2). In Vojvodina, carcinoma of endometrium also ranks fifth in frequency (3).

According to Bokhman, histopathologic endometrium carcinoma is divided into two large groups: estrogen dependent or type I (90% of cases), which occurs in women exposed to high estrogen concentrations, and

estrogen independent or type II (10% of cases), which is more common among elderly and skinny women. Type I belongs to adenocarcinoma of endometrium, which is the first in frequency with 75%-80%. Type II belongs to poorly differentiated carcinomas, often referred to as high grade, of which the most common are clear cell, serous adenocarcinoma and carcinosarcoma. They are characterized by aggressive behavior and poor prediction. Of other types, mucinous, mixed adenocarcinoma, squamous cell, carcinoma of transient epithelium, small cell and non-differentiated carcinomas can occur (4-7).

The prognosis of endometrial carcinoma depends on several factors. Poor prognosis is associated with poor tumor differentiation (grade 3), presence of lymphovascular invasion, non-endometrial histology (serous, clear cell, undifferentiated, small-cell, anaplastic type of carcinoma), cervical stromal invasion and FIGO stage of the disease. For the first stage, five-year survival is 92%, for the second 75%, for the third 50%, and for the fourth stage of the disease, five-year survival is 20% (4).

AIM OF THE STUDY

The aims of this study were as follows: to determine the degree of upgrading and downgrading in relation to preoperative and postoperative histopathologic findings in endometrioid histological type of endometrial cancer; and to determine the degree of agreement between preoperative and postoperative histologic type/subtype and degree of tumor differentiation.

MATERIAL AND METHODS

We performed retrospective analysis of data on 393 patients with endometrial carcinoma, reviewed by the Oncology Tumor Board for Gynecologic Tumors at the Oncology Institute of Vojvodina in Sremska Kamenica and hospitalized at the Division of Operative Oncology, Department of Gynecology for operative treatment between October 2012 and October 2017. The data relevant for this research were collected retrospectively using patient medical records through the BIRPIS21 information system.

We analyzed data on 393 patients aged 30-87 at the time of surgery. These data included age, preoperative histologic type/subtype and histologic grade of tumor, as well as postoperative histological type/subtype and histologic grade. Of these, data on 317 patients meeting the inclusion criteria listed below were included in statistical processing. Inclusion criteria were preoperatively and postoperatively clearly defined histo-

pathologic diagnosis of endometrial carcinoma with histologic type/subtype and histologic grade of the tumor. All endometrial carcinomas in this study were divided histologically into two groups: endometrioid adenocarcinoma and non-endometrial carcinoma (of which in our study we encountered serous, serous-papillary, mucinous, clear cell and mixed adenocarcinomas, which we also classified as non-endometrial). The remaining 76 patients were not included in statistical processing because they had an incomplete preoperative histopathologic diagnosis of endometrial carcinoma (most often lacking the degree of histologic differentiation), or had a diagnosis of benign change or precancerous lesion, either preoperatively or postoperatively.

Results of the analysis are shown numerically, graphically and in tables. Kohen's coefficient of cap was used to calculate the matching ratio, where the value of the coefficient 0-0.2 was considered as insufficient, 0.21-0.4 as poor, 0.41-0.6 as moderate, 0.61-0.8 as very good and 0.81-1 as almost perfect matching. The values of $p<0.05$ were considered statistically significant. For statistical data processing, the IBM SPSS Statistics 23 program was used.

RESULTS

In this study, a total of 317 patients were included in statistical processing. In the examined sample, the youngest patient was aged 30 and the oldest 87 years at the time of surgery, mean age 58.5±9.25 years. Preoperative histopathologic diagnosis of endometrial carcinoma and non-endometrial carcinoma was recorded in 293 and 24 patients, respectively. Postoperative histopathologic analysis of the tissue revealed that the exact preoperative histopathologic diagnosis of endometrioid adenocarcinoma was found in 262 of 293 (89.4%) patients and non-endometrial carcinoma in 20 of 24 (83.33%) patients. In 31 patients with preoperative diagnosis of endometrioid adenocarcinoma, non-endometrial carcinoma was found postoperatively, and four patients with preoperative diagnosis of non-endometrial tumor were postoperatively found to have endometrioid adenocarcinoma (Table 1, Fig. 1).

