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Discordance Between Clinicopathological and Molecular Risk Classification in Endometrial Carcinoma: A Prospective Observational Study

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Abstract

Background: Endometrial carcinoma is commonly managed using clinicopathological risk stratification to guide adjuvant treatment. However, p53 and mismatch repair (MMR) status may identify biological risks not captured by conventional classifications. Local evidence regarding discordance between clinicopathological and molecular risk profiles remains limited. This study aimed to assess this discordance and to describe treatment allocation and one-year outcomes among patients with molecular abnormalities. ***Methods:*** This prospective observational study was conducted at the National Institute of Cancer Research and Hospital, Dhaka, from October 2021 to May 2023 and included 42 women with endometrial carcinoma who underwent definitive surgery. Risk was assigned by the ESGO/ESTRO/ESP 2021 consensus, p53 and MMR proteins were assessed by immunohistochemistry and patients were followed for one year. Fisher's exact test was used for outcome comparisons. ***Results:*** Conventional classification identified 17 low-risk (40.5%) and 18 high-risk (42.9%) patients, with seven in intermediate categories. Abnormal p53 expression was found in five patients (11.9%) and MMR deficiency in 16 (38.1%). Among the 17 low-risk patients, one (5.88%) had abnormal p53 and seven (41.17%) were MMR deficient; among the 18 high-risk patients, four (22.2%) had abnormal p53 and five (27.78%) were MMR deficient. No low-risk patient with a molecular abnormality received adjuvant treatment or progressed. Freedom from progression was 60.0% with abnormal p53 versus 97.3% with normal p53 (p=0.001) and 93.8% versus 92.3% for MMR-deficient and MMR-retained tumours (p=0.414). ***Conclusion:*** Molecular abnormalities occurred in conventionally low-risk endometrial carcinoma, indicating that clinicopathological classification alone does not capture molecular risk. Combined assessment may refine risk stratification, pending larger confirmatory studies.

Keywords: Endometrial carcinoma; risk stratification; molecular classification; p53; mismatch repair; immunohistochemistry.

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INTRODUCTION

Adjuvant treatment after surgery for endometrial carcinoma has traditionally depended on clinicopathological risk groups that combine histological type, grade, depth of myometrial invasion, lymphovascular space invasion and stage [1,2]. The disease is the sixth most commonly diagnosed cancer in women worldwide [3] and the third most common genital tract malignancy in Bangladesh [4]. Although most tumours are diagnosed at an early stage, 15%–20% recur and ultimately result in death; identifying these patients remains challenging [5]. Risk groups defined without molecular information may incorrectly classify some patients. In addition, histological assessment is subject to interobserver variability, limiting the reproducibility of risk groups based on these assessments [6,7].

Molecular profiling has altered this picture. The Cancer Genome Atlas defined four prognostic subgroups, namely POLE mutant, microsatellite unstable (mismatch repair deficient), copy-number low and copy-number high, the last characterised by frequent p53 mutation and an unfavourable outlook [8]. Pragmatic classifiers based on immunohistochemistry (IHC) made the scheme applicable in routine practice and a combined analysis of the PORTEC cohorts showed that integrating molecular and clinicopathological factors improves risk assessment in early-stage disease [9,10]. The 2020 World Health Organization classification, the 2021 ESGO/ESTRO/ESP guidelines and the ESMO guideline now incorporate molecular subgroups into risk assignment [1,11]. In the high-risk PORTEC-3 population, molecular class influenced both prognosis and benefit from adjuvant therapy [12].

Two IHC markers are central to this approach. Abnormal p53 staining, whether complete absence, overexpression or cytoplasmic localisation, strongly predicts a TP53 mutation [13] and identifies tumours with an unfavourable prognosis, yet such tumours account for only about 9% of low and low-intermediate risk carcinomas [10]. Loss of mismatch repair (MMR) proteins reflects defective repair of base mismatches during DNA replication, leads to microsatellite instability [14] and is found in up to 40% of type 1 endometrial carcinomas [15,16]. MMR IHC has a reported sensitivity of 83% and specificity of 89% [17,18] and it is also an effective screening step for Lynch syndrome [19,20].

