Evaluation of Preoperative Endometrial Biopsy Grade vs Final Pathologic Diagnosis in Patients with Endometrioid Carcinoma Endometrium

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Introduction

Endometrioid adenocarcinoma is the most common type of Carcinoma Endometrium (75-80%). The grade of a tumour is a well-known prognostic factor for endometrial carcinoma and correlates with the depth of myo invasion, lymph node involvement, surgical stage and survival (1,2).

Preoperative tumour grading with pre and/or intraoperative assessment of the depth of myometrial invasion, as well as the histologic subtype, is frequently used to decide the extent of surgery. The staging for endometrial carcinoma has been suggested as a surgical-pathologic system which includes peritoneal cytology, pelvic and para-aortic lymphadenectomy apart from a Hysterectomy and bilateral salpingo oophorectomy (3). In 2005, the American College of Obstetricians and Gynecologists (ACOG) recommended surgical staging for women with endometrial cancer, except for young or perimenopausal women with grade 1 endometrioid adenocarcinomas, as well as atypical endometrial hyperplasia, and women at high risk of mortality secondary to comorbidities (4).

The role of lymphadenectomy has not been clearly defined in the management of endometrial cancer, especially in patients with grade 1 and 2 disease that is limited to the uterus. Some authors advise performing a routine pelvic and/or para-aortic lymphadenectomy in all women (5), whereas others have questioned the clinical utility of this procedure because of the complications of lymphadenectomy, especially in patients at low risk of nodal involvement (grade 1 or 2 with no or minimal myometrial invasion) (6, 7).

Approximately 52% of women with endometrial carcinoma desire future fertility and uterine preservation. In addition, preoperative endometrial biopsy is often the basis of referral to higher centres. Approximately 52% of women with endometrial carcinoma have a preoperative endometrial biopsy showing grade 1 (8). The accuracy of preoperative grading is an extremely important issue in young patients with well- differentiated endometrial carcinoma who desire future fertility and uterine preservation. Most of the well-differentiated tumors are managed by general gynecologists and often without appropriate incision or surgical staging. Recently, two randomized multicenter studies reported no evidence of benefits in terms of overall or recurrence-free survival for pelvic lymphadenectomy in women with preoperative International Federation of Gynecology and Obstetrics (FIGO) stage I endometrial cancer (9, 10). Most of the studies which have investigated preoperative tumour grading by various endometrial sampling methods have shown that these methods are poorly correlated with the final pathologic grade (8,11-13).

A higher FIGO grade on final uterine pathologic examination will be diagnosed in 24% of patients with preoperative FIGO grade 1 and the vast majority of cases will be upgraded to FIGO grade 2, but approximately 3% will be upgraded to FIGO grade 3 or be diagnosed as a serous or clear cell carcinoma on final pathologic assessment of the hysterectomy specimen (7-12). However, there are some studies that show nearly perfect agreement between preoperative and final pathologic grades (14,15).

The objective of this study is to compare preoperative grading with the final pathological assessment of the hysterectomy specimen. The second objective of the study is to determine the high risk group who will most probably be upgraded in the postoperative evaluation.

Objectives

To correlate preoperative grading in endometrioid endometrial cancer with the final pathologic assessment of the hysterectomy specimen.

The second objective is to identify the characteristics of the cohort of patients who possibly will be upgraded in the postoperative evaluation.

Aim

The study aims to compare the accuracy of the tumour grade in the endometrial sampling with that of the hysterectomy specimen to determine the reliability of the pre-treatment clinical assessment.

Review of Literature

Uterine endometrial cancer is the most common gynaecologic malignancy in the developed countries and fourth most common in india. Epidemiologically Endometrial carcinoma is associated with estrogen replacement therapy (usually well differentiated and endometrioid with good prognosis). Rare if ovarian dysgenesis or castration, rates much higher in white vs. black women. 80% arise in postmenopausal women, and manifest with symptoms of bleeding. Etiologically both carcinoma and hyperplasia are linked to prolonged estrogenic stimulation without progestational agents; both are also associated with estrogen secreting tumors.

Risk Factors for Endometrial Carcinoma

Older age Nulliparous state

Anovulatory infertility, history of irregular menstruation Early menarche, late menopause

Obesity PCOS

Functioning ovarian tumour- Granulosa cell tumour

Unopposed hormone replacement therapy (HRT)

Clinical decision-making starts from the initial histological biopsy diagnosis of pre-operative endometrial cancer with or without imaging studies to estimate the extent of the disease. Endometrial biopsy IHC study with PTEN, P 53 & MIB-I increase the predictive value in the diagnosis. After obtaining a surgical specimen, the final histological diagnosis is made based on a post-operative permanent section to triage the patient for adjuvant therapy. Pathological information is used to stratify endometrial cancers into risk groups, based on low and high risk for lymphatic dissemination and disease recurrence.

Endoionmetrial carcinoma classification-**Table.1**

Recently TCGA classification of endometrial carcinoma based on molecular features is being evolved.

1.POLE-ultra mutated,

2.microsatellite unstable(MMR D),

3.copy-number low(NSGP),

4.copy-number high(P53).

Figure-1: high grade endometrial carcinoma

Figure-2: Endometrial carcinoma with growth filling the cavity

Extensive EC with minimal Myo invasion

Figure-3

FIGO Staging of Endometrial Carcinoma

Stage	Description
I	Tumor confined to the uterus
IA	<50% invasion of the myometrium
IB	≥50% invasion of the myometrium
II	Tumor invades the cervical stroma but does not extend beyond the uterus
III	Local or regional spread of tumor
IIIA	Serosal or adnexal invasion
IIIB	Vaginal or parametrial involvement
IIIC	Metastasis to pelvic or paraaortic lymph nodes
IIIC1	Pelvic lymph node involvement
IIIC2	Paraaortic lymph node involvement (with or without pelvic nodes)
IV	Extension to the pelvic wall, lower one-third of the vagina, or hydro-nephrosis or nonfunctioning kidney
IVA	Invasion of bladder or bowel mucosa
IVB	Distant metastases, including ab-dominal, or involvement of inguinal lymph nodes

Table-2; FIGO 2014 REVISED STAGING

Age
Histologic type
Histologic grade
Nuclear grade
Myometrial invasion
Vascular space invasion
Tumor size
Peritoneal cytology
Hormone receptor status
DNA ploidy and other biologic markers
Type of therapy (surgery vs. radiation)

FIGO, International Federation of Gynecology and Obstetrics.

