Comparison of Pre- and Postoperative Histopathology Results in Patients with Endometrial Carcinoma

Yinglan Zhang (drzhangyinglan530@163.com)  
Beijing Chao-Yang Hospital: Beijing Chaoyang Hospital

Yu Zhao  
Peking Union Medical College Hospital

Yuan Li  
Beijing Chaoyang Hospital

Research

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Abstract

Background: Preoperative histopathology is considered the most effective method for evaluation of endometrial carcinoma, and plays a crucial role in deciding the extent of surgical resection. In this study, we analysed clinical data to evaluate the accuracy of preoperative diagnosis by comparing preoperative hysteroscopic biopsy results with postoperative histopathological results.

Methods: This was a cross-sectional, retrospective study of patients who underwent hysteroscopic biopsy and subsequent hysterectomy for endometrial carcinoma. Clinical data were collected for 289 patients who were diagnosed with endometrial carcinoma based on hysteroscopy. We compared the histotype and tumour differentiation grade to evaluate the accuracy of diagnosis based on preoperative hysteroscopic biopsy.

Results: Compared with the postoperative histotype results, the overall accuracy of the preoperative histotype results was 94.8%, and the kappa value was 0.725 (p < 0.001). The weighted kappa value for agreement between preoperative and postoperative histopathological grade was 0.616, indicating the level of agreement was "substantial" (95% CI 0.538–0.695). The rate of misdiagnosis based on hysteroscopy was significantly higher for grade 3 cancer than for grade 1 cancer, and there was no significant difference for grade 2 cancer compared with the other two grades.

Conclusions: Hysteroscopy is a reliable method for preoperative diagnosis of endometrial carcinoma. Preoperative assessment of histotype by hysteroscopy showed high consistency with postoperative results. However, there was a significantly higher rate of misdiagnosis for patients with poorly differentiated tumour, which may lead to overtreatment. For these patients, we recommend analysing frozen sections before determining a final treatment strategy.

Background

Endometrial cancer (EC) is the most common gynecological malignancy in developed countries and the second most common in developing countries [1]. In 2020, an estimated 65,620 women were diagnosed with EC in the United States and approximately 12,590 women died from this disease [2]. The incidence of EC is increasing yearly. Overall, 14% of reported cases of EC occur in premenopausal women, with 5–29% occurring before the age of 40, and 70% of patients are nulliparous at the time of diagnosis [3, 4]. Surgical options include total hysterectomy, bilateral salpingo-oophorectomy, and possibly pelvic and para-aortic lymphadenectomy, depending on the histotype and the tissue grade of the carcinoma [5]. Although most cases are diagnosed at an early stage, when the disease is still limited to the uterus [6], the prognosis for advanced-stage and recurrent disease is still poor [1].

Given the current trend of women of delayed child-bearing and the increasing incidence of EC amongst nulliparous women [7,8], accurate preoperative diagnosis of EC by endometrial biopsy is becoming increasingly crucial, especially in this population, as surgery results in removal of reproductive organs,
which means that child-bearing is no longer an option. Therefore, fertility preservation and early accurate diagnosis of EC are topics of considerable interest in gynecological oncology.

Preoperative pathology is extremely important in deciding the extent of surgical resection [9]. Differences in the histopathological features of the disease impact both prognosis and the recommended treatment approaches [10]. The malignancy of endometrial tumour is related to histotype and tumour grade [11]. Low-grade (G1/2) endometrioid carcinoma has a more favourable outcome, while high-grade (G3 endometrioid/non-endometrioid) carcinoma is associated with a poor outcome. In clinical early-stage endometrioid carcinoma, the risk of pelvic lymph node metastasis varies from 3–12%, depending on the grade [12,13]. Barlin et al. demonstrated that after tumour stage, the next most informative prognostic division in EC is between high-grade and low-grade tumour by tumour classification and regression tree statistical analyses, with high-grade tumour including G3 endometrioid carcinoma and non-endometrioid carcinoma [14,15].