Whether molecular testing adds value in women who appear low risk by conventional criteria remains uncertain. Their risk of recurrence is low, at roughly 5% [21], so the yield of testing depends on how often an adverse molecular profile is concealed within this group. At the other end of the spectrum, molecular findings may allow treatment to be reduced or intensified, an approach being tested prospectively in the PORTEC-4a trial [22] and supported by cost-effectiveness modelling that prioritises molecular classification in selected patients [23]. Studies that compare conventional and molecular classifications directly in the same patients, with outcome follow-up, are scarce in South Asia. Such data would show how many patients might be reclassified if molecular testing were adopted.

In Bangladesh, adjuvant therapy is chosen on clinicopathological features alone and the extent to which this approach overlooks molecular abnormalities is unknown. Quantifying that gap is a necessary first step before molecular testing can be considered for routine use in local practice, where cost and access to testing are important constraints. Immunohistochemistry is inexpensive, quick and available in most pathology laboratories, which makes it a realistic candidate for such a role. This study therefore aimed to determine the degree of discordance between conventional clinicopathological and IHC-based molecular risk profiles in endometrial carcinoma and to describe treatment allocation and one-year outcomes among patients with molecular abnormalities.

MATERIALS AND METHODS

This prospective observational study was conducted in the Department of Gynaecological Oncology, National Institute of Cancer Research and Hospital, Dhaka, from October 2021 to May 2023, with enrolment during the first four months. Women with endometrial carcinoma confirmed by endometrial sampling, dilatation and curettage or fractional curettage, who attended the outpatient department and were selected for definitive surgery, were recruited purposively. Patients with ECOG performance status 3 or 4, previous pelvic radiotherapy or chemotherapy, incomplete surgery, stage IV disease or without consent were excluded. Forty-two patients were enrolled; a minimum of 75 had been calculated, but recruitment was limited by time and financial constraints. After informed consent, sociodemographic, clinical, examination and investigation data were recorded on a pre-designed data collection sheet with a checklist. Surgical specimens were sent to the Armed Forces Pathology laboratory for histopathology and for immunohistochemistry of p53 and the MMR proteins MLH1, MSH2, MSH6 and PMS2. Abnormal p53 expression was defined as complete absence, overexpression or cytoplasmic staining and MMR deficiency as loss of nuclear expression of any MMR protein. Tumour grade followed the binary FIGO system and each patient was assigned to a low, low-intermediate, high-intermediate or high clinicopathological risk group after surgery according to the ESGO/ESTRO/ESP 2021 consensus. The tumour board selected adjuvant treatment from the clinicopathological risk profile, without knowing of the immunohistochemistry results, which were recorded separately. Patients were reviewed six weeks, six months and one year after completion of treatment and disease progression, recurrence and death were documented. Data were entered in a master sheet, backed up in Excel and checked and cleaned before analysis to ensure accuracy and consistency. The NICRH Institutional Review Board approved the protocol, written informed consent was obtained from each participant or legal guardian, confidentiality was maintained and participants could withdraw at any stage without any effect on their treatment. Categorical data were summarised as frequencies and percentages and the proportions of p53 abnormal and MMR deficient tumours were calculated within each conventional risk category. One-year outcomes in the molecular subgroups were compared using Fisher's exact test in IBM SPSS Statistics version 25.0 and $p<0.05$ was considered statistically significant.

RESULTS

Table 1: Baseline demographic and clinical characteristics of the study participants (n=42)

Characteristic	Category	Frequency (n)	Percentage (%)
Age, years	≤40	5	11.9
	41–50	9	21.4
	51–60	18	42.9
	61–70	9	21.4
	>70	1	2.4
	Mean age ± SD	55.0 ± 9.8	
Menopausal status	Menopausal	33	78.6
	Pre-menopausal	8	19.0
	Menstruating	1	2.4
Parity	0–2	25	59.5
	≥3	17	40.5
	Mean parity ± SD	2.5 ± 0.9	
Major risk factors	Hypertension	29	69.0
	Diabetes mellitus	24	57.1
	Hypothyroidism	13	31.0
	Family history of cancer	6	14.3
BMI, kg/m²	18.5–24.9	13	31.0
	25.0–29.9	27	64.3
	≥30.0	2	4.8
	Mean BMI ± SD, kg/m²	26.1 ± 2.5	

Table 1 shows the baseline demographic and clinical characteristics of the 42 patients with histologically confirmed endometrial carcinoma. The mean age was 55.0±9.8 years, ranging from 35 to 78 years, with the largest proportion of patients aged 51 to 60 years (18/42, 42.9%). Thirty-three patients (78.6%) were menopausal. The mean parity was 2.5±0.9. Hypertension was present in 29 patients (69.0%), diabetes mellitus in 24 (57.1%), hypothyroidism in 13 (31.0%) and a family history of cancer in six (14.3%). Twenty-seven patients (64.3%) were overweight and the mean BMI was 26.1±2.5 kg/m².