Table-3 Prognostic variables in Endometrial carcinoma other than FIGO stage

Patients in whom screening should be done

1. Postmenopausal women on exogenous estrogen

2. Women with significant family history

3. Premenopausal women with anovulatory cycleslike in PCOD Importance of Grade (29)

The standard diagnostic evaluation for endometrial cancer includes pelvic ultrasonography and endometrial biopsy regardless of the diagnostic method: dilatation and curettage(D&C), Pipelle, or hysteroscopy.

	Histologic Grade		
Depth of Myometrial Invasion	G1 ($n = 180$)	G2 ($n = 288$)	G3 ($n = 153$)
Endometrium only ($n = 86$)	0/44 (0%)	1/31 (3%)	0/11 (0%)
Inner third ($n = 281$)	3/96 (3%)	7/131 (5%)	5/54 (9%)
Middle third ($n = 115$)	0/22 (0%)	6/69 (9%)	1/24 (4%)
Outer third ($n = 139$)	2/18 (11%)	11/57 (19%)	22/64 (34%)

Table-4; Grade, depth of invasion and pelvic lymph nodal metastases

Stage I disease; grade, Depth of invasion and aortic nodal metastases (29)

Depth of Myometrial Invasion	Histologic Grade		
	G1 (n = 180)	G2 (n = 288)	G3 (n = 153)
Endometrium only (n = 86)	0/44 (0%)	1/31 (3%)	0/11 (0%)
Inner third (n = 281)	1/96 (1%)	5/131 (4%)	2/54 (4%)
Middle third (n = 115)	1/22 (5%)	0/69 (0%)	0/24 (0%)
Outer third (n = 139)	1/18 (6%)	8/57 (14%)	15/64 (23%)

Variable	Number	Metastases	Percent
Histologic grade			
Grade 1	93	2	2.2
Grade 2	88	9	10.2
Grade 3	41	16	39
Myometrial invasion			
None	92	4	4.3
Inner third	80	8	10
Middle third	17	2	11.8
Outer third	33	13	39.4

Table-5 Stage I endometrial carcinoma; distant metastases vs myoinvasion and grade (45)

1. Patients with grade 3 lesions
2. Patients with grade 2 tumors >2 cm in diameter
3. Patients with clear cell or serous carcinomas
4. Patients with greater than 50% of myometrial invasion
5. Patients with cervical extension

Table-6 Stage I Endometrial carcinoma, that requires surgical staging

Figure-4 Fundal growth with grade I carcinoma;

How to apply the INTERNATIONAL FEDERATION OF GYNECOLOGYAND OBSTETRICS (FIGO) grading system for Endometroid endometrial carcinoma

According to current practice standards, EECs are assigned a FIGO grade based on the degree of glandular differentiation. Grade 1 tumors exhibit ≤5% solid nonglandular, nonsquamous growth; grade 2 tumors from 6% to 50%; and grade 3 tumors >50% (16-18). The presence of marked cytologic atypia Increases the grade to 1 level. Since mucinous adenocarcinomas of the endometrium are closely related to endometrioid carcinomas, it is reasonable to use FIGO grade for those carcinomas as well. However, FIGO grading should NOT be used when endometrioid or mucinous differentiation is in doubt or cannot be established. All of the other endometrial tumor types carry an intrinsic tumor grade (i.e. serous, clear cell, and undifferentiated carcinomas and carcinosarcomas are high grade). Endometrioid and mucinous carcinomas are graded with a three tier system developed by the International Federation of Gynecology and Obstetrics (FIGO):

FIGO 1: predominant glandular growth and < 5% nonsquamous solid component; glandular architecture is identified by the presence of patent lumina within the gland, relatively preserved polarity of the epithelium and absent to mild epithelial stratification

FIGO 2: 6-50% non-squamous solid component

FIGO 3: more than 50% non-squamous solid component Architectural grading described above is upgraded by one if there is severe nuclear atypia (pleomorphism, enlargement, prominent nucleoli)

In general, a two-tier system can be also applied, with FIGO1 and FIGO2 being considered low grade, and FIGO 3 being considered high grade

Other carcinoma types (serous, clear cell, carcinosarcoma, undifferentiated, mixed) are by definition HIGH GRADE.

Well differentiated (FIGO grade 1)

Extensive, complex epithelial growth pattern with little intervening stroma

Usually budding and branching of large glands causing papillary structures.

May be villoglandular on low power

May have true papillae (DD: clear cell carcinoma, serous carcinoma), but without atypia

Mild to moderate atypia is allowed or only focal; if atypia is more severe, FIGO grade is increased to moderate (FIGO grade 2) Some are myoinvasive

Often has benign squamous differentiation (adenoacanthoma), focal mucinous, secretory or ciliated features

Usually stage 1, with 95% relapse free survival rate

Moderately differentiated (FIGO grade 2)

6% - 50% of nonsquamous tumor is composed of sheet-like tumor cells without glandular features

Tumor cells have moderate pleomorphism, prominent nucleoli

Poorly differentiated (FIGO grade 3)

> 50% of nonsquamous tumor is composed of sheet-like tumor cells without glandular features

Tumor cells have high grade features

Glands poorly formed when present

May contain malignant squamous cells

Angiolymphatic invasion common

It appears that many pathologists consider tight, small microacini with barely visible lumens as solid growth, although FIGO grading rules do not specifically discuss this and some pathologists characterize such patterns as "glandular" (Fig. 1). For the purposes of grading, we endorse that a confluent

microacinar pattern constitutes "solid" growth, although this is not evidence based. As stated in the FIGO criteria, squamous differentiation should be discounted as evidence of solid growth, but there are inevitable problems with grading tumors containing solid growth that resembles immature squamous epithelium and tumors that feature transitions between non keratinizing squamous epithelium and spindle cell change. It is reasonable to adjudicate these types of cases by paying attention to the nuclear grade, first in the glandular component and then, if that approach is not informative, in the solid component. We designate a tumor as FIGO grade 3 if the solid areas ressemble poorly differentiated non keratinizing squamous cell carcinoma.

