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Clinical Article

Gynecology; *and Gynecological Oncology*

Comparison of Frozen and Final Pathology Results in Patients Operated for Endometrial Hyperplasia

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ABSTRACT

OBJECTIVE: Our study aimed to determine the frequency of endometrial cancer in patients undergoing surgery with a diagnosis of endometrial hyperplasia and to evaluate the concordance between preoperative diagnosis, frozen section examination, and final pathology results.

STUDY DESIGN: The clinical findings, imaging results, and all pathology reports of patients who underwent total abdominal hysterectomy for endometrial hyperplasia (atypical or non-atypical) between January 2020 and January 2023 at our hospital were retrospectively evaluated. Demographic and clinical characteristics (age, menopausal status, parity, body mass index, presence of diabetes and hypertension) and pathology results were recorded from patient records.

RESULTS: 144 patients diagnosed with endometrial hyperplasia were included in the study. The frozen section and final pathology results of all patients diagnosed with non-atypical endometrial hyperplasia were reported as benign lesions. In the atypia group, the intraoperative frozen section results of 80.7% of the patients were classified as benign lesions, while the results of 19.3% were reported as malignant pathology. A statistically significant difference was found between the benign and malignant lesion groups, which were classified based on the final pathology results, with respect to age, menopausal status, and average endometrial thickness before biopsy.

CONCLUSION: In cases of endometrial hyperplasia with atypia, the possibility of cancer appearing in the final pathology results should be taken into consideration. In the preoperative evaluation of patients, characteristics such as endometrial thickness, age, and menopausal status may suggest the likelihood of encountering endometrial cancer during surgery in this patient group.

Keywords: Endometrial hyperplasia, Final pathological examination, Frozen section examination

Gynecol Obstet Reprod Med (Articles in Press)

Introduction

Endometrial hyperplasia denotes an aberrant increase in the proliferation of endometrial glands, arising from unopposed estrogenic stimulation of the endometrial tissue, coupled with a relative insufficiency of progesterone's counteracting effects. This hormonal imbalance manifests in various scenarios, originating from either internal or external sources of estrogen surplus (1).

Irregular endometrial proliferation leads to an abnormal glandular-to-stromal ratio, causing a range of alterations in the endometrial tissue. This encompasses diverse levels of histopathological intricacy, incorporating atypical attributes in both cellular and nuclear aspects. Left untreated, endometrial hyperplasia carries a predisposition to progress into endometrial cancer (1,2).

Endometrial hyperplasia risk increases with advanced age, nulliparity, obesity, genetic predisposition, diabetes, anovulatory processes, ovarian tumors, the use of certain hormonal medications, and some hereditary syndromes (1,3,4).

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Submitted for Publication: 30.03.2024 *Revised for Publication: 23.05.2024*
Accepted for Publication: 04.10.2024 *Online Published: 14.10.2024*

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	DOI:10.21613/GORM.2023.1493

How to cite this article: *Turker Ergun G. Zorlu U. Elmas B. Baris Akcan BN. Kurtaran G. Cetinkaya K. Doganay M. Comparison of Frozen and Final Pathology Results in Patients Operated for Endometrial Hyperplasia. Gynecol Obstet Reprod Med. 2024 (Articles in Press)*

A comprehensive epidemiological study on endometrial hyperplasia revealed that women with non-atypical hyperplasia were typically between the ages of 50-54. In contrast, hyperplasia with atypia was most commonly observed in the 60-64 age group, and cases were notably rare in individuals under 30 (5).

The frozen section aids in swift intra-operative diagnosis. It is frequently employed in surgeries to identify malignancies, enabling real-time adjustments to the surgical approach. Furthermore, frozen section analysis is conducted to assess surgical margins and detect lymph node metastasis. Additionally, it helps detect uncommon pathological conditions (6). This procedure is commonly utilized in gynecological surgery and gynecological oncological surgery operations. It is highly recommended for guiding the surgical course and disease management. The frozen section analysis is accurate in more than 95% of instances, leaving approximately 2% for subsequent formalin examination. It's worth noting that about 1-2% of cases may produce inaccurate findings (7). The objective of our research was to determine the rate of endometrial cancer in patients undergoing surgery with an initial diagnosis of endometrial hyperplasia. Additionally, we aimed to assess the agreement between preoperative diagnosis, frozen section examination, and ultimate pathological findings.

