Pattern of Lymph Node Metastasis and p53 Abnormal (p53abn) Expression in Preoperative Early-stage Endometrial Cancer: A 5-year Institutional Experience

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ABSTRACT

Background. Early-stage endometrial cancer often presents with favorable survival rates, but high-risk factors, including TP53 mutations and high-grade serous pathology, can lead to recurrence and poor prognosis. The standard primary treatment for endometrial cancer is surgical staging, and lymph node metastases significantly impact adjuvant therapy decisions. The subgroup of p53-abnormal (p53abn) indicates the worst prognosis and potential benefits from adjuvant chemotherapy. Molecular classification, while recommended, faces practical challenges due to resource constraints.

Objectives. The study aimed to assess the incidence of p53 abnormal expression in clinical stage 1 endometrial cancer cases that underwent surgery at a government tertiary hospital, and assess its relationship with clinicopathologic factors and pelvic and paraaortic lymph node metastasis (LNM).

Methods. A cross-sectional retrospective analysis was conducted on clinical early-stage endometrial cancer cases that underwent surgical primary treatment between January 2018 and December 2022. Patient records were reviewed to gather demographics, surgical information, and pathological evaluations. Preoperative clinical staging was determined through imaging, and surgical staging involved comprehensive lymphadenectomy. Immunohistochemistry studies for p53 were carried out on formalin-fixed paraffin-embedded tissue samples.

Results. A total of 233 endometrial cancer cases were included. The mean age at diagnosis was 53.7 years. Common comorbidities included hypertension (47.2%) and dyslipidemia (20.6%). Most cases were endometrioid histology (82.8%) and low-grade tumors (85.8%). Tumor grade (p=0.010), myometrial invasion (p<0.001) and lymphovascular space invasion (p<0.001) significantly correlated with lymph node metastasis. However, tumor size and p53abn were not significantly associated with lymph node metastasis. p53abn overexpression was significantly associated with non-endometrioid histology at 33% and Grade 3 tumors at 23%. Preoperative grading demonstrated moderate reliability (0.51) with postoperative grading, with an agreement of 65.4%.

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Conclusion. Tumor grade, myometrial invasion, and LVSI were all significantly associated with lymph node involvement. While p53 immunohistochemical stains show promise in predicting metastasis and has been associated with tumor aggressiveness, this should still be correlated with clinicopathological parameters to carry out a more accurate risk stratification of early-stage patients.

Keywords: endometrial neoplasm, immunohistochemistry, tumor suppressor protein p53, lymph node excision, risk assessment

INTRODUCTION

Most endometrial cancers (EC) are typically detected in their early stages, resulting in a relatively favorable 5-year overall survival rate of 95% among patients with localized disease. Nonetheless, certain ECs characterized by high-risk factors, including high-grade serous pathology and TP53 mutations, exhibit a higher likelihood of recurrence. This recurrent pattern translates into a notably unfavorable prognosis for patients, with a 5-year overall survival rate falling below 20%, especially in cases where metastatic disease is present.[1]

In the last decade, important advances in ECs have been made including molecular classification based on four molecular subclasses identified in The Cancer Genome Atlas (TCGA). However, aspects of diagnosis and treatment remain to be controversial, including the role of surgical lymph node assessment, especially in early stages. This is because pelvic lymphadenectomy has been associated with increased risks of intraoperative injury, chronic lymphedema, and other complications associated with complete lymphadenectomy.[2] Lymph node metastases (LNM) is the most common site of extrauterine spread occurring in 10% of apparent early-stage EC.[3] Hence, different practices of lymph node evaluation have been described, including complete or selected pelvic and paraaortic lymphadenectomy, intraoperative palpation, and sentinel lymph node dissection, but complete pelvic lymphadenectomy remains to be the gold standard.[2,4]

After surgery, single or multimodal adjuvant therapy is recommended based on clinicopathologic factors including stage, grade, myometrial invasion, and lymph node involvement, which predicts the risk for relapse.[5] The emerging insights from molecular classification have transformed our understanding of risk assessment in EC, providing valuable prognostic information and the capacity to identify individuals who could benefit from adjuvant treatments. While the ESGO-ESTRO-ESP guidelines advocate for molecular classification for all EC patients, the practicality of implementing this recommendation is currently hindered by resource constraints and the high costs associated with surrogate immunohistochemical (IHC) stains in our specific setting.