Another common problem in grading concerns the degree and extent of nuclear atypia that is sufficient to upgrade a tumor from 1 FIGO category to another (19,20). The philosophy underlying our approach to this problem is that discordance between architectural grade and nuclear grade should be uncommon in endometrioid adenocarcinomas. The first step is to ensure the nuclear features are sufficiently atypical. An easy guideline is to ask yourself, "Is this focus easily appreciated on scanning or intermediate power examination?" and "Is the atypia so bad that I would consider it grade 3 on a 3-point scale?" If the answers are "yes," you should sample the tumor extensively to determine whether the finding is limited only to a few glands. If the change is diffuse, it is advisable to at least question whether part or all of the tumor could be a serous carcinoma or a clear cell carcinoma, instead of an endometrioid carcinoma (21). It is acceptable to move such a tumor from 1 FIGO grade to another only after determining that the tumor is indeed endometrioid throughout. A mixed epithelial carcinoma with an endometrioid component should be diagnosed when the cytologically atypical area is determined to be serous or clear cell on further study.

One should not upgrade endometrioid carcinomas containing only a few glands with atypical nuclei, especially if it took a prolonged search at high-power magnification to recognize them. We endorse the severe nuclear atypia qualification described by Zaino et al. (19), that is, that severe nuclear atypia in the majority of cells (>50%) is required to upgrade a grade 1 or 2 EEC. "Upgrading" a case based on nuclear features is only rarely prudent, as in most cases, tumors are upgraded inappropriately (nuclear atypia is mild-moderate and diffuse, or severe and only focally found) or are not endometrioid at all. Classification and regression tree statistical analyses have demonstrated that after tumor stage, the next most informative prognostic division in EEC is between high grade (grade 3) and low-grade (grade 1/2) tumors (21,22). Although it is reported that there is a small but statistically significant difference in survival of up to 5% between clinically low-stage grades 1 and 2 EECs (23), this has not been consistently demonstrated. Therefore, the key consideration in tumor grading at hysterectomy should be to identify the presence of grade 3 EEC or any other high-grade components that may adversely affect patient prognosis, and not in trying to distinguish between grades 1 and 2 EEC. We have designated this system as "binary FIGO," which entails combining grades 1 and 2 tumors into a low-grade category and grade 3 tumors into a high-grade category (24,25). Said another way, EECs with low nuclear grade and

harboring ≤50% solid tumor components would be considered "low-grade EEC" (Fig. 1). This is in keeping with current risk assessment/treatment guidelines, such as those of the National Comprehensive Cancer Network (NCCN), European Society of Medical Oncology (26), the Mayo Clinic (27), and Memorial Sloan Kettering Cancer Center (MSK) in which grades 1 and 2 EECs are managed the same way. Although NCCN (NCCN guideline version 1.2018) still recognizes 3 EEC grades, the staging and therapeutic guidelines for grades 1 and 2 are very similar. Differences in the risk of lymph node metastasis in grades 1 and 2 EEC are most pronounced when decisions for staging are undertaken by evaluating biopsy or curettage material only. As will be discussed subsequently, the distinction between grades 1 and 2 is unimportant in the setting of planned lymphadenectomy or sentinel lymph node mapping, and distinguishing between these grades does not stratify patients who have had comprehensive surgical staging into different risk categories. A literature review of various proposed binary grading schemes and a recent review on grading EEC) (16) reveals that EECs can readily be divided into either a low-risk or high-risk prognostic group based on a number of factors.
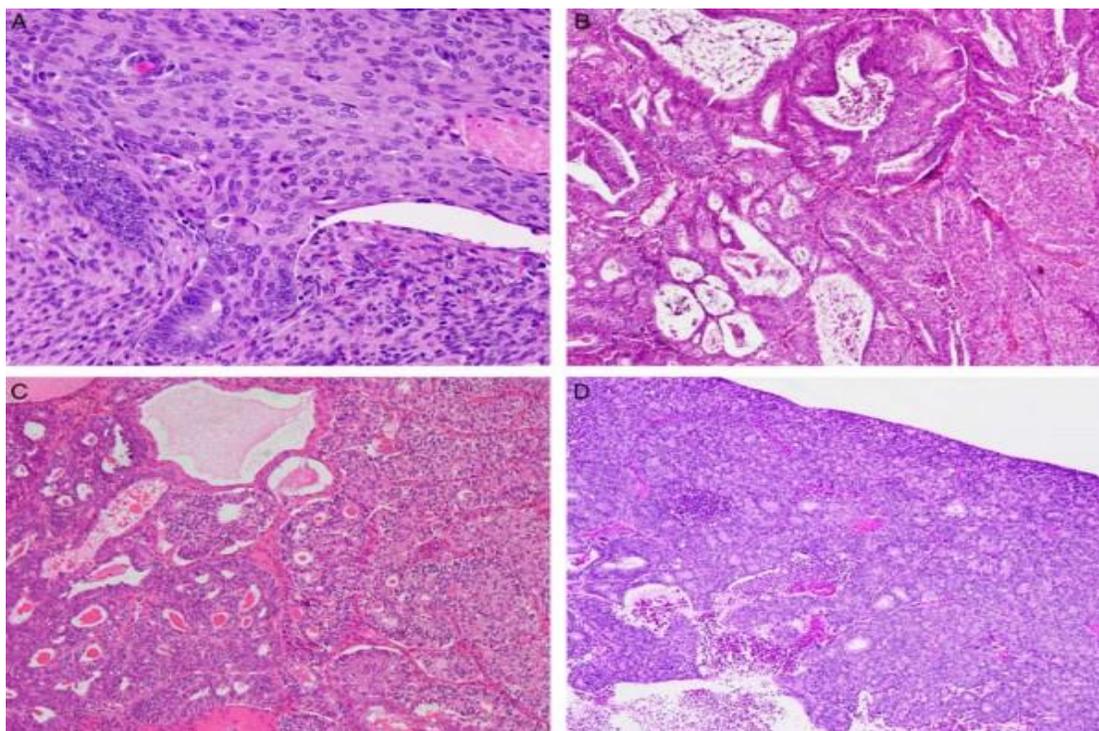
Figure.5; Examples of low-grade and high-grade endometrial endometrioid carcinomas (EEC): (A) low-grade EEC [International Federation of Gynecology and Obstetrics (FIGO) grade 1) with extensive squamous differentiation that does not qualify as "solid" for the purposes of grading; (B) low-grade EEC (FIGO grade 2) with <50% solid nonsquamous growth; (C) low-grade EEC (FIGO grade 2) with <50% solid nonsquamous growth; and (D) high-grade EEC with a microacinar growth pattern that qualifies as "solid growth." The presence of micro acini should not be considered "glandular" for the purposes of assigning binary or FIGO grade.

