

The reliability of preoperative determination of tumour grade in endometrial cancer

Zanesljivost določitve stopnje diferenciacije raka endometrija pred operacijo

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Abstract

Endometrial carcinoma is the most common among gynaecological cancers. The most frequent symptom of this disease is postmenopausal bleeding. The diagnosis of endometrial cancer has to be histologically confirmed and there are several methods for endometrial sampling with which we obtain the cells or the endometrial tissue. The reliability of these methods differs. With histologically confirmed diagnosis we determine histological subtype and tumour grade. Those are the two key features that have the most important impact on the probability of disease spread and recurrence, but the most important fact is that they help us to determine the optimal extent of surgical treatment. The reliability of the preoperative determination of tumour grade weakly correlates with the final histological diagnosis, especially with preoperatively diagnosed G1-G2 endometrioid adenocarcinomas, while with G3 carcinomas, which are high-risk histologies, the concordance of the preoperative and postoperative interpretation of the histological findings is much higher.

Izvleček

Rak endometrija je najpogostejši maligni tumor ženskih spolov. Najpogostejši znak bolezni je krvavitev po menopavzi. Diagnoza raka mora biti potrjena histološko. Na voljo je več metod, s katerimi pridobimo celice ali tkivo iz maternične votline. Metode se po zanesljivosti med seboj razlikujejo. Pri histološki diagnostiki določamo histološki podtip in stopnjo diferenciacije (gradus) tumorja, ki pomembno vplivata na verjetnost širjenja in ponovitve bolezni. Najbolj pa je pomembno, da pomagata pri določitvi obsega zdravljenja. Zanesljivost določitve stopnje diferenciacije pred operacijo slabo korelira s končno histološko diagnozo, sploh pa pri pred operacijo diagnosticiranemu G1-G2 endometrioidnemu adenokarcinomu, med tem ko je pri G3 karcinomih, ki jih uvrščamo v visokorizične tipe, višje ujemanje interpretacije histoloških izvidov pred in po operaciji.

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1. Introduction

Endometrial carcinoma (EC) is, by definition, a malignant tumour of the endometrium and is the most common gynaecologic cancer (1,2). In Slovenia, it has a crude incidence rate of 29.9 per 100,000 women, and it consequen-

tly affects approximately 311 Slovenian women every year. More than 75 % of endometrial cancers are at stage I at the time of the diagnosis. The reported 5-year survival rate is 80.3 % (1).

The preoperative diagnosis of endometrial cancer is based solely on tissue pathology. The histological subtype and the grade of tumour are the most widely known prognostic factors in women with endometrial carcinoma. The latter correlates with the depth of myometrial invasion, lymph node involvement, surgical stage and survival (3,4). Tumours can be divided into low- and high-grade lesions. Low-grade cancer is diagnosed when the pathology reports grade 1 or 2 endometrioid adenocarcinoma. These carcinomas are commonly associated with less than half of the myometrial invasion, less than 10 % of pelvic and paraaortic lymph node metastasis, and more than 90 % five-year survival rate. High-grade cancer is associated with a high risk for early spread and recurrence. The adequacy of the tissue obtained from endometrial sampling is a matter of major concern since the diagnosis is based on histological morphology (5). There are selected methods of endometrial sampling that are used in practice, including invasive and non-invasive methods, and those used on an inpatient or outpatient basis (6). Studies have shown that various methods are weakly correlated with the final pathological grade. Tumours diagnosed preoperatively as FIGO grade 1 will be in a high percentage upgraded on a final pathological evaluation, mostly to grade 2, but approximately 3 % will be diagnosed as grade 3 or will be diagnosed as a serous or a clear cell carcinoma at the final pathological assessment of hysterectomy specimen (3).

