Southern African Journal of Gynaecological Oncology 2020; 12(1):13–16
https://doi.org/10.1080/20742835.2020.1754659

South Afr J Gynaecol Oncol
ISSN 2074-2835 EISSN 2220-105X

ARTICLE

Discrepancy between preoperative endometrial sampling and hysterectomy diagnosis in endometrial cancer

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Background: A study was conducted to determine the accuracy of preoperative endometrial sampling histology type and tumour grade results compared with the final postoperative diagnosis.
Methods: This was a retrospective chart audit of patients with endometrial cancer and atypical hyperplasia admitted to Grey's Hospital in Pietermaritzburg, South Africa, from January 2013 to December 2017.
Results: Sixty patients met the inclusion criteria. For endometrial cancer histological types, the accuracy of preoperative endometrial sampling was 94.7% (36/38) for endometrioid adenocarcinoma, 42.9% (3/7) for serous papillary carcinoma, 85.7% (6/7) for carcinosarcoma and 75% (9/12) for atypical hyperplasia. A kappa value of 0.825 was obtained with a *p*-value of 0.000 for agreement between preoperative endometrial sampling and the final postoperative diagnosis. For endometrioid adenocarcinoma tumour grading 1–3 (G1–3), only 16/38 (42.1%) patients met the criteria to compare the pre- and postoperative results, which were as follows: of the eight patients with grade 1 tumour on preoperative sampling one patient (1.25%) was upgraded to grade 2 tumour postoperatively. There were no changes in tumour grading for grade 2 and 3 tumours, 3/3 and 5/5 respectively.
Conclusion: Our study results for endometrioid adenocarcinoma are comparable to previous literature. However, there were significant discrepancies for non-endometrioid adenocarcinoma. Deficiencies that need to be addressed by laboratories in order to improve both preoperative surgical staging and postoperative adjuvant therapy planning were also highlighted.

Keywords: endometrial cancer, endometrial sampling versus hysterectomy diagnosis

Introduction

Endometrial cancer is an uncommon gynaecological malignancy in developing countries; however, its frequency has increased due to obesity and reduced fertility. The overall risk in South Africa is 1 in 146 across all races.[1] The majority of endometrial cancers are diagnosed early (80% in stage 1) with a five-year survival of over 95%; however, five-year survival rates are much lower if there is regional or distant disease (68% and 17% respectively).[2]

Endometrial cancer is divided into two main clinicopathological and molecular types: Type I is the much more common endometrioid adenocarcinoma (80% to 90%) and Type II comprises non-endometrioid subtypes such as serous, clear cell, undifferentiated and carcinosarcoma (10 to 20%).[3] Endometrioid adenocarcinoma is associated with exposure to unopposed oestrogen, tends to be low grade and has an excellent prognosis.[4] Non-endometrioid subtypes are typically high grade, often oestrogen-receptor negative and may arise from an atrophic endometrium, and have a poor prognosis even if diagnosed at an early stage.[4]

Endometrial cancer is surgically staged with pelvic and para-aortic lymph node status forming part of the comprehensive FIGO staging.[5] Accurate preoperative endometrial sampling diagnosis is one of the important factors in planning the extent of surgical staging. While surgical nodal staging plays an important role in triaging of patients for adjuvant treatment, it also carries significant intraoperative and postoperative morbidity.[6] Low-risk endometrioid cancer (grade 1 or 2 and superficial myometrial invasion < 50%) has a low risk of lymph node involvement, therefore lymphadenectomy is not recommended.[7,8] Lymph node dissection in high-risk endometrial cancer has not shown any survival benefit, and is therefore indicated for surgical staging and adjuvant treatment planning.[7,8]

Previous literature showed that the sensitivity of pipelle and curettage was 93.8% and 97% in patients with low-grade cancer and 99.2% and 100% in patients with high-grade cancer respectively. Good agreement was observed between the preoperative and the final postoperative diagnosis.[9]

Our retrospective study aimed to determine the accuracy of preoperative endometrial sampling histology and tumour grade results compared with the final postoperative diagnosis in our institution.

Materials and methods

Study design and population

This was a retrospective study that included all patients with histologically confirmed endometrial cancer and atypical hyperplasia of the endometrium at Grey's hospital from January 2013 to December 2017. A review of preoperative histology reports for tumour type and grade compared with the final postoperative report was conducted. Exclusion criteria included patients who had advanced disease, those who were deemed unfit for surgery, and those with missing clinical data on their medical records. Files were retrieved from the hospital records department. Demographic and clinical information was obtained from patients' files according to the data collection sheet. Data collected included patient's age, race, parity, co-morbidities, family history, drug history; preoperative data included laboratory, sample method, tumour type and grade compared with the final postoperative diagnosis.