Associated with increased tumor aggressiveness; the different grading systems show only slight disagreement over the distribution of a small number of gray-area cases between the 2 main prognostic groups. All of the proposed 2-tiered grading systems have been shown to be equal or superior to the current 3-tiered FIGO system in terms of interobserver variability kappa score, and the binary FIGO system, in the studies in which it was assessed, consistently exceeded the 3-tiered FIGO system. The binary FIGO system also performs as well as or better in terms of prognostication, compared with other binary grading schemes, and has the added advantage of being based on the currently used FIGO grading system (i.e. practicing pathologists are already familiar with the system's criteria). Soslow and colleagues recently analyzed a departmental database of clinical stage 1 EECs (n=1544) to better understand relationships between preoperative tumor grade, depth of myometrial invasion, and the risk of positive sentinel lymph nodes. The analysis demonstrated that while grade 1 tumors were associated with a significantly lower rate of lymph node metastases compared with grade 2 tumors overall (6.6% vs. 11.6%; P=0.003), the difference disappeared after adjusting for depth of myometrial invasion (16). Those findings further endorse the view that preoperative tumor grade alone should not be used to assess the indication for extensive surgical staging. The use of preoperative tumor grade alone to select patients for lymphadenectomy is clearly not supported by the evidence and does not reflect the complex interplay between the various pathologic parameters. In summary, it would be appropriate to adopt a binary FIGO system for grading EEC by combining the grades 1 and 2 categories into a single low-grade category in biopsy or curettages when comprehensive surgical staging is planned and in hysterectomy specimens. For patients desiring a fertility-sparing therapeutic approach, it will continue to be necessary to distinguish grades 1 and 2 based on currently used clinical criteria for conservative, hormonal therapy whereby grade 1 tumors can be considered for this approach and grade 2 tumors will generally not (NCCN guideline version 1.2018). It is also propose to retain the severe nuclear atypia qualification, based on the work of Zaino et al. (19), whereby severe nuclear atypia in the majority of cells (>50%) in an architecturally low-grade EEC would lead to a high-grade designation.

This proposed system should be beneficial in terms of simplification and diagnostic reproducibility.

Clinical features of Endometrial carcinoma -80% of endometrial carcinoma are Endometroid type carcinomas, local or diffuse, invades through myometrium. Most women have Stage I disease, moderate or well differentiated tumors. 5 year survival -Stage 1 (90%), Stage 2 (30% - 50%), Stage 3 / 4 (20%).

Patients with low-risk endometrioid adenocarcinomas that are confined to the uterus typically undergo simple hysterectomies and bilateral salpingo-oophorectomies alone, whereas other patients require complete surgical staging. After obtaining a surgical specimen, the final histological diagnosis is made to triage the patient for adjuvant therapy. A clinical controversy arises when the grade differs between the pre- operative endometrial biopsy and the final post-operative diagnosis.

Correlations between the pre-operative endometrial biopsy and post- operative final pathology have been reported to range from 60% to 80%. (21–28) To date, the largest study on this topic included 1804 patients, and it found that the concordance rates of grade 1, grade 2, and grade 3 endometrioid adenocarcinomas were 73%, 52%, and 53%, respectively. Moderate correlations between pre-operative endometrial biopsies and post-operative permanent pathologies were evident based on the observed Spearman correlation coefficient (ρ) of 0.52.6. Clinically discordant pathology, especially when the final pathology is a lower grade than the pre-operative pathology (downgrade discordancy), can be difficult to interpret, and clinicians do not have clear guidelines for choosing adjuvant therapies in such cases. Given this gap in knowledge, our objective was to evaluate the concordance between pre-operative and post-operative pathology in our patient population.

Prognostic factors are: Histologic type, FIGO stage (includes depth of invasion, regional nodal metastases and tumor spread), tumor grade, angiolymphatic invasion (particularly for stage 1 tumors), ER, p53, HER2 and ploidy.