However, due to the limited amount of tissue and technologies available for biopsy, preoperative diagnosis is always challenging. While there have been several studies addressing this issue, they are limited by relatively small sample sizes of fewer than 200 patients and the use of different endometrial sampling techniques [16]. Previous studies have reported that the agreement rate of tumour grade between pre- and postoperative endometrial sampling ranges from 32–97%[17,18], and thus varies widely. As an example, Larson et al. found that 56% of grade 3 tumour were accurately diagnosed preoperatively [19], whereas Traen et al. reported an accuracy rate of 88% [20]. Discrepancies between pre- and postoperative results can lead either to underestimation of extrauterine and lymph node metastasis or overtreatment with unnecessary surgical resection, which may cause infertility and perioperative complications.

In this study, we compared preoperative hysteroscopic biopsy results with hysterectomy pathology results to assess the accuracy of diagnosis based on preoperative hysteroscopy in women with EC.

**Methods**

We retrospectively reviewed the records of 289 women who were treated for EC at Peking Union Medical College Hospital from January 2008 to August 2015. The patients’ ages ranged from 26 to 88 years (average 57.8 ± 9.6 years). In total, 222 of the patients (222/289, 76.8%) were postmenopausal, and 33 of the premenopausal patients (33/289, 11.4%) were nulliparous. The primary complaints included abnormal uterine bleeding (AUB) (198/289, 68.5%), overly thick endometrium (thicker than 5 mm for postmenopausal women [173/222, 77.9%]; thicker than 20 mm for the premenopausal women [25/67, 37.3%]), vaginal discharge without blood (6/289, 2.1%), vaginal discharge with spotting (16/289, 5.5%), and infertility (21/289, 7.3%). Thirty-six of the patients were asymptomatic (36/289, 12.5%). We obtained the patients’ data from their electronic medical records. When the electronic record was not complete, we filled in any missing information from the patient’s paper medical records. Patients whose clinical information was incomplete were excluded. We also excluded patients whose preoperative pathology
results indicated cancer but whose final pathology assessment indicated no malignancy. The study was approved by the Ethics Committee of the Peking Union Medical College University (B2013001079) and conformed to the provisions of the Declaration of Helsinki (as revised in Tokyo 2004).

All patients underwent hysteroscopic biopsy at our hospital (74/289, 25.6%) or at a local hospital (215/289, 74.4%). All patients who underwent hysteroscopy at other hospitals provided the original pathology slides, which were rechecked by our own pathologist. All the patients underwent hysterectomy at our hospital, and their pre- and postoperative pathology results both revealed EC. Pathological and clinical information was reviewed for histotype and tumour grade. For each patient, we compared the histotype and grade with the final hysterectomy results.

Agreement between tumour grade and histotype results from the preoperative endometrial samples and the final diagnosis was assessed by percentage and kappa value. The agreement strength was considered poor for weighted kappa values less than 0.2, fair for values of 0.21–0.40, moderate for values of 0.41–0.60, substantial for values of 0.61–0.80, and almost perfect for values of 0.81–1.00. Chi-square test was used for comparing the misdiagnosis rate between each pair of groups (grade1 vs. grade 2, grade 2 vs. grade 3, and grade 3 vs. grade 1). All statistical analyses were performed using SPSS for Windows (version 16.0.0, USA).

**Results And Discussion**

To determine the accuracy of preoperative diagnosis, we compared EC histotype determined pre- and postoperatively. Preoperative diagnosis based on endometrial biopsy identified 257 cases of endometrioid carcinoma and 32 cases of non-endometrioid carcinoma. Final pathology after hysterectomy identified 260 cases of endometrioid carcinoma and 29 cases of non-endometrioid carcinoma. Out of the 257 preoperative diagnoses of endometrioid carcinoma, 251 were confirmed by final pathology, while six cases were postoperatively determined to be non-endometrioid carcinoma; and 23 of the 32 preoperative diagnoses of non-endometrioid carcinoma were confirmed postoperatively, while nine cases were diagnosed as endometrioid carcinoma after the operation; for an agreement rate of 94.8% (Table 1). The kappa coefficient for agreement between the two sets of pathology results was 0.725. The sensitivity of preoperative pathology assessment for detecting endometrioid and non-endometrioid carcinoma was 96.5% and 79.3%, respectively. Taken together, these data suggest that preoperative diagnosis was highly consistent with final histopathology results.
Table 1
Comparison of histopathological types determined based on preoperative hysteroscopic biopsy and postoperative hysterectomy.