For EC, p53 alteration is more commonly associated with non-endometrioid ECs, where it is present in almost 90% of cases. It is also present in 10-20% of endometrioid EC.[5] Next-Generation Sequencing (NGS) assays best document TP53 mutations, but Singh and colleagues have demonstrated that p53 immunohistochemistry studies can serve as a surrogate biomarker and are concordant with TP53 mutation studies, even with only a biopsy specimen of EC.[6]

Huvila et al. carried out eight (8) different tissue biomarkers on 306 endometrioid EC and showed p53 and ASRGL1 as the most accurate predictor of relapse-free and disease-specific survival.[7] p53 alterations have also been found to be more commonly found in patients with LVSI (38%) than tumors without LVSI (18.5%).[5] Therefore, the focus of this study was to investigate the utility of p53 IHC stains as a potentially more accessible and cost-effective alternative in providing valuable insights for patient management. Prior to this study, no research had been conducted on the Philippine population in relation of p53 in early EC.

OBJECTIVES

The study aimed to assess the incidence of pelvic and paraaortic LNM in clinical stage 1 EC cases that underwent surgery at the Philippine General Hospital and assess its relationship with clinicopathologic factors and p53 abnormality. Specific objectives were to: 1) Describe the clinical and demographic characteristics as to age, menopausal status, body mass index, and preoperative grade of patients diagnosed with EC undergoing surgery; 2) Determine the median number of harvested pelvic lymph nodes and paraaortic lymph nodes; 3) Determine the prevalence of pelvic LNM, pelvic and paraaortic LNM, and isolated paraaortic LNM; 4) Measure the prevalence of p53 mutation-type protein expression; 5) Determine the association of histologic type, tumor grade, myometrial invasion, peritoneal disease, tumor size, and LNM to p53 overexpression; 6) Determine the effect of p53 determination on the postoperative prognostic risk group based on ESMO ESTRO ESP Guidelines 2020; 7) Determine the reliability of preoperative grading of EC in predicting postoperative grading.

MATERIALS AND METHODS

Patient Selection

All patients who had primary surgical treatment for histologically confirmed EC at a government tertiary hospital from January 2018 to December 2022 were selected utilizing the Division's patient census (Figure 1). Several exclusion criteria were applied, including patients with preoperative imaging showing cervical extension or extrauterine spread, those with a history of prior EC treatment (including chemotherapy and/or radiotherapy), those with inadequate pelvic lymphadenectomy defined as involving fewer than 10 total pelvic lymph nodes in the final pathology, individuals

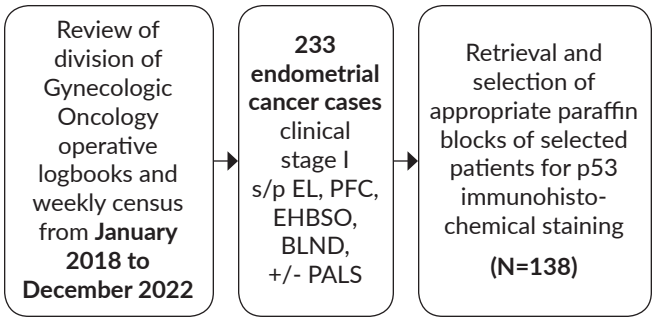

Figure 1. Flow chart of patient selection.

with incomplete or untraceable clinicopathological records, patients with incidental findings of double gynecologic primary tumors on final histopathology, and those with limited availability of formalin-fixed paraffin-embedded (FFPE) samples, including those with only one FFPE block, no accessible FFPE blocks, or sections lacking viable tumor tissue. For the latter, if they have accessible records, they were still included in the clinicopathologic data but were excluded in the p53 assessment.