The only predictive histologic features determined preoperatively are cell type and tumour grade. High grade (G3) endometrioid cancers as well as non-endometrioid histological subtypes are at high risk for early spread and recurrence. The risk of microscopic lymph node involvement was found to be as high as 20% for G3 endometrioid tumours (29), On the other hand, low-grade endometrioid endometrial cancers are consistently found to have a low risk for lymphatic dissemination and recurrence ranging from 0–10%, depending on the presence of other features (29). Tumour grade and histology alone are insufficient predictors of tumour behaviour; in fact, depth of invasion, cervical stromal invasion and LVSI have been consistently found to correlate with the risk of lymphatic dissemination and factor into most risk prediction models (30) The predicted outcomes of various staging policies based on preoperative and intraoperative information are summarised in Table 7. Based on these calculations, the negative predictive value of a selective lymphadenectomy policy for G2–3 endometrioid cancers only would be 97%, with a 3% rate of missed nodal involvement (false negatives). This low false negative rate explains the similar survival and recurrence outcomes when employing such a staging policy, as compared with a universal staging policy. Moreover, selective lymphadenectomy using grade and intraoperative assessment of myometrial invasion as suggested by the Mayo Clinic group (28) would yield a negative predictive value of 99% with only 1% node-positive cases missed, while avoiding lymphadenectomy in more than 40% of patients.The issue of shifts between pre-operative and final surgical pathology interpretation only becomes meaningful if preoperative histological features are used to guide surgical staging decisions. In spite of the frequent shift from a low-risk to a high-risk classification on final pathology, avoiding lymphadenectomy in low-grade endometrial cancer has been shown to have no deleterious impact on overall or disease-free survival (30).

Patients staged	n	Staging information		NPV	FN
		Node-positive cases identified	Node-positive cases missed		
Everyone	1000	100	0	100%	0%
No one	0	0	100	90%	10%
G3 only	180	34	66	93%	7%
G2–3	450	72	28	97%	3%
G2–3 and G1DMI	585	89	11	99%	1%

Abbreviations: DMI = deep myometrial invasion; FN = false negative; G1,2,3 = Grade 1, 2 and 3 endometrioid adenocarcinoma of the endometrium; NPV = negative predictive value. Assumptions: 10% overall lymph node involvement: 3% for G1, 9% for G2, 19% for G3 (GOG33 data). Grade distribution of 55% G1, 27% G2, 18% G3 tumours. A total of 25% of preoperatively defined G1 tumours have deep myometrial invasion.

Table 7-Preictive model for risk and outcome

This model demonstrates that in spite of predicted shifts in pathology and grading and the addition of other uterine risk factors, basing staging decisions on preoperative and intraoperative information will result in a small number of missed nodal metastases. Perceived advantages of surgical staging include collecting prognostic information, guiding adjuvant treatment decisions and a potential therapeutic advantage with the removal of pathologically involved lymph nodes. Although no study has been able to demonstrate a therapeutic benefit to lymphadenectomy (28,30) it improves overall survival in advanced disease (31). Selective lymphadenectomy based on risk factors available pre- and intraoperatively may maximise the benefits of surgical staging while limiting the complications of a more extensive surgical procedure. The selection of an acceptable cutoff for selective staging may vary according to a surgeon's or institution's philosophy, but can be guided by the predictive model suggested here. This model is innovative in accounting for the expected shifts between pre- and post-operative pathological diagnoses.

Lymphadenectomy omitted	· grade 1-II · < 50% myoinvasion · no evidence of extrauterine disease · absence of cervical involvement, · tumour size less than 2 cm
Only Bilateral pelvic lymphadenectomy	· in Grade– II disease with tumor size >2cm, PA LND if Pelvic node(S) +ve
Pelvic and para aortic lymphadenectomy	· FIGO Grade 3 tumour, · Evidence of extrauterine disease · Nonendometrioid endometrial cancer, · Depth of myoinvasion >50% · Cervical extension · When pelvic node(s) positive

Table-8 Lymphadenectomy for Endometrial carcinoma

Risk group	Description	LOE
Low	Stage I endometrioid, grade 1–2, <50% myometrial invasion, LVSI negative	I
Low–Intermediate	Stage I endometrioid, grade 1–2, ≥50% myometrial invasion, LVSI negative	I
High–intermediate	Stage I endometrioid, grade 3, <50% myometrial invasion, regardless of LVSI Status	I
	Stage I endometrioid, G1–2, LVSI unequivocally positive, regardless of depth of invasion	II
High	Stage I endometrioid, G 3, ≥50% myometrial invasion, regardless of LVSI status Stage II Stage III endometrioid, no residual disease Non endometrioid,(serous or clear cell or undifferentiated carcinoma, or carcinosarcoma)	I I I I
Advanced	Stage III residual disease and stage IVA	I
Metastatic	Stage IVB	I

Table-9; Risk stratification after surgical treatment

Material and Methods

A prospective observational study of all patients undergoing surgery for endometroid endometrial carcinoma at AHRCC from 2018 january onwards.

All patients who had pre-operative endometrial sampling(D&C/DHEB) are included. Operative reports are reviewed to determine intra-operative findings. Sample size-100

Exclusion criteria-

1. Patients who had no pre-operative endometrial sampling.

2. Patients who had no residual malignancy on final pathology. 3.Patients with non endometroid histology.

Characteristics	*Total no-100*
Age(median)	*53.3yrs*
Parity	*P3(40%)*
Post menopausalstatus	*59%*
Co morbidities	*25%*
USG finding	*Growthinthe cavity (53%)*
Endomettoid histology	*79%*
Stage I	*73%*
Surgery done	*TAH+BSO+/- PLND/RPLND*

Table-10 clinicopathological characteristics in most of the patients

Results

A total of 100 patients with endometrial cancer were evaluated. The mean age of the patients was 53.8±9.6 and the majority of the patients were postmenopausal (59%). Table 10 summarizes the demographic and clinic characteristics of the patients. Of the 100 patients, 79 of them were found to be of endometroid histology. Most of the patients had grade 2 disease (n=33, 41%).