The treatment for endometrial cancer is mainly surgical. Preoperative histo-

logical examination is one of the most important keys for surgical management. Apart from histological diagnosis, preoperative imaging is also an essential part of the diagnostic work-up and the methods such as ultrasound, MR, CT and PET-CT help us to determine the depth of myometrial invasion, cervical stromal invasion and extra uterine disease spread, including lymph node metastasis (3,7,8). Takač compared the diagnostic accuracy of saline infusion ultrasonography (SIUS) to transvaginal ultrasonography (TVUS) in the assessment of myometrial invasion of endometrial cancer. Fifty-three patients were examined preoperatively and all patients were postmenopausal. He concluded that TVUS and SIUS provide relatively accurate detection of myometrial invasion in patients with endometrial cancer, especially with better sensitivity for detecting deep myometrial invasion (9). The surgical approach, extent of surgery, and adjuvant therapy depend on the microscopic examination assessing the histological type and grade of cancer, and the depth of myometrial invasion. The other predictors are identified by the final diagnosis according to the recommended surgical-pathological staging (3,7,8).

The purpose of this article is to review the literature on the topic of endometrial sampling methods and their accuracy for the preoperative determination of tumour grade.

2. Classification of endometrial carcinoma

The endometrial carcinomas are broadly classified into two major types based upon clinicopathologic features:

- Type I endometrial carcinoma is an endometrioid adenocarcinoma that is associated with endo- or exogenous

oestrogen exposure. It includes three subtypes that are categorized by their histology into well (grade 1), moderately (grade 2) and poorly (grade 3) differentiated tumours. The incidence of this type is expected to rise due to the production of oestrogen by the adipose tissue and due to obesity is becoming more and more common. Type I endometrial carcinoma commonly develops in perimenopausal, obese women with endometrial hyperplasia as a precursor (2).

- Type II endometrial carcinoma is non-oestrogen dependent. It typically occurs among older women and generally has a much poorer prognosis than type I disease. Type II includes particularly papillary serous or clear cell subtypes and may exhibit a mixed endometrioid component. The endometrial carcinosarcoma, which is a poorly differentiated metaplastic carcinoma by its histological properties, is included in type II endometrial carcinoma (2). Serous carcinomas, which constitute only 10 % of endometrial carcinomas, have a higher propensity for lymphovascular invasion and intraperitoneal spread as well as extra-abdominal spread than endometrioid carcinoma (10).

All tumours have to be microscopically verified. The endometrial histology is classified according to the World Health Organization system (11). The histopathological types are:

- Endometrioid carcinoma: is the most common type of EC, considered in more than 75 % of cases. This tumour characteristically contains glands which are similar to those found in normal endometrium. It represents a spectrum of histological differentiation from a very well differentiated carcinoma to minimally differentia-

ted tumours which can be confused not only with undifferentiated carcinoma but also with various sarcomas. The tumour is classified with a higher grade when glandular component decreases, and is replaced by solid nests and sheets of cells. In addition to the characteristic appearance there are several variants of endometrioid adenocarcinoma, including squamous, villoglandular, secretory and ciliated cell variants. The endometrioid ECs are graded according to the FIGO classification system, which assesses the architectural pattern and nuclear grade:

- Grade 1: less than 5 % of solid growth patterns;
- Grade 2: 6 to 50 % of solid growth pattern;
- Grade 3: greater than 50 % of solid growth patterns (12,13).
- Mucinous adenocarcinoma: about 1 % to 2 % of the endometrial cancers have mucinous appearance that involves more than half of the tumour. These tumours are typically grade 1 and generally have a favourable prognosis (12).
- Serous adenocarcinoma: is the second most common type of EC, but it only accounts for about 10 % of the cases. Usually it is characterized by a papillary architecture with cells that demonstrate the nuclear atypia, atypical mitoses and psammoma bodies in about 30 % of the cases. This type also has a tendency to develop deep myometrial and extensive lymphatic invasion (12).
- Clear-cell adenocarcinoma: is an uncommon histologic type of EC (< 5 %), often associated with an aggressive clinical behaviour, and a poor outcome. It can exhibit different microscopic patterns: papillary, glandular, tubulocystic and diffuse, and it

is composed of cells with abundant clear cytoplasm. The glycogen-filled and hobnail cells, nuclear atypia, and high mitotic activity are typical for this type (12,14).