Material and Method

After obtaining the necessary approval from the Local Ethics Committee (E2-23-4580, date: 19.07.2023), a retrospective data scan covering the period from January 2020 to January 2023 was conducted. Within this scope, examination findings, imaging results, and all pathology results of patients who underwent total abdominal hysterectomy in our hospital with a diagnosis of endometrial hyperplasia (either atypical or non-atypical) between January 2020 and January 2023 were retrospectively evaluated.

Patient data were accessed through the hospital's electronic information system and the patient file archive. Demographic and clinical characteristics of the patients (age, menopausal status, parity, body mass index, presence of diabetes, and hypertension) along with pathology results were recorded from the patient records. Imaging results reported by radiology, and obstetrics and gynecology specialists were retrieved from the electronic system and recorded. Surgical notes of the patients were examined to investigate if there were any unusual practices during surgery. Data based on macroscopy through intraoperative observation were recorded. Information regarding patients whose endometrial biopsy resulted in endometrial hyperplasia was screened. Patients who did not undergo total abdominal hysterectomy at our hospital were excluded from the study. Patients with both frozen and final pathological examination reports during surgery were divided into two groups based on the 2014 World Health Organization (WHO) classification of atypical or non-atypical hyperplasia (8). In the atypical hyperplasia group, there were 88 patients, while the non-atypical hyperplasia group included 56 patients after applying exclusion criteria. The groups were compared in terms of age, parity, preoperative menopausal status, presence of diabetes and/or hypertension, body mass index, and pre-biopsy endometrial thickness. Following this comparison, the patients were assessed for differences between frozen data and final pathology results. Finally, the patients were categorized into benign and malignant final pathology groups and compared in terms of age, parity, preoperative menopausal status, presence of diabetes and/or hypertension, body mass index, and pre-biopsy endometrial thickness.

The data were analyzed statistically utilizing the SPSS 25.0 software program. Descriptive statistics such as standard deviation, mean, frequency, median, and ratio were computed. Pearson's Chi-Square test and Fisher's Exact tests were utilized to compare the data. The significance level was set at $p<0.05$.

Results

After applying exclusion criteria, a total of 144 patients diagnosed with endometrial hyperplasia were included in the study. Among these patients, 88 had a biopsy result indicating atypical endometrial hyperplasia, while 56 were reported to have non-atypical endometrial hyperplasia. When comparing the atypical and non-atypical groups, statistically significant differences were observed in terms of age, presence of diabetes, pre-biopsy endometrial thickness, and preoperative menopausal status. Nonetheless, there were no significant differences between the two cohorts regarding the occurrence of hypertension, parity, and body mass index. The average age in the atypical hyperplasia cohort was 57.2±5.21 years, while in the non-atypical group, it stood at 51.7±5.1. Before the surgical procedure, 44.3% of individuals in the atypical hyperplasia group had entered menopause, as opposed to 25% in the other group. When looking at the sonographically measured pre-biopsy endometrial thickness values of the patients, it was found to be 11.21±1.8 mm in the atypical group and 8.1±1.4 mm in the non-atypical group. When we look at values where no statistically significant difference was detected, in the atypical hyperplasia group, the rate of hypertension is 28.4%, while in the non-atypical group, this rate is 26.7%. The body mass index in the non-atypical group is 30.3±4.7 kg/m^2, whereas in the atypical group, it is 31.4±5.5 kg/m^2. In the non-atypical group, only 3.57% of the patients have a parity of less than 2, whereas in the atypical group, this rate is 4.54% (Table I). According to our study, the group with a higher average age, menopausal status, and greater endometrial thickness measured by sonography showed a higher rate of cellular atypia.