Histology	Stage
Endometroid- 79	I -73
Papillary serous-8	II -8
Squamous cell CA.-6	III -19
Clear cell-4	
MMMT-1	
Others-2	

Table-11; Type of tumour and stage
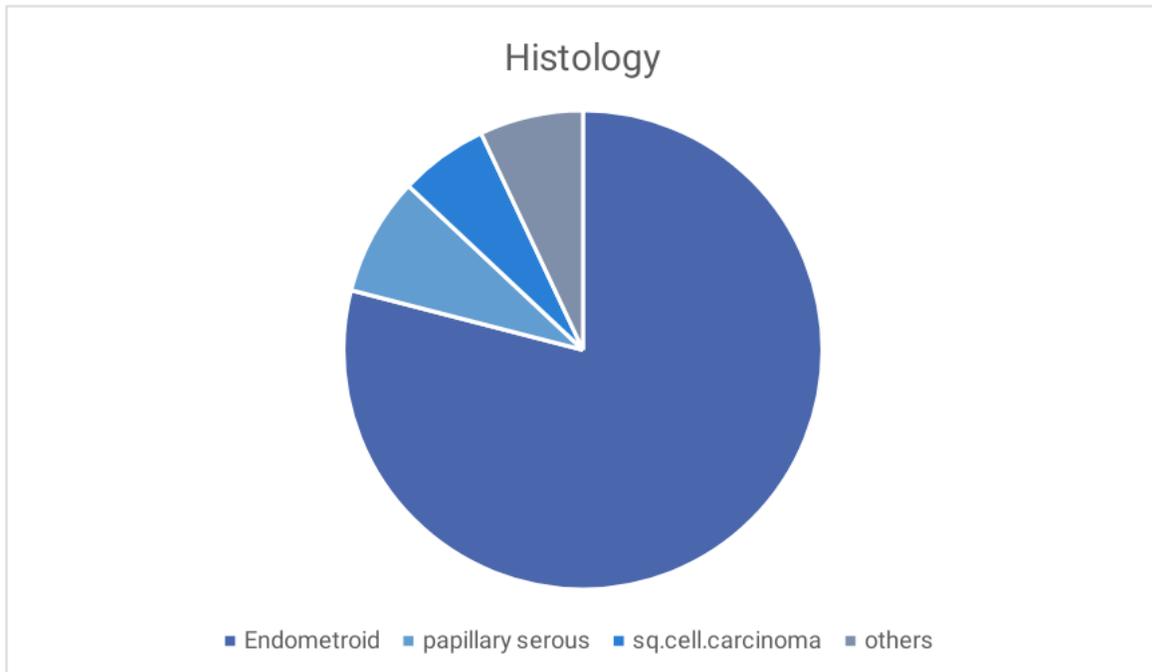
FIG-6: Histological distribution

Grade Correlation

Preoperatively the grade1 was found in 21 cases, grade 2 was found in 33 cases and grade 3 was found in 20 cases. In 5 cases grade was not known. While post operatively g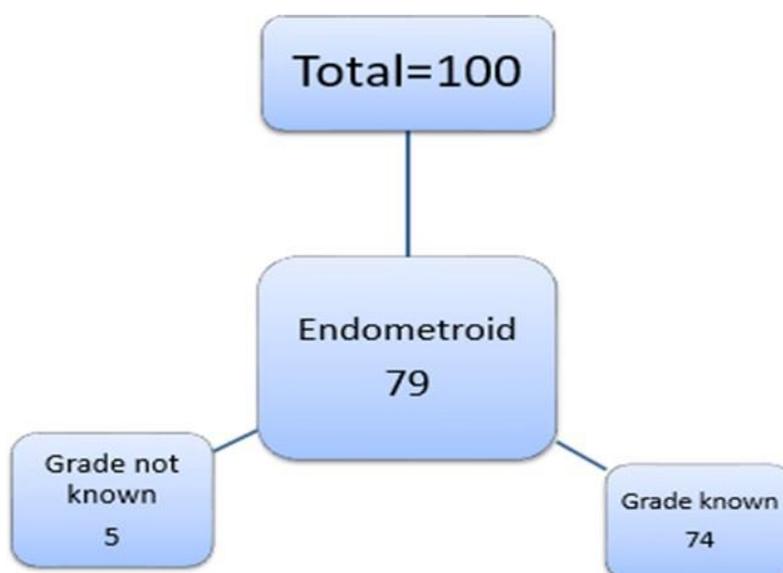rade 1 in 25 cases, grade 2 in 39 cases and grade 3 in 11 cases. Grade was not mentioned in 4 cases post operatively too. Myoinvasion of less than 50% was observed in 52 cases and more than 50% was seen in 21 cases. Myo invasion was not known in 6 cases.

Study group:

Lymphnodes were involved in 10 cases. Peritoneal cytology was positive in 9 cases.

Most of the grade 1 cases did not have any other risk factors or high risk features except that 2 of them were found to be having the cervical infiltration and one of them had isthmus of the uterus involved at final histopathology.

Among the 21 G1 cases from preoperative diagnosis, 5 cases got upgraded into grade 2 and 1 case got upgraded to grade 3(23.8%); among grade 2 cases 5 cases (i.e 15%) got upgraded into grade 3 after final histopathology. Where as among the downgraded cases-5 (15%) among grade 2 were found to be of grade 1 after final histopathology, 4(20%) among grade 3 were downgraded to grade 2 None of the grade 3 cases were found to be down graded to grade 1.

Pre op grade	Number	post op grade			Up graded	Down graded
		G1	G2	G3		
G1	21	15	5	1	23.8%	
G2	33	5	23	5	15%	15%
G3	20	0	4	16		20%

Table-12 Grade correlation pre op & post op

Total no=74		Upgraded	not upgraded
Age	<60	9	37
	>60	2	26
Menopausal status	pre	5	34
	post	6	29
Stage	I	7	32
	II	2	1
	III	2	10
Co morbidities		9	6
LN involvement		2	5
Peritoneal cytology+ve		3	4
Depth of invasion	<50%	6	43
	>50%	5	20

Table 13 Correlation with clinicopathological features in upgraded cases

No significant differences were found among the demographic and clinicopathological characteristics like menopausal status, myo invasion, peritneal cytology, lymph node positivity between the patient groups who were upgraded and were not upgraded post operatively.