| Hysteroscopic biopsy | Hysterectomy |       | Total | Sensitivity (%) |
|----------------------|--------------|-------|-------|-----------------|
|                      | Endometrioid | Non-endometrioid |     |                 |
| Endometrioid         | 251          | 6     | 257   | 96.5            |
| Non-endometrioid     | 9            | 23    | 32    | 79.3            |
| Total                | 260          | 29    | 289   |                 |

The agreement rate was 94.8%, and the kappa value for the two histotype was 0.725 (p < 0.001).

Preoperative pathology was classified according to histopathological grade (G1 for well-differentiated endometrioid carcinoma, G2 for moderately differentiated endometrioid carcinoma, and G3 for poorly differentiated endometrioid and non-endometrioid carcinoma). There were 126 cases identified as G1, 92 cases as G2, and 71 cases as G3 before hysterectomy. The weighted kappa value for agreement between preoperative and postoperative histopathological grade was 0.616 (Z = 13.34, p < 0.001) (Table 2), indicating that the rate of agreement was “substantial”. Postoperative pathology indicated that there were 124 cases of G1, 107 cases of G2, and 58 cases of G3. Out of 126 cases that were classified as G1 preoperatively, 98 were confirmed to be G1 by postoperative grading, while 28 were upgraded postoperatively to G2 or G3 (misdiagnosis rate of 22.2%). Furthermore, out of 92 cases diagnosed preoperatively as G2, 68 were confirmed to be G2 by postoperative grading, while 24 were reclassified postoperatively as G1 or G3 (misdiagnosis rate 26.1%). Finally, the group preoperatively diagnosed as G3 included 71 cases, of which 45 were confirmed to be G3 by postoperative grading, while 26 were downgraded to G1 or G2 (misdiagnosis rate 36.6%). The overall agreement rate was 73.0%. Pairwise chi-square analysis showed that the rate of misdiagnosis of G3 group was significantly higher than that of G1 group (p = 0.03), but that there was no significant difference between the rate of misdiagnosis of G2 compared with the other two groups (p > 0.05) (Table 3). Taken together, our results suggest that the level of differentiation as determined by histopathological analysis of preoperative biopsies is often underestimated compared with that observed by postoperative hysterectomy pathology.
Table 2
Chi-square analysis of rates of misdiagnosis between each pair of groups (G1, G2, and G3).

| Kappa statistics                      | Misdiagnosis rate (%) | Chi-Square | p-value | Overall agreement |
|---------------------------------------|-----------------------|------------|---------|-------------------|
| G1/G2                                 | 22.2/26.1             | 4.731      | 0.03    | 0.73              |
| G2/G3                                 | 26.1/36.6             | 0.437      | 0.508   |                   |
| G3/G1                                 | 36.1/22.2             | 2.091      | 0.148   |                   |

G1: well differentiated; G2: moderately differentiated; G3: poorly differentiated.

Misdiagnosis rate of G1 group was 22.2%; G2 group 26.1%; G3 group 36.6% respectively, the overall coincidence rate was 73.0%. The misdiagnosis rate of G3 group was significantly higher than that of G1 group (P = 0.03), but there was no significant difference between G2 group and other two groups (P > 0.05).