- Mixed carcinoma: EC may demonstrate combinations of two or more pure types; an admixture of endometrioid and high-grade nonendometrioid patterns (mostly serous) are the ones which may occur most commonly. The minimum amount of the minor type must be comprised with at least 10 % of the total tumour volume (12).
- Squamous cell carcinoma: is not as common, and it usually occurs in postmenopausal women. It is often associated with cervical stenosis and pyometra. Histologically, it is identical as squamous cell carcinoma of the cervix, and it similarly includes a rare verrucous variant (12).
- Transitional cell carcinoma: is a very unusual variant of endometrial carcinoma and 90 or more % of the cells are similar to the urothelial transitional cells (12).
- Undifferentiated carcinomas: are rare endometrial carcinomas, lacking any evidence of differentiation. It is a high-grade carcinoma, characterised by proliferation of the medium-sized, monotonous epithelial cells, which are growing in solid sheets with no specific pattern (12).

3. Methods of preoperative endometrial sampling

Various methods of endometrial sampling are used in practice, including invasive and non-invasive, or those on an inpatient or outpatient basis (6). Most frequently used are the dilation and curettage (D&C), the Pipelle sampling and hysteroscopy with biopsy.

4. Dilation and curettage

D&C is an invasive, inpatient procedure performed under general anaesthesia (3). This has been the most standard procedure for evaluating suspicious endometrial lesions, but this procedure also has several disadvantages. Besides of its tendency to cause pain, injury, infection and its high price, there is also the disadvantage where in approximately 60 % of the cases, less than half of the uterine cavity is curetted, which can result in false-negative diagnosis (15). This has led to the beginning of discovering new and simpler methods for early detection of the endometrial lesions, especially carcinoma and its precursors.

4.1. The Accuracy of the preoperative determination of the tumour grade by the D&C

Vorgias et al. determined the reliability of the tumour typing and grading at the pre-hysterectomy curettage biopsy in patients with endometrial cancer. Their data indicated that regarding endometrioid carcinomas, the diagnostic accuracy of the D&C is quite high and relatively balanced for all diagnostic indices. On the other hand, the diagnostic profile of the D&C, regarding the aggressive variant tumours (clear-cell, serous-papillary, mixed) is inverse: very high specificity and NPV (negative predictive value), but low sensitivity and PPV (positive predictive value). The results corroborate the findings of both Lampe and colleagues and Jacques and colleagues, who also concluded that there is a significant discrepancy between the two pathologic diagnoses and that the reliability of the D&C diagnosis depends on the tumour type (11,16,17).

Regarding preoperative tumour grading by the D&C, it seems that the

more aggressive the tumour becomes, the more accurate is the diagnosis. The exclusion capability of the method is higher than the detection capability. It seems logical because grade 3 tumours can be easily and safely characterized in a sample specimen (from the D&C), as compared with well-differentiated grade 1 tumours, in which the possibility of missing a more aggressive area always exists. That is the reason why the D&C pathology tends to underestimate the tumour grade. Overall in Vorgias study group, there was a grade underestimation in 37.3 % (98/263) of patients, whereas overestimation was detected in only 7.2 % (19/263); (this also includes the 7 patients with no residual carcinoma at hysterectomy) (16).

Göksedef et al. retrospectively reviewed 335 patients. In all cases D&C was used as the method of the endometrial sampling. They showed that almost 35 % of the patients with preoperatively determined FIGO grade I endometrial adenocarcinoma, were diagnosed with worse FIGO grade after the hysterectomy. Their explanation was that on the final pathological assessment greater tissue volume and higher percentage of solid growth was examined (3).

5. The endometrial sampling Pipelle

Introduced by Cornier in 1984, the Pipelle is the most studied biopsy device in the literature (15). It is also the most popular office sampling device because it is easy to perform, convenient, less expensive and has a good patient acceptability (15,18). The Pipelle is a thin plastic tube, 3 mm in diameter and can be performed without anaesthesia or analgesia during the routine pelvic examination (6,18). When the inner plunger is withdrawn, negative pressure gradient

makes suction (15). In a typical procedure, approximately 5 % of the endometrial surface area is sampled, so this method may be less efficient as a screening tool, and has a limited ability to identify focal lesions (15,18).