Artefact about the age <60 yrs and stage I in the up graded cases was because the median age of presentation is below 60 yrs and most of them presented with stage I disease.

SN	Preop grade	Post op grade	surgery	Size of the lesion	Myo invasion	Nodes	Other risk factors	Treatment given
1	II	III	CSS	Filling cavity	<50%	-ve	-	VBRT
2	I	II	Type I Hyst BLPLND	NK	<50%	-ve	-	-
3	I	II	Type II Hyst +BLPLND	<2cm	-	-ve	cytology +ve	-
4	II	III	CSS	>5cm	>50%	-ve	Serosa involved	CT + RT
5	II	III	CSS	3cm	<50%	+ve	Cytology +ve	CT + RT
6	I	II	Type I hyst+ BLPND	2cm	>50%	-ve	-	lost for f/u
7		II	Type I Hyst + BPLND	Filling cavity	<5O96	-ve	Cervix involved	EBRT+VBRT
8	II	III	Type II hyst + BPLN D	>2cm	>50%	+ve		CT + RT
9	I	III	Lap staging	2cm	< 5O96	-ve		
10	I	II	TLH+BSO + BPLND	2.Scm	<5O°A	—ve	Cervix involved	EBRT+VBRT
11	II	III	CSS	<2cm <5O9t				VBRT

Table-14 Summary of upgraded cases

Discussion

The surgical approach for endometrial cancer varies from only total hysterectomy with bilateral oophorectomy to hysterectomy with full pelvic and para-aortic lymphadenectomy. Preoperative tumor grading with pre- and/or intraoperative assessment of the depth of myometrial invasion, as well as the histologic subtype, is frequently used to decide whether lymph node dissection is necessary at the time of hysterectomy. According to FIGO guidelines, lymphadenectomy should be performed when myometrial invasion is greater than 50% and/or when the tumor is undifferentiated (16).

Decision on staging for CA. Endometrium is based on-Preop imaging, histopathology report from D&C/DHEB i.e grade & histotype, gross findings on opening the uterus in OR and frozen section of resected uterus. The surgical approach for endometrial cancer varies from only total hysterectomy with bilateral oophorectomy to hysterectomy with full pelvic and para-aortic lymphadenectomy.

Mariani et al. (17) reported that patients with FIGO grade 1 or 2 endometrial cancer with macroscopically no or superficial myometrial invasion (<50%) can be treated safely with only hysterectomy. However, pre- and intraoperative assessment of the myometrium is an inaccurate predictor of the actual depth of myometrial invasion (11). In a series of 112 patients, Frumovitz et al. (11) reported that a frozen section diagnosis of no myometrial invasion is not accurate in 72% of cases, and 26% of cases with a frozen section of myometrial invasion <50% will actually have deeper invasion, cervical invasion and/or extra-uterine disease.

Preoperative tumor grade based on endometrial sampling is also reported to be poorly correlated with the final pathologic grade (8, 11-13, 18, 19) and a greater FIGO grade on final hysterectomy pathological assessment will be diagnosed as high as in 30% of patients with preoperative FIGO grade 1 (12). These grade discrepancies on final pathological assessments may be partly explained by the low volume of tissue available at the initial biopsy in comparison with the entire tumor specimen after hysterectomy. This theory is also reinforced by findings in a study showing that tumor size was the only factor that was independently associated with correlation between preoperative biopsy and final specimen. These findings support the theory revealed in renal cell tumors by Gerlinger et al. (46) They outlined that there is intratumor heterogeneity in every tumor determined by heterogeneous somatic mutations and chromosomal imbalances located in separated zones. Although the tumor arises from one clone, a mutational diversity occurs during tumor growth. Therefore, the tumor is formed by a sort of different clones presenting different mutations and diverse microscopic aspects in the pathological study. As the biopsy captures only a small part of the tumor, it can underestimate several underneath aspects such as the tumor grade. The evidence of this theory has been recently demonstrated in endometrial cancer as well. (47,48). We should note that endometrial carcinomas are uniform, with respect to genetic events that occur early during oncogenesis, such as MMR loss, POLE mutation, or TP53 mutation.26,28 Thus, endometrial biopsy or curettings can predict genomic subtypes of endometrial cancer more accurately

than grade. Genetic analysis may figure out the tumor heterogeneity and overcome the lack of correlation between biopsy sample and final specimen. (49) In a retrospective study on 332 patients assessing correlation between pre and post operative grade they concluded that Concordance between the biopsy and hysterectomy specimen is less likely to happen in the case of preoperative G1 or G2 tumors, as well as in big tumors >3 cm (50)

In another study, which compared histological grades between D&C and the hysterectomy specimen in grade 1 tumors on the final hysterectomy pathological assessment showed an overall upgrade rate of 50% and a concordance rate of 32.5% (20)

Hemida et al showed with 83 cases that there were non-significant differences between findings of curattage and hysterectomy specimens, and the concordance rate between curattage and hysterectomy was 79.5%. (21) The study by Sany et al that describes 191 cases shows that pre-operative endometrial sampling has good overall histological correlation with hysterectomized corpus specimens. (22)

GOG protocol 210, ACOG practice bull 2004 recommend comprehensive surgical staging for all patients. Majority of the studies till date did not show any survival advantage with routine staging procedure for early Endometrial carcinoma. Rate of adnexal metastases based on the grade is..Grade 1-6%, Grade 3-10% (clin gyn oncol-2002). Lymph node affection based on the grade is following. Grade I with minimal myoinvasion:3-5%, Grade III with deep myoinvasion:34%. (GOG).