Table 2: Histopathological and surgico-pathological characteristics (n=42)

Characteristic	Category	Frequency (n)	Percentage (%)
Histological type	Endometrioid	40	95.2
	Non-endometrioid	2	4.8
Tumor grade	Low grade (G1–G2)	36	85.7
	High grade (G3)	6	14.3
Tumor size	<2.0 cm	9	21.4
	≥2.0 cm	33	78.6
Myometrial invasion	<50%	19	45.2
	≥50%	23	54.8
LVSI	Present	12	28.6
	Not identified	30	71.4
Cervical stromal invasion	Present	5	11.9
	Absent	37	88.1
Lymph-node metastasis	Pelvic	10	23.8
	Para-aortic	1	2.4
	Absent	31	73.8
Surgico-pathological stage	IA	18	42.9
	IB	11	26.2
	II	2	4.8
	IIIC1	10	23.8
	IIIC2	1	2.4

Table 2 presents the histopathological and surgico-pathological characteristics of the cohort. Endometrioid carcinoma accounted for 40 cases (95.2%) and two cases (4.8%) were non-endometrioid. Low-grade tumours (FIGO grades 1 and 2) predominated, occurring in 36 patients (85.7%), whereas six patients

(14.3%) had grade 3 tumours. Tumour size was 2 cm or more in 33 patients (78.6%) and myometrial invasion was 50% or more in 23 (54.8%). Lymphovascular space invasion was present in 12 patients (28.6%) and cervical stromal invasion in five (11.9%). Pelvic lymph-node metastasis was identified in 10 patients (23.8%) and para-aortic lymph-node metastasis in one (2.4%). No malignant peritoneal washing or omental metastasis was reported.

Stage IA was the most frequent surgico-pathological stage, accounting for 18 patients (42.9%), followed by stage IB in 11 (26.2%). Two patients (4.8%) had stage II disease, 10 (23.8%) had stage IIIC1 disease and one (2.4%) had stage IIIC2 disease.

Table 3: Conventional clinicopathological risk classification (n=42)

Clinicopathological risk category	Frequency (n)	Percentage (%)
Low risk	17	40.5
Low-intermediate risk	6	14.3
High-intermediate risk	1	2.4
High risk	18	42.9
Total	42	100.0

Table 3 describes the conventional clinicopathological risk classification. According to this assessment, 17 patients (40.5%) were classified as low risk, six (14.3%) as low-intermediate risk, one (2.4%) as high-intermediate risk and 18 (42.9%) as high risk. The low-risk and high-risk categories together accounted for 35 of the 42 patients (83.3%).

Table 4: Molecular characteristics of the study participants (n=42)

Molecular characteristic		Frequency (n)	Percentage (%)
p53 status	Abnormal	5	11.9
	Normal	37	88.1
MMR status	Deficient	16	38.1
	Retained/proficient	26	61.9
Individual MMR protein loss	PMS2	11	26.2
	MSH6	8	19.0
	MLH1	6	14.3
	MSH2	6	14.3

Table 4 summarises the molecular characteristics of the cohort. Abnormal p53 expression was detected in five patients (11.9%), whereas 37 (88.1%) had normal p53 expression. MMR deficiency was identified in 16 patients (38.1%), while MMR proteins were retained in 26 (61.9%). Among the individual MMR proteins, PMS2 loss was the most frequent finding (11/42, 26.2%), followed by MSH6 loss (8/42, 19.0%) and loss of MLH1 and MSH2 expression (6/42, 14.3% each).

Table 5: Molecular abnormalities according to conventional clinicopathological risk group

Conventional risk group	Total n	p53 abnormal, n (%)	MMR deficient, n (%)
Low risk	17	1 (5.9)	7 (41.2)
Low-intermediate risk	6	0 (0.0)	4 (66.7)
High-intermediate risk	1	0 (0.0)	0 (0.0)
High risk	18	4 (22.2)	5 (27.8)

Table 5 compares the molecular profile with the conventional risk groups. Out of the 17 patients in the conventional low-risk group, one (5.88%) had abnormal p53 expression and seven (41.17%) had MMR deficiency. Among the six low-intermediate-risk patients, none had abnormal p53 expression, while four (66.7%) had MMR deficiency. The single high-intermediate-risk patient had neither abnormality. Among the 18 patients classified as high risk, four (22.2%) had abnormal p53 expression and five (27.78%) had MMR deficiency. In total, eight molecular abnormalities (one abnormal p53 and seven MMR deficiency) were recorded among the 17 conventional low-risk patients, equivalent to 8 of 17 (47.1%) if no patient had both. Molecular abnormalities were therefore not confined to conventionally high-risk disease.