5.1. The accuracy of the preoperative determination of tumour grade by Pipelle

In the study by Demirkiran et al., 637 patients were evaluated by Pipelle biopsy. Compared with pathological examination after hysterectomy, the histological concordance rate was 67 % for Pipelle biopsy and 70 % for D&C (18).

A retrospective study by Larson et al. examined the use of office Pipelle sampling compared with D&C to determine the histological grade in patients with known endometrial cancer. Pipelle biopsy correctly identified the hysterectomy tumour grade in 76 out of 131 patients (58 %), and D&C correctly identified tumour grade in 40 out of 52 patients (77 %). The office biopsy was inaccurate in 42 % of the cases, and notably 26 % of these discrepant cases were upgraded in the final pathology. When using grade to determine the need for lymphadenectomy, the method of sampling must be considered (19).

Huang et al. evaluated the ability of preoperative endometrial sampling to accurately diagnose high-grade endometrial tumours. They compared Pipelle and curettage in 346 patients and concluded that Pipelle or curettage were highly sensitive and accurate for the diagnosis of high-grade endometrial tumours and also nonendometrioid histological types. They also showed great compliance between preoperative histology and grade and the final pathology. In patients with a high-grade preoperative diagnosis, 95 % of their final pathology was

indeed high graded but 10 % of patients with preoperatively determined low grade were diagnosed with a high-grade tumour after hysterectomy. Overall, they concluded that the preoperative endometrial sampling more often underestimates rather than overestimates tumour grade (20).

6. Hysteroscopy with biopsy

Hysteroscopy is a valuable, simple, low-risk technique which allows an adequate exploration of the uterine cavity under visual control (21). It is a method of observation of the uterine cavity using a hysteroscope, which is introduced through the cervical canal. It allows from 20- to 150- fold magnification. Hysteroscopic examination requires the cavity to be distended with either CO₂ or liquid. It allows the targeted biopsy or excision of lesions identified during the procedure (22). Hysteroscopy, especially combined with endometrial biopsy, has high diagnostic accuracy and high sensitivity of 98 % for the detection of endometrial cancer (22). The hysteroscopic appearance of endometrial carcinoma is characteristic, the endometrial cavity is changed because of neoplastic growth (23). Based on the morphologic appearance, endometrial cancer can be divided into four types of tumour growth: polypoid, nodular, papillary, and ulcerated type. In one of his studies, where he included 53 patients, Sugimoto described the polypoid, nodular, and papillary types as exophytic and circumscribed diseases, but the ulcerated type as endophytic and diffuse (24). Features commonly associated with malignancy are: papillary aspect, size larger than a half of the uterine cavity, irregular and ulcerated surface, mixed colour, diffuse vascularisation with anarchical or slightly branched aspect, discordance

between the main vascular axis and the direction of the lesion growth (23).

6.1. The Accuracy of the preoperative determination of tumour grade by hysteroscopy and biopsy

Zhu et al. evaluated hysteroscopy and directed biopsy in the diagnosis of the endometrial carcinoma in comparison with the dilation and curettage (D&C). They confirmed that hysteroscopy diagnosed endometrial carcinoma more accurately and with greater sensitivity than D&C. These results are similar to those of Bedner et al. who compared the effectiveness of D&C with hysteroscopy and guided biopsy in perimenopausal women at risk of developing endometrial hyperplasia or cancer. They found that hysteroscopy with directed biopsy was more sensitive than D&C, especially for detecting all types of uterine lesions. Out of total 734 patients, hysteroscopy failed to diagnose endometrial pathology in just four of the cases, compared to 21 cases that were undiagnosed by D&C. They concluded that hysteroscopy is a very accurate method for diagnosing endometrial carcinoma (25). Koutlaki described hysteroscopy as a highly accurate and thereby clinically very useful method of diagnosing endometrial cancer in women with abnormal uterine bleeding (23). Clark et al. reported that hysteroscopic diagnosis has a positive predictive value of 78.5 % in diagnosing endometrial cancer and a negative predictive value of 0.6 %, which further aids achieving a well-targeted biopsy (25).