Pre-operative Clinical Staging Determination

Preoperative clinical staging was determined through a metastatic evaluation, which included Computerized Tomography (CT) scans (chest and abdominopelvic), or a combination of chest X-ray, whole abdominal ultrasound, and transvaginal ultrasound, given the low resource setting. Surgical staging included extrafascial hysterectomy, bilateral salpingo-oophorectomy (EHBSO), and bilateral pelvic lymphadenectomy (PLND) with or without para-aortic lymphadenectomy (PALND). PLND includes the removal of bilateral external iliac lymph nodes and obturator lymph nodes, while PALND includes the removal of nodal tissue anterior to the aorta and inferior vena cava up to the inferior mesenteric artery. Extended surgical staging with infracolic omentectomy and random peritoneal biopsy was done for patients with poor histologic type or for patients with adnexal involvement noted intraoperatively.

Immunohistochemistry

FFPE blocks that were available were retrieved and reviewed. The reported histopathologic results of all selected patients were considered final and did not undergo repeat reading by the co-investigators. For each patient, two cylindrical cores with a diameter of 5.0 mm were obtained from each tumor-containing paraffin-embedded tissue block to create tissue microarray paraffin blocks. The tissue blocks were cut into 4-μm sections. Immunohistochemistry (IHC) staining was performed on the tissue sections of the primary tumor and on the positive lymph nodes following the manufacturer's protocol, using the monoclonal mouse anti-human p53 (DO-7, Agilent DAKO) as the primary antibody. The resulting IHC slides were subsequently examined, assessed, and interpreted independently by two board-certified pathologists. Clinical data of the patients under study were also withheld from the pathologists.

Ethical Considerations

This study underwent thorough review and received approval from both the department's Technical Review Board and the university's Research Ethics Board. Informed consent was waived as all extracted data had been anonymized to ensure that subsequent identification of individuals was not possible. Furthermore, the planned research poses no harm to the selected cases and imposes no additional financial burden upon them.

Data Analysis

All cases meeting the eligibility criteria within the specified time frame were included. A cross-sectional study was made using retrospective chart reviews to retrieve clinical profile and surgicopathologic findings. Descriptive statistics were generated for sociodemographic and clinicopathologic characteristics of patients. Continuous variables were expressed as mean, and standard deviation, while categorical variables were expressed as frequency and percentage. Chi-square test or Fisher's Exact test (for variables with low observations per cell) was used to determine the association of pathologic characteristics with LNM and to determine the association of clinicopathologic features to p53 abnormal expression. Chi-square test/Fisher's Exact test was also used to determine the association of p53 determination on the postoperative prognostic risk group. Kappa statistic was used to determine reliability of preoperative grading of EC in predicting postoperative grading. A p-value <0.05 was used for statistical significance. Statistical analysis was performed using STATA v24 (TX: Stata Press).

The FIGO (International Federation of Gynecology and Obstetrics) 2009 staging system was utilized in this study since the patients had undergone surgery prior to the release of the FIGO 2023 staging system. Interpretation of IHC results were classified into either p53 abnormal or p53 wildtype, as follows:

1. ***p53 Abnormal (p53abn):***
    - ***p53abn (overexpression)***: Strong diffuse staining affecting 90% to 100% of the tumor
    - ***p53abn (null):*** Complete absence of nuclear staining in tumor cells, in conjunction with a positive internal control. Cases with no nuclear staining on both tumor cells and background stroma (internal control), even on repeat staining of the corresponding whole FFPE block, were considered invalid and were subsequently excluded.
    - ***p53abn (cytoplasmic):*** significant cytoplasmic staining with variable intensity