Table 1.
Overview of preoperative and postoperative histologic findings of endometrial carcinoma type/subtype

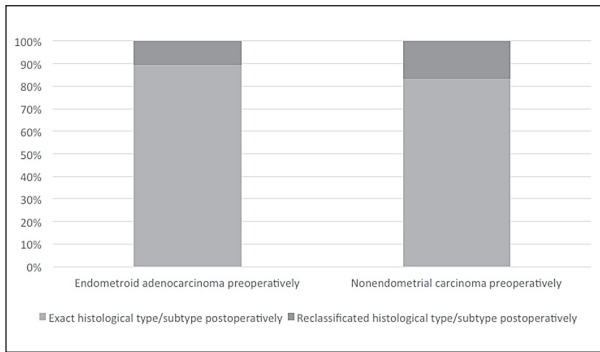|	Histologic type/subtype postoperatively	
Histologic type/subtype preoperatively	Endometrioid adenocarcinoma	Non-endometrial carcinoma
Endometrioid adenocarcinoma n=293	262 (89.4%)	31 (10.58%)
Non-endometial carcinoma n=24	4 (16.66%)	20 (83.33%)

Fig. 1. *Percentage agreement of preoperative and postoperative histologic type/subtype of endometrial carcinoma.*

Statistical analysis showed moderate agreement between preoperative and postoperative histologic type/subtype of endometrial carcinoma (k=0.559, p<0.001).

Analyzing the degree of histologic differentiation of the tumor, irrespective of the histologic type/subtype analysis, in 71/129 patients (55.04%) they were graded exactly as G1. Of the 129 patients who were preoperatively graded as G1, postoperatively they were upgraded to G2 (41.08%) and 5 patients to G3 (3.88%).

In 82/143 patients with G2 preoperatively, the final histopathologic finding of G2 was confirmed in 57.34%. Of 143 patients who were preoperatively graded as G2, 44 of them were downgraded to G1 (30.77%) and 17 were upgraded to G3 (11.89%).

In 33 of 45 patients who were preoperatively diagnosed as G3, in 73.33% diagnosis was confirmed by final histopathologic findings. Postoperatively, 4 patients were downgraded as G1 (8.88%) and 8 patients as G2 (17.78%) (Table 2, Fig. 2).

Table 2.
Agreement of histologic grade of preoperative and postoperative histopathologic findings

Histologic tumor grade preoperatively	Histologic tumor grade postoperatively		
	G1	G2	G3
G1 n=129	71 (55.04%)	53 (41.08%)	5 (3.88%)
G2 n=143	44 (30.77%)	82 (57.34%)	17 (11.89%)
G3 n=45	4 (8.88%)	8 (17.78%)	33 (73.33%)

Statistical analysis showed that there was a low degree of agreement between the preoperative and postoperative histologic grade of the tumor in the test sample (k=0.423, p<0.001).
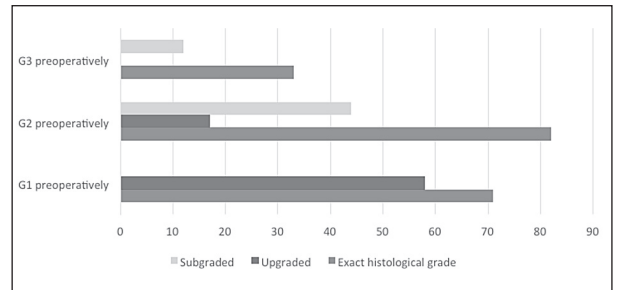

Fig. 2. *Histologic grade accuracy in postoperative relation to preoperative finding.*

The lowest agreement in histologic grade was found in patients with histologic grade 1 (55.04%), grade 2 (57.34%) was on the second place, and the most accurate agreement was found in grade 3 group of patients (73.33%).