Several studies were concerned with the intraperitoneal dissemination of endometrial cancer cells after hysteroscopy due to distention of the uterine cavity, which may facilitate the dissemination of malignant cells through the fallopian

tubes into the abdominal cavity. Takač and Žegura evaluated the incidence of tumour cell dissemination, and have shown that diagnostic hysteroscopy significantly increases the risk of positive peritoneal cytology, but not the risk of adnexal, abdominal or retroperitoneal lymph node metastases in patients with EC (26). Chang et al. also showed that it may increase the risk of dissemination, but also evaluated the effect of hysteroscopy on the disease prognosis, and showed that there is no evidence to support the association between the preoperative hysteroscopic examination and worse prognosis (27). Dovník et al. compared the frequency of positive peritoneal washings in the endometrial cancer patients after either hysteroscopy or D&C and discovered that the diagnostic procedure did not influence the overall incidence of positive peritoneal washings. Hysteroscopy, on the other hand, was associated with a significantly higher rate of positive peritoneal cytology in stage I endometrial carcinoma compared to D&C (28).

The impact on the prognosis and survival has to be evaluated in the future, but from the available data there is no reason to avoid diagnostic hysteroscopy in the initial workup of endometrial cancer.

7. Conclusion

Endometrial carcinoma is the most common gynaecological malignancy, and it usually affects postmenopausal women. The grade of the tumour is a well-known prognostic factor for women with endometrial carcinoma and it correlates with the depth of myometrial invasion, cervical stromal involvement and lymphovascular space invasion. There are many ways in which the tumour grade can be assessed preoperatively,

including dilation and curettage, Pipelle sampling and hysteroscopy with biopsy. The accuracy of each of these methods differs but all the analysed methods had a high specificity rate of 98 %. The preoperative determination of tumour grade is extremely important but most of the studies have shown that the endometrial sampling methods poorly correlate with the final pathologic grade. The dilation and curettage is a reliable and accurate method but it has a tendency to underestimate the final tumour grade. It is a reliable method in grading aggressive tumours. According to Practice Bulletin No. 169, if a surgical approach is favoured, D&C with hysteroscopic guidance is recommended over D&C alone because it has a higher accuracy and superior diagnostic yield (29). Pipelle aspiration biopsy is a minimally invasive outpatient method, and is an excellent tool for identifying endometrial cancer and its histological subtypes. As stated by Burke et al., Pipelle has a high detection rate of 99.6 % and 98 % for endometrial cancer and endometrial hyperplasia (7). It is an accurate and sensitive method for diagnosing low- and high-grade tumours, but it appears to be inferior to D&C in predicting the final posthysterectomy tumour grade. It has the advantage of being more economical, less invasive and easily performed. Hysteroscopy, especially when combined with endometrial biopsy, has a high diagnostic accuracy in making the diagnosis of endometrial cancer and establishing the extent of the disease, so it remains the gold standard for endometrial diagnosis (7). Many patients with endometrial cancer can be diagnosed by office biopsy, which is preferred as the first diagnostic step. If the biopsy result is negative and further evaluation is needed, we can proceed to hysteroscopy, which can also help us with biopsy of focal lesions that might be

missed by D&C. None of these methods have 100 % sensitivity, so if the symptomatology persists despite the negative findings, further evaluation is needed and the approach should be dictated by the order of investigative evaluation. If the initial assessment involved only pelvic ultrasonography, endometrial sampling should be performed. Also, if office sampling has already been performed and has demonstrated no evidence of hyperplasia or malignancy, hysteroscopy with D&C is recommended (7,29).

In conclusion, studies have shown that high-risk histologies have the highest concordance for the preoperative and

postoperative pathology interpretation, however, endometrioid tumours have shown more frequent shifts between risk groups when comparing preoperative and postoperative histology. These grade shifts in the final pathological assessments may be explained by the volume of the tissue available for examination; a larger tissue volume may allow better assessment. The vast majority of shifts occur from low – (G1) to intermediate (G2) grade; only small minorities (0.5–5 % in different studies) of G1 tumours are reclassified as high grade in the final surgical pathology.

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