Table 3
Comparison of histopathological grades as determined by preoperative hysteroscopic biopsy and postoperative hysterectomy.

| Hysteroscopic biopsy | Hysterectomy | Weighted kappa value |
|----------------------|--------------|----------------------|
|                      | G1 | G2 | G3 | Total |                      |
| G1                   | 98 | 22 | 6  | 126   | 0.616*               |
| G2                   | 17 | 68 | 7  | 92    |                      |
| G3                   | 9  | 17 | 45 | 71    |                      |
| Total                | 124| 107| 58 | 289   |                      |

G1: well-differentiated; G2: moderately differentiated; G3: poorly differentiated.

*The weighted kappa value for agreement indicates “substantial” agreement.

Histopathology is considered to be the most important method for preoperative evaluation of EC, and its reliability in clinical practice has been recognized by experts for decades. Hysteroscopy can target the lesion site under direct vision to improve the accuracy of diagnosis and reduce the risk of misdiagnosis of endometrial disease due to blind curettage, so it is strongly recommended for the diagnosis of patients with a high risk of cancer [21,22], and is currently considered the gold standard for endometrial biopsy [23].

In current study, the rate of agreement between histotype as determined by preoperative hysteroscopic biopsy and postoperative pathology was 94.8%. Some researchers demonstrated there may be some overlap between the two types of endometrial carcinoma [24]. It has been reported that 10–19% of
endometrioid carcinomas are deemed high-grade but have histopathological and molecular features that are more akin to non-endometrioid carcinomas [25,26] and that there are mixed histopathological patterns incorporating features of both types [27]. The identification of new cytokines and proteins associated with non-endometrioid carcinoma, as well as new technologies, may help improve diagnostic accuracy [28].

Histopathological grading is an important reference for determining the scope of surgery, including the need for lymphadenectomy and adjuvant therapy after surgery. Bernardini et al. previously reported that endometrial biopsy only correctly diagnosed tumour grade in 58% of cases [29], while Cutillo et al. demonstrated that hysteroscopy-directed biopsy accurately determined tumour grade in 97% of cases [17], and Ørtoft et al. reported an accuracy rate of 81% in their study [18]. In the current study, the agreement rate between pre- and postoperative histopathological grading was 73.0% (with a weighted kappa value of 0.616), which is higher than the accuracy rate reported by Bernardini et al. but lower than those reported by Cutillo et al. and Ørtoft et al. [17,18,29]. Regarding determination of tumour grade, Eltabbakh et al. found that, among 182 patients with well-differentiated endometrial carcinoma as diagnosed preoperatively based on endometrial pathology, 29.2% were reclassified postoperatively as having moderately or poorly differentiated carcinoma; in comparison [30], Neubauer and Lurain reported a similar reclassification rate of 25%, and in our study this proportion was 22.2% [31]. Furthermore, 43.7% of preoperative samples classified as poorly differentiated were misdiagnosed, indicating that the misdiagnosis rate for the G3 group was significantly higher than that for the G1 group (p = 0.03); however, there was no significant difference in the rate of diagnosis between the G2 group and other two groups (p > 0.05). That is to say, the degree of histopathological differentiation detected by preoperative hysteroscopic biopsy is somewhat lower than that observed by postoperative hysterectomy. This finding is similar to results reported by Nicole et al., who found that 25% of the endometrial samples were downgraded, while 21% were upgraded, after surgery [16]. In contrast, however, Karateke et al. found that the differentiation grades of 31% of samples determined based on dilatation and curettage were upgraded, whereas 8% were downgraded [32].

Some researchers have pointed out that “upgrading” a case based on nuclear features is only rarely prudent, as in most cases tumour are upgraded inappropriately (nuclear atypia is mild-moderate and diffuse, or severe and focal) or are not endometrioid at all [33]. Overgrading may lead to more extensive surgical treatment, with associated rates of perioperative morbidity that may be up to 20% [34]. The accuracy of preoperative histology is particularly crucial for patients who wish to receive conservative treatment in order to retain their fertility, or for those who have surgical contraindications.