Considering that endometrioid adenocarcinoma is the most common histologic type of endometrial carcinoma, we specifically considered the degree of preoperative and postoperative collapse of the histologic grade in patients who had both preoperatively and postoperatively confirmed the histopathologic diagnosis of endometrioid adenocarcinoma.

Endometrioid adenocarcinoma was confirmed in 262 patients. Histologic grade 1 was preoperatively detected in 107 and confirmed postoperatively in 58 (54.2%) patients. In 47 patients with histologic grade 1 preoperatively, grade 2 postoperatively was confirmed in 43.92%, while two patients with histologic grade 3 (2.8%) were confirmed by final histopathologic findings.

Histologic grade 2 was preoperatively confirmed in 139 patients. Of these, histologic grade 2 was postoperatively confirmed in 87 (62.6%), grade 1 in 39 (28.06%) and grade 3 in 13 (9.4%) patients.

Histologic grade 3 was preoperatively confirmed in 16 patients. Postoperatively, histologic grade 3 was confirmed in 10 (62.5%) patients, histological grade in one (6.25%) patient and grade 2 in five (31.25%) patients (Table 3, Fig. 3) .

Table 3.
Degree of agreement between preoperative and postoperative histologic grade in patients with endometrioid adenocarcinoma

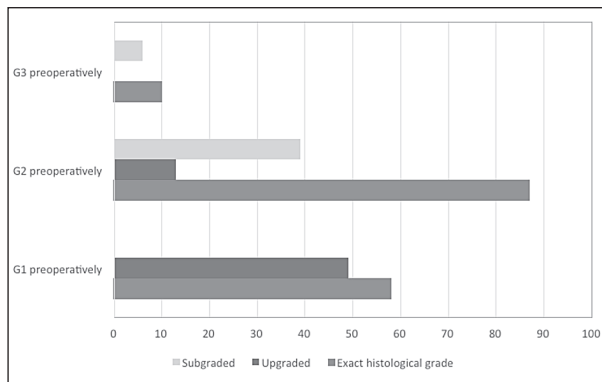| Endometrioid adenocarcinoma	Histologic grade postoperatively		
Histologic grade preoperatively	G1	G2	G3
G1 n=107	58 (54.2%)	47 (43.92%)	2 (2.8%)
G2 n=139	39 (28.06%)	87 (62.6%)	13 (9.4%)
G3 n=16	1 (6.25%)	5 (31.25%)	10 (62.5%)

Fig. 3. *Histologic grade accuracy postoperatively compared to preoperative findings in endometrioid adenocarcinoma.*

Statistical analysis of the preoperative and postoperative histopathologic findings revealed a low degree of histologic grade compliance between preoperative and postoperative findings in patients with confirmed endometrioid adenocarcinoma in both cases (k=0.358, p<0.001).

The lowest accuracy in the agreement of histologic grade was recorded in G 1 (54.2%), while histologic grade 2 (62.6%) and grade 3 (62.5%) were similar in the degree of agreement.

Considering the small number of patients with preoperatively and postoperatively confirmed diagnosis of non-endometrial carcinoma, comparison of the agreement in relation to clinical relevance was not performed. However, it is important to emphasize that of 293 patients with preoperatively diagnosed endometrioid adenocarcinoma, non-endometrial carcinoma was postoperatively confirmed in 31 (10.58%) patients.

DISCUSSION

The degree of agreement of preoperative and postoperative histologic grade of tumor ranges from 32% to 97%, which represents a wide range of accuracy (8,9). Unlike histologic grade, the clinical relevance of disagreement of the preoperative and postoperative histologic type/subtype of tumor is not yet clear enough, but most authors agree that prognosis is worse for non-endometrial carcinoma (primarily serous and clear cell adenocarcinoma) (10).