Table 6: Molecular abnormalities, conventional risk category, treatment and one-year outcome

Molecular finding	Conventional risk group	No. with molecular abnormality	Treatment	One-year outcome
p53 abnormal	Low risk	1	No adjuvant treatment	No disease progression
p53 abnormal	High risk	4	CCRT	No progression (n=2); bone metastasis (n=1); death (n=1)
MMR deficient	Low risk	7	No adjuvant treatment	No disease progression
MMR deficient	Low-intermediate risk	4	VBT (n=3); EBRT (n=1)	No disease progression
MMR deficient	High risk	5	CCRT (n=3); EBRT (n=1); EBRT+VBT (n=1)	No progression (n=4); vault recurrence (n=1)

Table 6 shows the conventional risk category, treatment and one-year outcome of patients with molecular abnormalities. Among the five patients with abnormal p53 expression, one belonged to the low-risk group and received no adjuvant treatment, with no disease progression during one year of follow-up. The remaining four were in the high-risk group and all received CCRT; two remained free of progression, one developed bone metastasis and one died during follow-up.

Among the 16 patients with MMR deficiency, seven were conventionally classified as low risk. None of these seven received adjuvant treatments and no disease progression was observed at one year. Four MMR-deficient patients were in the low-intermediate-risk group; three received VBT and one received EBRT, with no disease progression. The remaining five were in the high-risk group; three received CCRT, one received EBRT and one received EBRT plus VBT. One of these five developed vault recurrence, while four remained free of progression at one year.

Adjuvant treatment according to the study cohort

Overall, 25 patients (59.5%) received adjuvant treatment and 17 (40.5%) did not. CCRT was the most frequently used modality (16/42, 38.1%), followed by EBRT (4/42, 9.5%), VBT (3/42, 7.1%) and EBRT plus VBT (2/42, 4.8%). No separate statistical comparison of treatment allocation by molecular class was performed. Treatment decisions were based on the conventional clinicopathological risk profile rather than on knowing of the molecular results, so these findings describe the observed management pattern and do not represent molecular-guided treatment effects.

One-year clinical outcomes in molecular subgroups

At one year, 39 of 42 patients (92.9%) had no documented disease progression. The proportion without progression was 60.0% among patients with abnormal p53 expression compared with 97.3% among those with normal p53 expression, a statistically significant difference (p=0.001). In the abnormal p53 group, one patient developed bone metastasis and one died.

Among MMR-deficient patients, 15 of 16 (93.8%) remained free of disease progression, compared with 24 of 26 (92.3%) among MMR-proficient patients. One MMR-deficient patient developed vault recurrence, whereas one MMR-proficient patient developed bone metastasis and one died. The difference in outcome by MMR status was not statistically significant (p=0.414).

DISCUSSION

This prospective study compared conventional clinicopathological risk assignment with immunohistochemistry-based molecular findings in 42 women with endometrial carcinoma. The central observation was that molecular abnormalities were not confined to conventionally high-risk disease: one of 17 low-risk patients (5.88%) had abnormal p53 expression and seven (41.17%) were MMR deficient, while in the high-risk group four of 18 (22.2%) had abnormal p53 and five (27.78%) were MMR deficient.

The cohort resembled those from other regions in several respects. The mean age of 55.0±9.8 years lies close to the 56.16 and 58.47 years reported by Ali *et al.,*and Shekhar *et al.,*[24,25] and 78.6% of patients were postmenopausal compared with 83% and 90% in the studies of Shekhar *et al.,*and Dossus *et al.,*[25,26]. Endometrioid histology was present in 95.2%, a little higher than the 82.5% found by Deodhar *et al.,*[27] and stage I disease predominated, as in the report of Raffone et al., in which 75.4% of patients had stage I tumours [28].