- ***p53abn (subclonal):*** heterogeneous staining, characterized by the presence of both wild- and mutant-type patterns in at least 5% of tumor cells, were classified as p53abn

2. ***p53 Wildtype (p53wt)***, normal p53 staining pattern is characterized by variable nuclear staining, encompassing 1-80% of the tumor

RESULTS

Sociodemographic Characteristics

A total of 233 EC cases was included in the study. Table 1 shows that the mean age at diagnosis was 53.7 years, with 42.0% being pre-menopausal. The most common comorbidities were hypertension (47.2%), dyslipidemia (20.6%), and diabetes mellitus (7.7%). The mean BMI was 27.1. Majority (82.8%) of histopathologic results were endometrioid type, and 85.8% had low grade (Grade 1-2) tumor.

Table 1. Sociodemographic Characteristics of the Study Population

Characteristic	N=233, %
Age at diagnosis (in years), Mean + SD	53.7 ± 11.0
Menopausal status	
Pre-menopausal	97 (42.0)
Post-menopausal	134 (58.0)
Comorbidities	
Hypertension	110 (47.2)
Dyslipidemia	48 (20.6)
Diabetes	18 (7.7)
BMI Mean + SD	27.1 ± 5.8
Histology	
Endometrioid	193 (82.8)
Non-endometrioid	40 (17.2)
Preoperative Tumor Grade	
1	74 (46.0)
2	64 (39.8)
3	23 (14.3)

Surgicopathologic Factors and Association with Lymph Node Metastasis

Among patients who underwent PLND, pelvic lymph nodes were categorized into external iliac and obturator lymph nodes. To ensure adequate nodal sampling, only those with total pelvic lymph nodes count of more than or equal to 10 were included. The study found a mean of 10.2±2.1 external iliac lymph nodes with a median of 9, and a mean of 11.6±2.4 obturator lymph nodes with a median of 10. Additionally, the mean number of harvested paraaortic lymph nodes was 4.2±1.1, with a median of 3. Non-endometrioid histology included: serous (40.7%), clear cell (7.4%), undifferentiated (3.7%), mixed cell (18.5%), and carcinosarcoma (11.1%). Furthermore, there were five additional histological subtypes - poorly differentiated and high-grade carcinoma - that necessitated further IHC to ascertain their final classification.

Table 2 shows association of pathologic factors with LNM. Final histology was not associated with pelvic or paraaortic lymph nodes metastasis (p-value=0.226). Among

Table 2. Association of Pathologic Characteristics with Lymph node Metastasis

	No.	No LN metastasis	Pelvic metastasis			Pelvic + paraaortic metastasis	Isolated paraaortic metastasis	*P*-value
			External iliac node metastasis only	Obturator node metastasis only	Both			
Final Histology								
Endometrioid	**206**	173 (83.9)	4 (1.9)	6 (2.9)	3 (1.4)	12 (5.8)	8 (3.9)	0.226
Non-endometrioid	**27**	22 (81.4)	0 (0.0)	2 (7.4)	2 (7.4)	1 (3.7)	0 (0)	
Final Grade								
Grade 1	83	78 (94.0)	2 (2.4)	0 (0.0)	0 (0.0)	1 (1.2)	2 (2.4)	**0.010**
Grade 2	93	77 (82.8)	1 (1.1)	1 (1.1)	1 (1.1)	8 (8.6)	5 (5.4)	
Grade 3	34	22 (64.7)	1 (2.9)	6 (17.6)	0 (0.0)	3 (8.8)	2 (5.9)	
Myometrial invasion								
<50%	151	140 (92.7)	3 (2.0)	2 (1.3)	1 (0.7)	4 (2.7)	1 (0.7)	**<0.001**
≥50%	82	55 (67.0)	2 (2.4)	6 (7.3)	2 (2.4)	9 (11.0)	8 (9.8)	
LVSI								
Negative	156	145 (92.9)	1 (0.1)	2 (1.3)	0 (0.0)	5 (3.2)	3 (1.9)	**<0.001**
Positive	77	50 (64.9)	4 (5.2)	6 (7.8)	3 (3.9)	8 (10.4)	6 (7.8)	
Tumor size (cm)								
≤2	14	14 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.000
>2	219	181 (82.6)	5 (2.3)	8 (3.6)	3 (1.4)	13 (5.9)	9 (4.1)	
p53								
abn								
overexpression (O)	9	7 (77.8)	1 (11.1)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0.941
null (n)	5	3 (60.0)	1 (20.0)	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	
subclonal (s)	2	2 (100)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Cytoplasmic	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
wildtype	**122**	99 (81.1)	1 (0.1)	7 (5.7)	2 (1.6)	9 (7.4)	4 (3.3)	