In recent literature, the degree of agreement between preoperative and postoperative histologic type/subtype of endometrial carcinoma ranges from 81% (for preoperatively non-endometrial carcinoma) to 95% (for preoperatively endometrioid adenocarcinoma) (11). Some authors even point to a lower degree of agreement be-

tween preoperative and postoperative histologic type/subtype in non-endometrial carcinoma (68.9%) (12). In this study, the agreement of preoperative and postoperative histologic type/subtype of tumor in preoperatively non-endometrial carcinoma was 83.33%, whereas in preoperatively endometrioid adenocarcinoma this degree was 89.4%, indicating moderate agreement, which is in accordance with the literature.

Observing the preoperative and postoperative degree of histologic differentiation of tumors in all patients, regardless of the preoperative or postoperative histologic type/subtype of tumor, the highest degree of agreement between the preoperative and postoperative degree of histologic differentiation was observed in preoperatively G3 tumors (73.33%) and lowest in preoperatively G1 tumors (55.04%); considering G3 tumors, this differs slightly from the results of the meta-analysis by Visser *et al.* (11), where the degree of collapse of the histologic grade in the preoperative G3 tumor was slightly higher (75%). Garcia *et al.* (12) also indicate a relatively high degree of agreement of histologic grade in preoperatively G3 tumor (about 79%). The lowest degree of agreement was observed in G1, which is different from literature data, where the degree of agreement of histologic grade is lowest in preoperatively G2 tumor (11,12).

According to the meta-analysis by Visser *et al.* (11), hysteroscopic biopsies show a higher agreement (89%) compared with dilation and curettage (70%) in the degree of histologic differentiation, suggesting that not only the amount of tissue, but also the accurateness of sampling is important. A study by Rosenblatt *et al.* (13) also showed advantages of hysteroscopic biopsies compared with dilation and curettage. Pandey *et al.* (14) in their study found that hysteroscopic pattern recognition could be used to detect endometrial pathology with good efficacy, with the degree of agreement for malignancy of almost 80%.

Inadequate grading leads to suboptimal clinical management, mainly in early-stage tumors. Undergrading often comes with omission of lymphadenectomy, which might result in systemic undertreatment, and overgrading leads to more extensive surgical treatment with associated perioperative morbidity of up to 20%.

CONCLUSION

Our results pointed to the following:

1) moderate association of preoperative and postoperative histologic type/subtype of endometrial carcinoma;

2) poor agreement of preoperative and postoperative histologic grade of tumor in patients with endometrial carcinoma but still in the range of literature data;

3) the lowest degree of agreement between preoperative and postoperative histologic grade of tumor was determined for preoperatively G1 tumors; and

4) the highest degree of agreement between preoperative and postoperative histologic grade of tumor was established for preoperatively G3 tumors, which is important because of the clinical significance of histologic grade 3 tumor.

R E F E R E N C E S

1. Amant F, Raza Mirza M, Koskas M, Creutzberg LC. Cancer of the corpus uteri. Int J Gynecol Obstet. 2018:143(2):37-50.

2. Institut za javno zdravlje Srbije „Dr Milan Jovanović Batut". Incidenca i mortalitet od raka u centralnoj Srbiji 2012. (in Serbian)

3. Institut za onkologiju Vojvodine | Registar za rak [Internet]. Sremska Kamenica: Institut za onkologiju Vojvodine. 2011 [cited 2018 Feb 22]. Available from: http://www.onk.ns.ac.rs/registarzarak.htm#deo2. (in Serbian)

4. Đurđević S, Kopitović V, Kapamadžija A. Ginekologija. 2. izdanje. Novi Sad: Medicinski fakultet Novi Sad. 2015:270-80. (in Serbian)

5. Mandić A, Gutić B, Ivković-Kapicl T et al. Clinical and histopathological characteristics in patients with postmenopausal bleeding. Arch Oncol. 2013:5-107.

6. Colombo N, Creutzberg C, Amant F et al. ESMO-ES-GO-ESTRO Consensus Conference on Endometrial Cancer: diagnosis, treatment and follow-up. Ann Oncol. 2016:16-41.