Abnormal p53 expression was found in 11.9%, comparable with the 14.1% described by Willvonseder *et al.,*[29] and 38.1% of tumours were MMR deficient, which sits within the range of 6.61% to 43.35% pooled by Jumaah *et al.,*[30]. Other series have recorded MMR deficiency in 22.4%, 21.6% and 33% of tumours [31-33]. Vermij *et al.,* stressed that recognising the abnormal p53 staining patterns is a prerequisite for correct molecular classification [34], which supports standardised interpretation when IHC is used as a surrogate.

The abnormal p53 finding in one low-risk patient fits the observation of Stelloo *et al.,*that abnormal

p53 accounts for roughly 9% of low and low-intermediate risk carcinomas and that these women showed a trend towards more distant recurrence and poorer survival in the combined PORTEC analysis [10]. Our patient, who received no adjuvant treatment, had no progression at one year, but follow-up of this length cannot exclude later relapse; Ito *et al.,* found p53 overexpression in 11 of 22 early-stage patients who subsequently died [35]. The high proportion of MMR deficiency among low-risk and low-intermediate-risk patients (seven of 17 and four of six) is of a different nature, because MMR-deficient tumours are generally assigned an intermediate rather than a poor prognosis. Jumaah *et al.,* observed that MMR-deficient carcinomas tend to show less aggressive endometrioid histology, but also higher odds of lymphovascular invasion and deep myometrial invasion [30] and Cosgrove *et al.,* linked MLH1 silencing to larger tumour volume, more lymph node involvement and reduced recurrence-free survival [36]. Backes *et al.,* reported that MMR deficiency identified the high-intermediate-risk endometrioid patients at highest risk of recurrence [37]. These data argue that MMR status can modify the apparent risk of a conventionally low-risk tumour, although none of our seven low-risk MMR-deficient patients progressed during follow-up.

Among high-risk patients, all four with abnormal p53 received concurrent chemoradiotherapy and one developed bone metastasis and one died, giving 60.0% freedom from progression in the abnormal p53 group against 97.3% in the normal group (p=0.001). This agrees with Huvila *et al.,* who identified p53 IHC as the most accurate predictor of relapse-free and disease-specific survival [38], with Obata *et al.,* who associated p53 immunoreactivity with metastasis and recurrence [39] and with León-Castillo *et al.,* who showed that molecular class shapes prognosis and benefit from adjuvant therapy in high-risk disease [12]. Outcome did not differ by MMR status (93.8% versus 92.3%, p=0.414) and among the five high-risk MMR-deficient patients only one, with vault recurrence, progressed. Cosgrove *et al.,* recorded 31 recurrences and 16 cancer-associated deaths among 84 p53 abnormal tumours in a large cohort [40], which is consistent in direction with our observations.

Adjuvant treatment was given to 59.5% of patients and 40.5% underwent surgery alone, which compares with the 47.2% reported to receive adjuvant treatment by Raffone *et al.,*[28]. Because decisions rested on clinicopathological risk and the molecular results were not known at that time, the abnormalities found in low-risk patients did not influence management. Current guidelines integrate molecular class into risk assignment [1], Orellana *et al.,*considered it cost-effective to prioritise molecular classification in patients with high-grade, advanced stage or lymphovascular space invasion positive tumours [23] and Wortman *et al.,*summarised how molecular risk factors could improve the selection of adjuvant treatment [41]. Our findings add that the conventional low-risk group should not be assumed to be molecularly homogeneous. Interpretation is limited by the small number of patients, the short follow-up and the fact that the p53 abnormal and MMR-deficient groups could not be shown to be mutually exclusive.

Limitations of the study

The study was conducted at a single centre with a small sample of 42 patients, which limits generalisability and precision. Follow-up was restricted to one year, which is insufficient to judge the clinical significance of discordant cases. Only p53 and MMR immunohistochemistry were assessed, so POLE status and a complete four-group molecular classification were not available. Patient-level overlap between the p53 abnormal and MMR-deficient groups could not be determined from the available data.

CONCLUSION

Molecular abnormalities were present in conventionally low-risk endometrial carcinoma: among 17 low-risk women, one had abnormal p53 and seven had MMR deficiency and abnormal p53 was also found in high-risk disease. Conventional classification therefore did not capture the full molecular profile. Routine p53 and MMR immunohistochemistry alongside clinicopathological assessment may refine risk stratification and adjuvant planning, but larger multicentre studies with longer follow-up are needed to define the clinical significance of discordant cases and their implications for adjuvant treatment.

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