Table 3. Tumor Grade and Nodal Metastasis

Grade (N)	Pelvic Nodes (%)	Paraaortic nodes (%)
1 (83)	3 (3.6)	3 (3.6)
2 (93)	11 (11.8)	13 (14.0)
3 (34)	10 (29.4)	5 (14.7)

cases with endometrioid histology, 16.1% had LN meta-stasis compared to 18.6% in non-endometrioid cases. Tumor grade was significantly associated with lymph nodes meta-stasis (p-value=0.010). Table 3 shows that patients with grade I, II and III tumours had pelvic nodal metastases of 3.6%, 11.8% and 29.4%, respectively and paraaortic nodal metastases of 3.6%, 14%, and 14.7%, respectively. Significant association was also observed between myometrial invasion and LNM (p-value<0.001). Patients with less than 50% myometrial invasion exhibited lower rates of metastasis to pelvic (6.6%) and paraaortic lymph nodes (3.3%). In contrast, those with more than 50% myometrial invasion had higher rates of metastasis, with 23.2% in pelvic nodes and 20.2% in paraaortic nodes. LVSI was also significantly associated with LNM (p-value<0.001). Patients with positive LVSI had higher rates of pelvic (27.3%) and paraaortic (18.2%) LNM, whereas those without LVSI had lower rates, at 4.6% and 5.1%, respectively. Tumor size and p53 overexpression were not significantly associated with lymph nodes metastasis (p-value=1.000 and 0.852, respectively). Only 14 (6%) patients had tumor less than or equal to 2cm, and none had nodal metastasis, but this did not reach statistically significance (p-value = 1.0).

Tumor grade was not consistently reported in the endometrial biopsy results, matched comparison of those with available preoperative and postoperative grading (n=153) was done. Table 4 shows that preoperative grading of EC showed significant (p-value<0.0001) and moderate reliability (0.51) with postoperative grading. The level of agreement was 65.4%. Majority of patients maintained their preoperative grading, but more patients in the lower grade had an increase in tumor grade in the final specimen, with 39.7% in Grade 1 compared to only 11.5% in Grade 2. There was also decrease in tumor grading among grade 2 at 21.3% and 21.1% among grade 3.

Association of Surgicopathologic Factors with p53 Abnormality

A total of 146 specimens were stained, five were excluded due to lack of concurrence among the pathologists and three due to invalid result. Table 5 shows that 138 cases were available for subsequent interpretation. Figure 2 shows the immunohistochemical localization of p53 proteins in representative cases. Majority (88.4%) of patients exhibited the p53wt. Among those with p53abn (n=16), the majority of

Table 4. Reliability of Preoperative Tumor Grade of Endometrial Cancer in Predicting Postoperative Tumor Grade

		Postoperative Tumor Grade, n (%)				Kappa statistic	*P*-value
		Grade 1	Grade 2	Grade 3	Total		
Preoperative Tumor Grade	Grade 1	44 (60.3)	27 (37.0)	2 (2.7)	73	0.51 (moderate reliability) Level of agreement = 65.4%	<0.0001
	Grade 2	13 (21.3)	41 (67.2)	7 (11.5)	61		
	Grade 3	1 (5.3)	3 (15.8)	15 (78.9)	19		
	Total	**58**	**71**	**24**	**153**		

Highlighted cases maintained the tumor grading.