Because of the limitations of preoperative histopathology, the value of analysing intraoperatively by frozen sections should be emphasized, particularly for those patients whose preoperative histology grade showed poorly differentiated tumour tissue, as well as for nulliparous patients, as a final verification step before organs are resected and to help determine the optimal therapeutic strategy.
Preoperative hysteroscopic biopsy is quite reliable for diagnosis of endometrial carcinoma, as it revealed relatively high consistency in determination of both histotype and tumour cell differentiation grade compared with final histopathology. However, clinicians must exercise caution when interpreting preoperative histopathological results, especially for patients diagnosed with high-grade tumour, before planning surgery and postoperative treatment.

**Abbreviations**

EC: Endometrial Carcinoma.

**Declarations**

**Competing interests**

All authors declare that they have no competing interests.

**Authors’ contributions**

Yinglan Z and Yuan L participated in study’s conception and design; Yinglan Z and Yu Z handled the original database, collected and analysed the data, and drafted the article; Yinglan Z and Yuan L revised data critically for intellectual content and final approval. All authors read and approved the final manuscript.

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**References**

1. Ferlay J, Colombet M, Soerjomataram I, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries and 25 major cancers in 2018. *Eur J Cancer*. 2018;103:356–387.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J. Clin.* 2020;70(1):7–30.
3. Mazzon I, Corrado G, Masciullo V, et al. Conservative surgical management of stage IA endometrial carcinoma for fertility preservation. *Fertility and Sterility*. 2010; 93(4):1286—1289.
4. Park JY, Kim DY, Kim JH, et al. Long-term oncologic outcomes after fertility-sparing management using oral progestin for young women with endometrial cancer (KGOG 2002). *European Journal of...*
Cancer. 2013;49(4):868–874.

5. Falcone F, Laurelli G, Losito S, et al. Fertility preserving treatment with hysteroscopic resection followed by progestin therapy in young women with early endometrial cancer. *Journal of Gynecologic Oncology*. 2017;28(1):e2.

6. Jemal A, Siegel R, Ward E, et al. Cancer Statistics, 2008. *CA: A Cancer Journal for Clinicians*. 2008;58(2):71–96.

7. Alonso S, Castellanos T, Lapuente F, et al. Hysteroscopic surgery for conservative management in endometrial cancer: A review of the literature. *Ecancer*. 2015; 9:505.

8. Navarria I, Usel M, Rapiti E, et al. Young patients with endometrial cancer: How many could be eligible for fertility-sparing treatment? *Gynecologic Oncology*. 2009;114(3):448–451.

9. Bogani G, Dowdy SC, Cliby WA, et al. Management of endometrial cancer: Issues and controversies. *European Journal of Gynaecological Oncology*. 2016;37(1):6–12.

10. Colombo N, Creutzberg C, Amant F, et al. ESMO-ESGO-ESTRO consensus conference on endometrial cancer: Diagnosis, treatment and follow-up. *International Journal of Gynecological Cancer*. 2016;26(1):2–30.

11. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: uterine neoplasms. Version 5, 2019.

12. Creasman WT, Morrow CP, Bundy BN, et al. Surgical pathologic spread patterns of endometrial cancer: A gynecologic oncology group study. *Cancer*. 1987;60(S8):2035–2041.

13. Zuurendonk, LD, Smit RA, Mol B W J, et al. Routine pelvic lymphadenectomy in apparently early stage endometrial cancer. *European Journal of Surgical Oncology*. 2006; 32(4):450–454.

14. Barlin JN, Soslow RA, Lutz M, et al. Redefining stage I endometrial cancer: Incorporating histology, a binary grading system, myometrial invasion, and lymph node assessment. *International Journal of Gynecological Cancer*. 2013; 23(9):1620–1628.

15. Barlin JN, Zhou Q, St Clair CM, et al. Classification and regression tree (CART) analysis of endometrial carcinoma: Seeing the forest for the trees. *Gynecologic Oncology*. 2013;130(3):452–456.

16. Visser NCM, Reijnen C, Massuger LFAG, et al. Accuracy of endometrial sampling in endometrial carcinoma: A systematic review and meta-analysis. *Obstetrics and Gynecology*. 2017;130(4):803-813.