In Table II, a comparison of preoperative, perioperative frozen, and postoperative final pathology results of cases with atypical and non-atypical endometrial hyperplasia is pre-

sented. In the non-atypical endometrial hyperplasia group, 100% of the patients had intraoperative frozen section results reported as benign pathology. Furthermore, no difference was observed in their final pathology results, as all patients were reported to have benign lesions. In the atypical group, 80.7% of the patients were classified as having benign lesions based on intraoperative frozen section, while 19.3% were reported to have malignant pathology. Upon examination of the final pathology results, the likelihood of observing low-grade lesions according to the frozen section results was 2.27%, whereas the likelihood of observing lesions of equivalent grade was 90.9%. The probability of observing high-grade lesions in the final pathology based on the frozen section result was 6.81% (Table II). The rate of discrepancy between the final pathology and frozen section was higher in the group with cellular atypia compared to the non-atypical group.

Our patients were categorized into two groups, benign and malignant, according to the final pathology outcomes. The mean age of the benign group was determined to be 50.2±5.15 years, whereas the mean age of the malignant group was 57.92±5. A statistically notable distinction in age was observed between the two groups (p=0.019). Before surgery, 33.07% of patients in the benign group were menopausal, while in the malignant group, this rate was 64.7. There was a statistically significant higher rate of menopausal patients in the malignant group (p=0.013). When comparing BMI, the av-

Table I: *Comparison of the characteristics of patients divided into two groups as non-atypical and atypical endometrial hyperplasia according to endometrial biopsy result*

Patient characteristic	Non-atypical endometrial hyperplasia group (based on endometrıal biopsy result)	Atypical endometrial hyperplasia group (based on endometrıal biopsy result)	p
Age (years) (mean, std)	51.7±5.1	57.2±5.21	**0.023**
Pre-existing diabetes			
Yes	%16.07	%6.8	**0.001**
No	%83.93	%93.2	
Pre-existing hypertension			
Yes	%26.7	%28.4	0.141
No	%73.3	%71.6	
Preoperative menopausal status			
Yes	%25	%44.3	**0.011**
No	%75	%55.7	
BMI (kg/m^2) (mean, std)	30.3±4.7	31.4±5.5	0.060
Preoperative endometrial thickness (mm) (mean, std)	8.1±1.4	11.21±1.8	**0.016**
Parity ≥2			
Yes	%96.43	%95.46	0.243
No	%3.57	%4.54	

BMI: Body-Mass Index. p<0.05 was considered statistically significant

Table II: *Comparison of preoperative, perioperative frozen, and postoperative final pathology results of cases with atypical and non-atypical endometrial hyperplasia*

Endometrial biopsy result	Perioperative frozen result	Low-grade lesion according to the frozen section in the final pathology	Equally graded lesion according to the frozen section in the final pathology	High-grade lesion according to the frozen section in the final pathology
Non-atypical endometrial hyperplasia group (n=56)	Benign %100 (n=56) Malign %0 (n=0)	(n=0) %0	(n=28) %100	(n=0) %0
Atypical endometrial hyperplasia group (n=88)	Benign %80.7 (n=71) Malign %19.3 (n=17)	(n=2) %2.27	(n=80) %90.9	(n=6) %6.81

erages of patients in both groups were at the obesity threshold, and there was no statistically significant difference between them. The average pre-biopsy endometrial thickness was 8.89±1.6 mm in the benign group, while it was 18.29±2.9 mm in the other group (p=0.001). There was no statistically significant difference in the presence of accompanying diabetes and hypertension between the benign and malignant groups. In conclusion, malignancy was more frequently observed in patients with higher average age, increased sonographic measurements of endometrial thickness, and menopausal status (Table III).