Myoinvasion is minimal with G1 lesion, deep invasion is common with G3 lesions. Evidence shows that grade conversion between preop and post op period is 15-20%. On the other hand, Kang et al. (14) recently evaluated a total of 122 patients with low-risk endometrial cancer for the necessity of lymphadenectomy and showed nearly perfect agreement between pre- and postoperative grades, even when Pipelle was used for the preoperative diagnosis. Similarly, in a study with a very large series of only preoperatively detected as grade 1 endometrial cancer, almost 15% of the pathology specimens were upgraded in the final hysterectomy specimen (15).

In our study, nearly 23.8% of the patients with FIGO grade 1 endometrial adenocarcinoma prior to hysterectomy were diagnosed with a greater FIGO grade after hysterectomy. The most frequent pattern of downgrade discordancy was a pre-operative diagnosis of G2 to a post-operative diagnosis of G1. This finding may be explained by the fact that FIGO grading is based on the percentage of solid growth within a specimen and will therefore vary once the final specimen is obtained and a greater tissue volume is examined. In addition to this, 9.5% of the patients with preoperative grade 1 disease had cervical involvement. No lymph node involvement or positive peritoneal cytology was detected in patients with preoperative grade 1. If the patients were selected for surgical staging according to preoperative grading, more than 10% of the patients with preoperative grade 1 would have been subjected to inappropriate surgery in our cohort. In an Italian multicenter study which evaluated the efficacy of systemic lymphadenectomy in patients with preoperative and intraoperative stage I disease, almost 25% of the

total cohort was upstaged (FIGO II, III, IV) after definitive surgery and patients undergoing systemic lymphadenectomy had a higher likelihood of being upstaged to FIGO IIIC disease compared the no lymphadenectomy arm (13.3% vs. 3.2%) (10). Another randomized trial (MRC ASTEC) also showed that 23% of patients with a preoperatively diagnosed stage I tumor were upstaged in both the standard surgery and lymphadenectomy arms (11).

Our second objective in conducting this study was to preoperatively determine the high-risk group in which patients will be upgraded in postoperative evaluation. However, there was no significant difference in the demographic and clinical features between patients with or without upgraded tumours. We found a significant relation only between the stage of disease and upgrading. However, those were mostly detected after surgical staging. Thus, it is not possible to predict the high-risk group for upgrading preoperative findings. Francis et al demonstrated with 1804 patients that the concordance rates between pre-operative and post-operative pathology were 73% with grade 1, 52% with grade 2, and 53% with grade 3, respectively. (23)

The study by Kwon et al observed with 450 patients that the overall discrepancy rate between pre-operative and post-operative pathology was 42.7% (24). Eltabbakh et al showed with 182 patients that approximately 30% of women with endometrial carcinoma whose pre-operative endometrial biopsy showed grade 1 tumors subsequently had grade 2 or 3 tumors in the hysterectomy specimen. (25) Wang et al showed with 52 women that the concordance rates were 20% for grade 1, 61.5% for grade 2, and 77.8% for grade 3.(26). Mitchard et al showed with 125 patients that concordance rates were 45% for grade 1, 63.3% for grade 2, and 75.6% for grade 3 carcinomas, with an overall concordance rate of 64.5%.(27) Obermair et al showed with 137 patients that 78% of all cases in which a well differentiated tumor was diagnosed with curettage before surgery were confirmed as differentiated tumors after surgery, whereas 20.4% had to be upgraded as moderately differentiated tumors.(28) Our results also showed that pre-operative endometrial sampling had overall histological correlation with hysterectomized corpus specimens from endometrioid carcinoma (74%).

Statistical analysis showed accuracy for Grade 1 -76%, for grade 2-87% and for grade 3 it is 73% which is in agreement with the other studies. Highest accuracy was for grade 2.

Study	Grade discrepancy
Eltabbakh et al	30%
Kwon et al	42.7%
Victor et al	7-34%
Leitao MM et al	15%
Neilsen et al	50%
Present study	26%

Table-15 Statistical analysis

Prediction

	Grade I	Grade II
Grade III Sensitivity%	78.88	73.68
57.36		
Specificity%	80.76	90.84
70.76		
PPV%	72.75	58.84
60.19		
NPV%	78.06	96.42
79.03		
Accuracy% 73.16	76.68	87.75

Sensitivity, specificity, PPV, NPV for pre operative grade

Conclusion

Grade of the tumour is one of the factors deciding the extent of surgery and along with other risk factors, directs adjuvant therapy. Good correlations were observed between pre-operative and final histological diagnoses of endometrioid carcinoma (74%). Pre op information regarding grading should be judiciously used keeping the other risk factors in mind to avoid over or under treatment. Decision as to the extent of surgery cannot be made based only on the preoperative grade but should be individualized based on the clinical scenario.

In conclusion, unpredictably, a moderate percentage of preoperatively diagnosed as grade 1 tumors were upgraded in the postoperative evaluation. According to our study, it is not possible to say that lymphadenectomy should be considered as comprehensive surgical staging in all patients with preoperatively diagnosed endometrial cancer, but it should be mentioned that patients with a preoperative diagnosis of grade 1 uterine cancers do have a risk of extra-uterine spread, and the information achieved from an appropriate surgical staging procedure affects the adjuvant treatment decision. Predemographic/ clinical features cannot predict the upgrading in the final histopathology. Inspite of frequent discrepancies in in the preoperative vs post operative histopathological assessment, the predicted rate of missed nodal metastases with a selecive staging policy remains low. Preoperative endometrial sampling is only a modest predictor of final histology in endometrial cancer, and can underestimate the potential risk of nodal spread and disease recurrence. Nevertheless, selecting cases for surgical staging based on pre- and intraoperative information would result in an acceptably low predicted rate of missed nodal metastases. In fact, omitting lymphadenectomy in low-risk endometrioid tumours, defined as G1 tumours without deep myometrial invasion as assessed intraoperatively, would only fail to identify 1% of node-positive cases. Decisions regarding a universal vs a selective surgical staging policy, and setting an acceptable cutoff for selective staging will undoubtedly vary between institutions and surgeons.

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