Table 5. Association of Surgicopathologic Features to p53 Immunohistochemical Pattern

	N=138	Overexpression n=9, 6.5%	Null n=5, 3.6%	Subclonal n=2, 1.4%	Wildtype n=122, 88.4%	*p*-value
Histology						
Endometrioid	117	4 (3.4)	5 (4.3)	0 (0.0)	110 (92.3)	**<0.001**
Non-endometrioid	21	5 (23.8)	0 (0.0)	2 (9.5)	14 (66.7)	
Tumor Grade						
Grade 1	42	0 (0.0)	1 (2.4)	0 (0.0)	41 (97.6)	**0.021**
Grade 2	60	2 (3.3)	1 (1.7)	0 (0.0)	57 (95.0)	
Grade 3	26	3 (11.5)	3 (11.5)	0 (0.0)	20 (76.9)	
Myometrial invasion						
<50%	85	4 (4.7)	3 (3.5)	2 (2.4)	76 (89.4)	0.596
≥50%	53	5 (9.4)	2 (3.8)	0 (0.0)	48 (86.8)	
LVSI						
Negative	75	2 (2.7)	2 (2.7)	1 (1.3)	70 (93.3)	0.155
Positive	63	7 (11.1)	3 (4.8)	1 (1.6)	52 (82.5)	
Tumor Size (cm)						
≤2	14	0 (0.0)	1 (7.1)	0 (0.0)	13 (92.9)	0.539
>2	124	9 (7.3)	4 (3.2)	2 (1.6)	109 (87.9)	