Discussion

In our study, we demonstrated that the group with atypical endometrial hyperplasia differed significantly from the non-atypical group in terms of age, menopausal status, presence of accompanying diabetes, and endometrial thickness. We believe that older age, menopausal status, and increased endometrial thickness are risk factors for the presence of cellular atypia. In their study, Zhao et al., emphasized, as in our study, that especially after the age of 50, there is a higher incidence of cellular atypia considering it as a risk factor for the transformation to endometrial cancer (9). Although estrogen-dependent conditions like endometriosis tend to manifest at an earlier age (with an average age of 35 according to studies by Coskun et al., hyperplasia, atypia, and cancer tend to develop at later stages compared to these conditions (10). We attribute this to cellular and immune changes associated with aging, as well as prolonged exposure to unopposed estrogen. There is information suggesting that certain hormone replacement therapy combinations and hormonal medications taken after entering menopause, especially with the increase in age, may be associated with the development of cellular atypia, hyperplasia, and cancer. Especially, preparations containing only estrogen are considered highly suspicious in terms of these effects, and it is strongly recommended to combine them with preparations containing progesterone (4). In their studies, Vitale et al. stated that endometrial thickness, especially in the postmenopausal period, can predict the development of atypia and cancer at certain cut-off values and that more diagnoses can be made (11). Considering that endometrial thickness changes during the hormone-dependent cycle in the premenopausal period, it is natural for this measurement to be more useful in postmenopausal patients. When considering the effects of atypia on the accumulation of both intracellular elements, intercellular elements, and intracellular secretions on the glandular background, it is expected that the increase in endometrial thickness will guide us prognostically for the development of hyperplasia, atypia, and cancer at certain cut-off values. Further prospective studies with a larger number of patients and confirmed pathological data are needed to determine these values. Diabetes, particularly Type 2, accelerates the advancement of endometrial hyperplasia by modulating the GALNT2-mediated phosphorylation of EGFR and amplifying cell proliferation. In our study, the group with non-atypical hyperplasia had a higher incidence of diabetes (12). However, most of the diabetic patients in our study had recently been diagnosed (73.3% within two years), and glucose regulation had been achieved (in monitored and regulated patients), which may not have yielded significant results in our study. Long-term follow-up of these patients could be investigated in future studies to determine if there is a progression to cellular atypia compared to a healthy population. Similarly, the progression toward cellular atypia in patients with regulated values and in unregulated, non-monitored patients can be investigated in future studies. However, our sample size may not be sufficient to make this inference.

The rate of discrepancy between the final pathology and the frozen section was found to be higher in the group with cellular atypia compared to the non-atypical group. In their detailed 7-year study, Günay et al. emphasized that endometrial carcinoma is often associated with atypical hyperplasia

Table III: *Comparison of the Characteristics of Patients Categorized into Benign and Malignant Lesions According to the Final Pathology Result*

Endometrial biopsy result	Perioperative frozen result	Low-grade lesion according to the frozen section in the final pathology	Equally graded lesion according to the frozen section in the final pathology	High-grade lesion according to the frozen section in the final pathology
Non-atypical endometrial hyperplasia group (n=56)	Benign %100 (n=56) Malign %0 (n=0)	(n=0) %0	(n=28) %100	(n=0) %0
Atypical endometrial hyperplasia group (n=88)	Benign %80.7 (n=71) Malign %19.3 (n=17)	(n=2) %2.27	(n=80) %90.9	(n=6) %6.81

BMI: Body-Mass Index. p<0.05 was considered statistically significant.