Sample size
A total of 79 patients with endometrial cancer were identified; 19 were excluded due to advanced disease and missing clinical data, 17 and 2 respectively. Sixty patients met the criteria for inclusion in the study.

Ethics
The study protocol was reviewed and approved by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal.

Statistics
IBM SPPS version 25 (IBM Corp, Armonk, NY, USA) was used for data analysis. Frequencies and the corresponding percentages were used to summarise the demographic variables. A two-sample proportions comparison using a z-test was used to compare differences of preoperative sample and postoperative histology. The kappa statistic was used to measure the agreement between the preoperative and hysterectomy diagnosis, with regard to the histology type and the grade of the tumour. The test for statistical significance was evaluated at 5% level of significance with a *p*-value of less than 0.05 considered significant.

Results
The majority of patients were above the age of 50, 37 (61.1%) of whom were black, and 38 were hypertensive (63.3%), with the majority 59 (98.4%) having no family history of malignancy. Cohort characteristics are given in Table 1.

Table 1: Cohort characteristics

Factor	Category	Frequency (*n*)	Percentage (%)
Age	< 50	01	1.6
	> 50	59	98.4
Race	Black	37	61.6
	Indian	19	31.6
	White	02	3.3
	Mixed race	02	3.3
Parity	0	01	1.6
	1–4	59	98.4
	≥ 5	0	
Co-morbidities	Hypertension	38	63.3
	Diabetes	33	55.0
	BMI > 30	07	11.6
Family history	Nil	59	98.4
	Colon cancer	01	1.6
Drug history	Nil	59	98.4
	Tamoxifen	01	1.6
Preoperative laboratory	Lab 1*	54	90.0
	Lab 2*	06	10.0
Preoperative sample method	Hysteroscopy and biopsy	01	1.6
	Pipelle	54	90.0
	Dilatation & curettage	05	8.3
Postoperative laboratory	Lab 1*	60	100
Postoperative histology	TAH & BSO	59	98.4
	TAH, BSO & LND	01	1.6

*Represents private laboratories' analysed specimen.

Tumour types
The sensitivities of preoperative endometrial sampling to determine final postoperative histology for the various sub-types of endometrial cancer are presented in Table 2.

The sensitivity of preoperative endometrial sampling to predict endometrioid adenocarcinoma was 94.7% (36/38); two tumours were reclassified to uterine papillary serous carcinoma (UPSC) on final pathology. The sensitivity of preoperative sampling for serous papillary carcinoma was 42.9% (3/7); of the four tumours, one was reclassified from complex atypical hyperplasia and the other three were reclassified from endometrioid adenocarcinoma. Among the three patients with UPSC preoperatively only one patient had immunohistochemistry (IHC) staining using vimentin and CEA stains only; p53 was not used. Four other patients were diagnosed with UPSC postoperatively; among those three had immunochemistry staining on their endometrial sampling specimens using vimentin, CEA and mucin only; p53 was also not performed in any of them and none of them had IHC staining on their hysterectomy specimens. Sensitivity for carcinosarcoma was 85.7% (6/7) with one tumour reclassified from complex atypical hyperplasia. Sensitivity for atypical hyperplasia was 75% (9/12), three tumours were reclassified to high-grade endometrioid adenocarcinoma, uterine papillary serous carcinoma and carcinosarcoma respectively. The overall sensitivity of endometrial sampling was 83.3% (50/60). A kappa value of 0.825 was obtained with a *p*-value of 0.000 for agreement between preoperative endometrial sampling and the final postoperative diagnosis. A difference of proportion test was carried out. We used the z-test. All the endometrial cancer subtypes had no statistically significant differences between the post- and preoperative diagnosis as evident by the non-significant *p*-values.

FIGO tumour grading of endometrioid adenocarcinoma
Thirty-eight (63.3%) preoperative histological reports reported endometrioid adenocarcinoma with 22/38 (57.9%) lacking tumour grade comment. However, 36 (60%) were confirmed to be endometrioid subtype on the final histology with 11/36 (30.6%) lacking tumour grading. Only 16/38 (42.1%) of reports of endometrioid adenocarcinoma met the criteria to compare the pre- and postoperative results, as displayed in Table 3.

Of the eight patients with endometrioid adenocarcinoma grade 1 on preoperative sample one patient was upgraded to grade 2. There were no changes in tumour grades for endometrioid adenocarcinoma grade 2 and grade 3. No patients were upgraded from low-risk to high-risk endometrioid adenocarcinoma and vice versa.