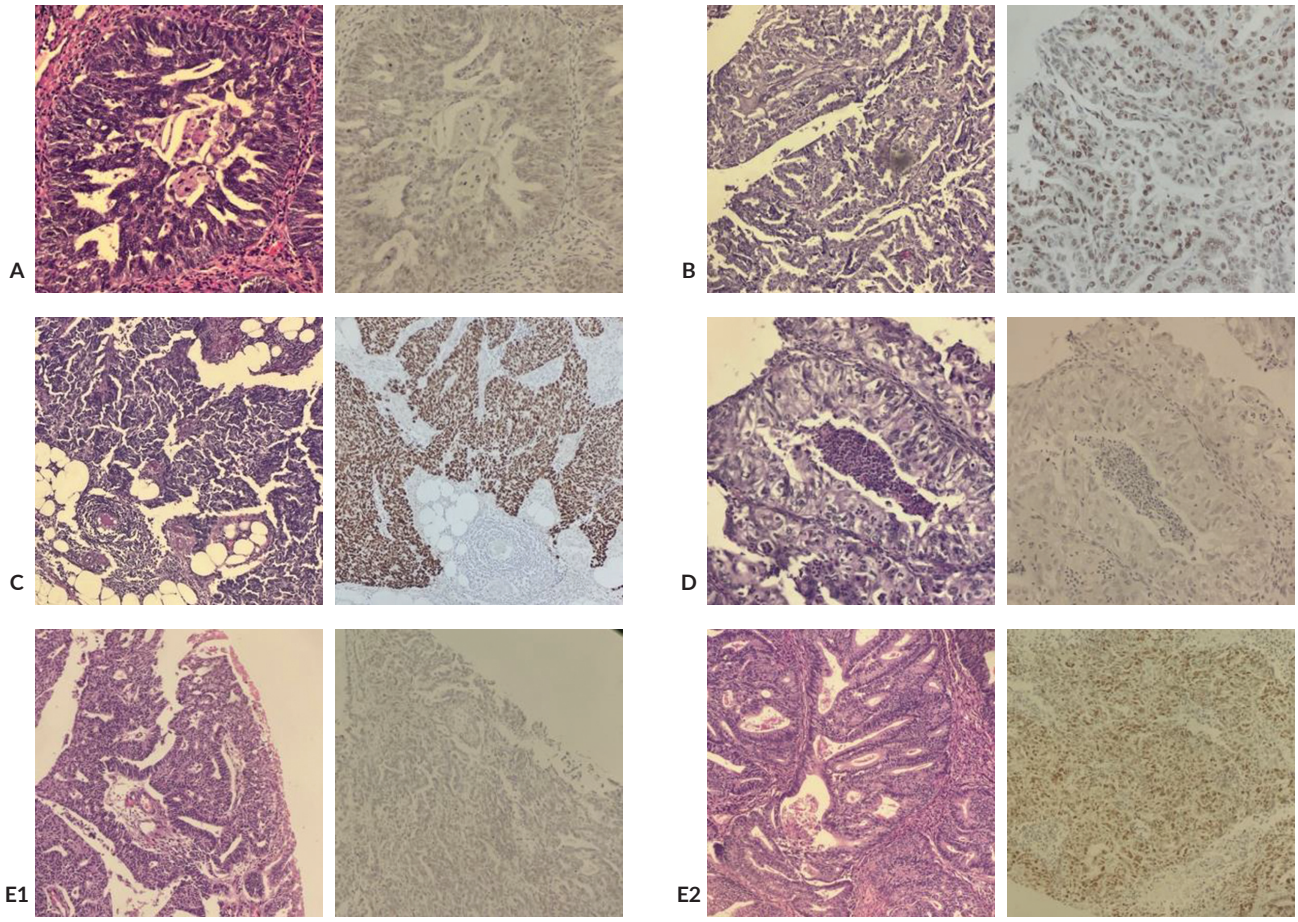

Figure 2. Immunohistochemical localization of p53 proteins in representative cases of endometrial cancer, 100x magnification: **(A)** p53 wildtype, **(B)** p53abn (overexpression), **(C)** p53abn (overexpression) in LNM, **(D)** p53abn (null), **(E)** p53abn (subclonal) – **(E1)** wildtype and **(E2)** overexpression found in one specimen.

staining patterns demonstrated p53 overexpression (56.3%), followed by null (31.3%), and subclonal (1.3%), while none were observed with the cytoplasmic staining pattern. Out of the 30 patients with positive pelvic lymph nodes, only 9 had available specimens for staining, and these showed p53wt staining similar to that of the endometrial tumor.

Histology exhibited a significant association with p53abn (overexpression) (p=0.001). The prevalence of p53abn was 7.3% in endometrioid histology and significantly higher at 42.9% in non-endometrioid histology. Significant association was found between p53abn and tumor grade (p=0.021), with higher prevalence in higher tumor grades: 2.4% for grade 1, 5% for grade 2, and 23% for grade 3. However, myometrial invasion, LVSI, and tumor size did not show a statistically significant association with p53 status.

Clinical Value of p53abn in the Context of Risk Classification

Following the ESMO ESTRO ESP Guidelines 2020, each case was assigned to a prognostic risk classification. Due to the unavailability of POLE testing at our institution and increase cost of surrogate markers for mismatch repair (MMR), the classification was based on stage, grade, presence or absence of LVSI, and only p53 IHC results. p53abn findings were considered adverse prognostic indicators that elevates patients' risk assessment. As shown in Table 6, of the 16 patients with p53abn, 37.5% (n=6) had increased risk classification. This included transitions from low to high risk (6.3%), intermediate to high risk (4.5%), and high-intermediate risk to high risk (20%). Meanwhile, 63.5% (n=10) maintained their original risk classifications, with 56.25% (n=9) at high risk and 6.25% (n=1) at an advanced metastatic risk level.