7. Tangjitgamol S, Anderson BO, See HT et al. Management of endometrial cancer in Asia: consensus statement from the Asian Oncology Summit 2009. Lancet Oncol. 2009:10:1119-27

8. Gerber B, Krause A, Müller H et al. Ultrasonographic detection of asymptomatic endometrial cancer in postmenopausal patients offers no prognostic advantage over symptomatic disease discovered by uterine bleeding. Eur J Cancer 2001:37(1):64-71.

9. Cutillo G, Cignini P, Visca P, Vizza E, Sbiroli C. Endometrial biopsy by means of the hysteroscopic resectoscope for the evaluation of tumor differentiation in endometrial cancer: a pilot study. Eur J Surg Oncol. 2007:33(7):907-10.

10. Di Cello A, Rania E, Zuccalà V et al. Failure to recognize preoperatively high-risk endometrial carcinoma is associated with a poor outcome. Eur J Obstet Gynecol Reprod Biol. 2015:194:153-60.

11. Visser NCM, Reijnen C, Massuger LFAG et al. Accuracy of endometrial sampling in endometrial carcinoma: a systematic review and meta-analysis. Obstet Gynecol. 2017:130(4):803-13.

12. Garcia TS, Appel M, Rivero R, Kliemann L, Wender MCO. Agreement between preoperative endometrial sampling and surgical specimen findings in endometrial carcinoma. Int J Gynecol Cancer. 2017:27(3):473-8.

13. Rosenblatt P, Barcia S, DiSciullo A, Warda H. Improved adequacy of endometrial tissue sampled from postmenopausal women using the MyoSure Lite hysteroscopic tissue removal system versus conventional curettage. Int J Women Health. 2017:9:789-94.

14. Pandey D, Kunamneni S, Reddy Inukollu P, Su H. Establishing pattern on hysteroscopy in abnormal uterine bleeding. Gynecol Minim Invasive Ther. 2017:6:178-82.

S A Ž E T A K

USPOREDBA PRIJEOPERACIJSKIH I POSLIJEOPERACIJSKIH NALAZA HISTOLOŠKIH TIPOVA TUMORA I HISTOLOŠKOG STUPNJA U BOLESNICA S ENDOMETRALNIM KARCINOMOM

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Namjena: Cilj nam je bio utvrditi stupanj podudaranja između prijeoperacijskog i poslijeoperacijskog histološkog tipa/podtipa i stupnja diferenciranosti tumora te utvrditi stupanj nadgradnje i podgradnje u odnosu na prijeoperacijski i poslijeoperacijski patohistološki nalaz. *Metode:* Analizirali smo podatke 393 bolesnice. Podatci su uključivali dob, prijeoperacijski i poslijeoperacijski histološki tip/podtip i histološki stupanj tumora. U statističku obradu uključeno je 317 bolesnica. *Rezultati:* Statistička analiza pokazala je umjeren stupanj slaganja između prijeoperacijskog i poslijeoperacijskog histološkog tipa/podtipa karcinoma endometrija te nizak stupanj slaganja između prijeoperacijskog i poslijeoperacijskog histološkog stupnja tumora. Najniži udjel u histološkom stupnju diferenciranosti bio je kod bolesnica s histološkom stupnjem G1 (55,04%), a najtočniji se slagao u skupini bolesnica s G3 (73,33%). U bolesnica s endometroidnim adenokarcinomom u oba slučaja postojao je nizak stupanj slaganja između prijeoperacijskog i poslijeoperacijskog histološkog stupnja. Najniža točnost u slaganju histološke ocjene bila je u G1, dok su stupnjevi 2 i 3 bili po stupnju slaganja slični. *Zaključci:* Postoji umjereno slaganje prijeoperacijskog i poslijeoperacijskog histološkog tipa/podtipa, a slabo je slaganje prijeoperacijskog i poslijeoperacijskog histološkog stupnja tumora. Najmanji stupanj slaganja utvrđen je za tumore G1 prijeoperacijski, a najviši za tumore G3 prijeoperacijski, što je važno zbog kliničkog značenja tumora histološkog stupnja 3.

Ključne riječi: karcinom endometrija, histološki tip, histološki stupanj