Discussion
This retrospective study aimed to evaluate the accuracy of preoperative endometrial sampling in terms of tumour subtype and tumour grade for EA when compared with the final postoperative diagnosis in our institution. Although endometrioid adenocarcinoma constituted the majority of the cohort at 60%, the prevalence was lower in comparison with the previous literature where it constituted 80–90% of endometrial cancers.[3]

Huang *et al*. showed excellent sensitivity of pipelle and curettage, which was 93.8% and 97% in patients with low-grade cancer and 99.2% and 100% in patients with high-grade cancer respectively.[9] Our study found comparable results for endometrioid adenocarcinoma. However, there was a

Table 2: Comparison between preoperative and postoperative diagnosis for various tumour subtypes

Tumour type	Preoperative *n* (%)	Postoperative *n* (%)	Discrepancy *n* (%)*	*p*-value	Sensitivity
EA	38 (63.3)	36 (60)	2 (5.3)	0.7101	94.7%
CCC	1 (1.7)	1 (1.7)	0	1.000	100%
UPSC	3 (5)	7 (11.7)	4 (57.1)	0.1847	42.9%
CS	6 (10)	7 (11.7)	1 (14.3)	0.7646	85.7%
AH	12 (20)	9 (15)	3 (25)	0.4711	75%
Total	60 (100)	60 (100)	10		

EA = endometrioid adenocarcinoma, CCC = clear cell carcinoma, UPSC = uterine papillary serous carcinoma, CS = carcinosarcoma, AH = atypical hyperplasia, *discrepancy percentage for tumour subtype.

Table 3: Comparison between preoperative and postoperative endometrioid adenocarcinoma grading

Grade (G)	Preoperative	Postoperative	Upgraded	Downgraded
G1	8	7	1 (1.25%) to Grade 2	–
G2	3	4	0	0
G3	5	5	–	0
Total	16	16	1 (6.25)	0

significantly lower sensitivity for non-endometrioid cancers with papillary serous subtype having the lowest sensitivity and they could have been offered comprehensive surgical staging laparotomy with omentectomy as per ESMO-ESGO-ESTRO consensus.[10] Analysis of immunohistochemistry staining use highlighted numerous inconsistencies in its use; IHC staining was not based on p53 for any of the patients.

More than 50% of preoperative endometrioid adenocarcinomas were ungraded. The literature highlights that a larger volume of endometrial sample tissue available for analysis preoperatively improves analysis of the solid growth component.[11] The histopathology reports with no tumour grading that were reviewed in our study did not highlight the volume or quality of the samples as the reason not to grade the tumours. However, there was a substantial agreement between the preoperative sampling and final diagnosis for the tumours that were graded. These findings were in keeping with the previous study for grade 3 tumours and superior to grade 1, which was rated as fair.[12]

The findings of 30.6% of ungraded endometrioid adenocarcinoma in the final histology reports were concerning as there were no reasons documented to justify the omission of this important detail. Tumour grade is one of the important factors to consider in the triaging of patients for adjuvant therapy. The omission of tumour grade in the histology report is highly likely to delay adjuvant treatment commencement or lead to overtreatment of low-risk patients and overburden the already struggling oncology facilities.

The incidence of endometrial cancer was 25% among patients with complex atypical hyperplasia in our study. In previous reports the incidence of endometrial cancer has been shown to be between 29% and 52% among patients with complex atypical hyperplasia.[13–15] The interesting finding in our study was that all three tumours were reclassified to high-grade endometrial cancer subtypes (one EA grade 3, one serous papillary and one carcinosarcoma). One would have expected atypical hyperplasia to progress to at least G1 or G2 endometrioid adenocarcinoma.

The limitations of this study are the retrospective nature of the design, a small sample size and that the study is based on a single institution experience. This makes it prone to bias. However, this was the first study of its kind to be conducted in KwaZulu-Natal. It also highlights the need for prospective trials to validate our findings, especially with regard to atypical endometrial hyperplasia.

Conclusion

The aim of this retrospective study was to evaluate the accuracy of endometrial sampling when compared with final hysterectomy diagnosis. Results for endometrioid adenocarcinoma are comparable to those in previous literature. However, there were significant discrepancies for non-endometrioid adenocarcinoma. The study also highlighted deficiencies that need to be addressed by laboratories in order to improve both preoperative surgical staging and postoperative adjuvant therapy planning.

Disclosure statement – No conflict of interest was reported by the authors.

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Received: 5-12-2019 Accepted: 8-04-2020