and stressed the importance of performing intraoperative frozen evaluation for these patients. In their study, when the frozen results of the 112 patients with atypical hyperplasia were compared with the paraffin sections, the sensitivity, specificity, positive predictive value, and negative predictive value of the frozen evaluation were found to be 87.8%, 97.1%, 94.7%, and 93.2%, respectively (13). In our study, frozen section examination was found to be highly successful when compared with the final pathology results. No difference was observed between the frozen examination and final pathology in the non-atypical group. In the atypical group, a concordance of 90.9% was achieved with the final pathologies. In the atypical group, frozen examination reported higher-grade lesions in only 2.27% of cases and lower-grade lesions in only 6.81% of cases compared to the final pathology. Our study, like other studies in our country, has demonstrated that frozen results provide a high degree of accuracy and should be utilized (13). Indeed, especially with the advancement of technology, improved imaging capabilities, and enhanced staining techniques over the years, it would not be incorrect to assume that frozen section examination has progressively aligned with the final pathology. In contrast to our perspective, Matsuo and colleagues have shown in the literature that frozen section examination has low negative predictive value and sensitivity (14). Research has indicated that there are difficulties in differentiating hyperplasia from carcinoma in pathological analysis, leading to a potentially lower diagnostic agreement in the frozen section. Nevertheless, given the low occurrence of false positives in frozen assessment and the tendency for cases with undetectable tumors during frozen examination to be generally in early stages, the evaluation of frozen sections is deemed critical in instances of atypical endometrial hyperplasia (15,16). In the studies conducted by Bilgin et al., it was emphasized that frozen section results, especially in patients without myometrial invasion, do not guarantee the exclusion of the possibility of cancer (17). Especially when the frozen result is reported as adenocarcinoma, the very low false positive rate in this situation provides confidence for surgeons who plan advanced surgery based on the frozen result (15,17). The primary focus should be on attempting frozen section examination in all cases to prevent the need for a second surgery for final pathology confirmation. Especially when the biopsy diagnosis is atypical hyperplasia, it is imperative to operate on the patient in a clinical setting with the option of an intraoperative frozen section for the best outcome. Indeed, both for the patient and the surgeon, secondary surgery is a more challenging process. Inadequate procedures during the initial surgery can lead to a decrease in the patient's life expectancy. In our study, malignancy was more frequently observed in patients with higher average age, increased sonographic measurements of endometrial thickness, and menopausal status. Age and being postmenopausal are widely accepted as risk factors for endometrial cancer (18). Sonographically, especially in postmenopausal symptomatic cases, an increase in endometrial thickness is associated with atypia and cancer (11). While diabetes and obesity are considered risk factors for cancer development, our study did not demonstrate this association (18). We believe that the relatively uniform weight status of the patients, with most of them being overweight, may have contributed to this result. In a larger patient group, the progression rates of cancer and atypia between the normal weight group and the overweight and/or obese group could be investigated in future studies.

Endometrial hyperplasias encompass a range of proliferative conditions. This spectrum starts with uncomplicated non-atypical hyperplasia, advances to potentially pre-cancerous lesions, and can ultimately lead to well-developed endometrioid cancers. As a result, the existing classification methods are considered inadequate in terms of consistent and dependable diagnosis. There is a necessity for classifications grounded on more objective criteria, ones that can reliably anticipate the progression of the disease and offer direction in clinical treatment. Continued research in this field is crucial.

Study Limitations

The retrospective design and limited sample size are the most important limitations of the study.

Conclusion

In cases of atypical endometrial hyperplasia, the possibility of cancer in the final pathology results should be considered. For these patients, conducting intraoperative frozen evaluation is important for determining the extent of surgery, postoperative treatment, and the approach to the patient. Completing surgical staging in the same session for cases where the frozen result is reported as malignant will prevent the patient from undergoing unnecessary surgery and delays in treatment. Frozen results in the non-atypical group are more reliable compared to the atypical group. Frozen examination, which is reliable in many aspects, should be applied especially in all cases with suspected malignancy. Preoperative assessment of patients, including ultrasonographically measured endometrial thickness, age, and menopausal status, can provide insights into the likelihood of encountering endometrial cancer or atypia intraoperatively in this patient group.

Ethics approval and consent to participate
All participants signed informed written consent before being enrolled in the study. The study was reviewed and approved by the ethics committee of Ankara Bilkent City Hospital (E2-23-4580, date: 19.07.2023). All procedures were performed according to the Declaration of Helsinki.
Availability of data and materials
The data supporting this study is available through the corresponding author upon reasonable request.
Competing interests
The authors declare that they have no competing interests.
Funding: None.

Authors' contributions: Concept: MD., KC., GK., Design: BE., BNBA, GTE., Data Collection or Processing: BNBA, KC., GK., Analysis or Interpretation: UZ., GTE., Literature Search: BE., UZ., Writing: BE., UZ., GTE.
Acknowledgments: We are grateful to the participants for their voluntary participation in this research.

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