17. Cutillo G, Cignini P, Visca P, et al. Endometrial biopsy by means of the hysteroscopic resectoscope for the evaluation of tumor differentiation in endometrial cancer: A pilot study. *European Journal of Surgical Oncology*. 2007;33(7):907–910.

18. Ørtoft G, Dueholm M, Mathiesen O, et al. Preoperative staging of endometrial cancer using TVS, MRI, and hysteroscopy. *Acta Obstetricia et Gynecologica Scandinavica*. 2013;92(5):536–545.

19. Larson D, Johnson K, Broste S, et al. Comparison of D&C and office endometrial biopsy in predicting final histopathologic grade in endometrial cancer. *Obstetrics and Gynecology*. 1995;86(1):38–42.
20. Traen K, Hølund B, Mogensen, O. Accuracy of preoperative tumor grade and intraoperative gross examination of myometrial invasion in patients with endometrial cancer. *Acta Obstetricia et Gynecologica Scandinavica.* 2007;86(6):739–741.

21. Committee on Gynecologic Practice. ACOG committee opinion no. 734: The role of transvaginal ultrasonography in evaluating the endometrium of women with postmenopausal bleeding. *Obstetrics and Gynecology.* 2018;131(5):e124–e129.

22. Litta P, Merlin F, Saccardi C, et al. Role of hysteroscopy with endometrial biopsy to rule out endometrial cancer in postmenopausal women with abnormal uterine bleeding. *Maturitas.* 2005;50(2):117–123.

23. Morice P, Leary A, Creutzberg C, et al. Endometrial cancer. *The Lancet.* 2016;387(10023):1094–1108.

24. Sanderson PA, Critchley HOD, Williams ARW, et al. New concepts for an old problem: The diagnosis of endometrial hyperplasia. *Human Reproduction Update.* 2017;23(2):232–254.

25. Brinton LA, Felix AS, McMeekin DS, et al. Etiologic heterogeneity in endometrial cancer: Evidence from a Gynecologic Oncology Group trial. *Gynecologic Oncology.* 2013;129(2):277–284.

26. Voss MA, Ganesan R, Ludeman L, et al. Should grade 3 endometrioid endometrial carcinoma be considered a type 2 cancer - A clinical and pathological evaluation. *Gynecologic Oncology.* 2012;124(1):15–20.

27. Mackenzie R, Talhouk A, Eshragh S, et al. Morphologic and molecular characteristics of mixed epithelial ovarian cancers. *The American Journal of Surgical Pathology.* 2015;39(11):1548–1557.

28. Kandoth C, Schultz N, Cherniack AD, et al. Integrated genomic characterization of endometrial carcinoma. *Nature.* 2013;497(7447):67–73.

29. Bernardini MQ, May T, Khalifa, MA, et al. Evaluation of two management strategies for preoperative grade 1 endometrial cancer. *Obstetrics and Gynecology.* 2009;114(1):7–15.

30. Eltabbakh GH, Shamonki J, Mount SL. Surgical stage, final grade, and survival of women with endometrial carcinoma whose preoperative endometrial biopsy shows well-differentiated tumors. *Gynecologic Oncology.* 2005;99(2):309–312.

31. Neubauer NL, Lurain JR. The role of lymphadenectomy in surgical staging of endometrial cancer. *International Journal of Surgical Oncology.* 2011;814649.

32. Karateke A, Tug N, Cam C, et al. Discrepancy of pre- and postoperative grades of patients with endometrial carcinoma. *European Journal of Gynaecological Oncology.* 2011;32(3):283–285.

33. Soslow RA, Tornos C, Park K J, et al. Endometrial carcinoma diagnosis: use of FIGO grading and genomic subcategories in clinical practice: Recommendations of the international society of gynecological pathologists. *International Journal of Gynecological Pathology.* 2019;38:S64–S74.

34. Frost JA, Webster KE, Bryant A, et al. Lymphadenectomy for the management of endometrial cancer. *The Cochrane Database of Systematic Reviews.* 2015;9:CD007585.