DISCUSSION

Endometrial cancer is the 2nd leading cause of gynecologic cancer and the 7th most common cancer among females in the Philippines corresponding to 589,051 new cases and 139,671 deaths in 2020.[8] In the study, the mean age at diagnosis was 53.7 years aligns with the typical demographic profile of EC patients. Based on Surveillance, Epidemiology,

Table 6. Association of p53 Pattern on the Postoperative Prognostic Risk Assessment

		After p53 testing, n (%)					
		Low	Intermediate	High-intermediate	High	Advanced/Metastatic	Total
Without p53 testing	Low	59 (93.6)	0 (0.0)	0 (0.0)	4 (6.3)*	0 (0.0)	63 (45.7)
	Intermediate	0 (0.0)	21 (95.5)	0 (0.0)	1 (4.5)*	0 (0.0)	22 (15.9)
	High-intermediate	0 (0.0)	0 (0.0)	4 (80.0)	1 (20.0)*	0 (0.0)	5 (3.6)
	High	0 (0.0)	0 (0.0)	0 (0.0)	47 (100)	0 (0.0)	47 (34.1)
	Advanced/Metastatic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	1 (0.8)
	Total	**59 (42.8)**	**21 (15.2)**	**4 (2.9)**	**53 (38.4)**	**1 (0.1)**	**138**

**Risk classification was changed by p53 testing.*

Highlighted cases were maintained on the same risk classification after p53 IHC.

and End Results (SEER) data from 2010-2019, 66% of cases were diagnosed at an early stage among Asians.[9]

Surgery with peritoneal fluid cytology, EHBSO, PLND with or without PALND remains the standard primary treatment of EC according to the FIGO (International Federation of Gynecology and Obstetrics) and the Society of Gynecologic Oncology of the Philippines (SGOP). However, outcomes of international studies, including MRC ASTEC and CONSORT, showed that while systemic PLND statistically improved surgical staging, it did not improve the disease-free and overall survival. Hence, they recommended omitting lymph node dissection in early-stage EC.[10,11] Consequently, some institutions have developed algorithms to determine the necessity of complete staging based on risk factors associated with lymph node metastases.

Lymph Node Metastasis

Individuals diagnosed with LNM in EC are typically classified as at least stage IIIC, or stage IV if accompanied by distant metastasis, following the FIGO staging guidelines from 2009. The present study showed that LNM was associated with higher tumor grade, LVSI, and myometrial invasion. However, preoperative tumor grading only showed moderate reliability in terms of consistency with tumor grading of the final specimen and LVSI can only be assessed histologically, making it difficult to solely rely on these factors.

Previous research has indicated that patients in FIGO stages I and II without lymph node involvement exhibit a 5-year disease-free survival rate of 90%. However, those with pelvic LNM show a lower rate at 75%, and patients with para-aortic LNM exhibit an even further reduced rate of 38%. Moreover, the overall recurrence rate for patients with metastatic lymph nodes was at 48%.[12] The present study showed that in cases where there is apparent absence of these high-risk factors, some patients would still present with pelvic and/or paraaortic LNM. This shows the significance of systemic lymphadenectomy, especially in institutions without readily available facilities for sentinel lymph node biopsy. Nodal dissection enables tailored adjuvant treatment and more accurate prognostication for patients.

Clinicopathologic Factors and Pattern of Lymph Node Metastasis

Predominance of endometrioid cases (83.9%) aligns with existing literature. Several studies have investigated the factors that contribute to LNM: non-endometrioid histology, worsening tumor grade, increasing depth of myometrial invasion, and LVSI have all been identified as major predictors of positive nodes.[3] However, in the present study, histology showed no significant association with pelvic or paraaortic LNM (p-value=0.226). On the other hand, tumor grade was significantly associated with lymph nodes metastasis (p-value=0.010) with higher prevalence of both pelvic and paraaortic nodal metastasis in those with high-grade tumor as shown in Table 3. This finding is consistent with existing literatures that preoperative tumor grade of 3 is five times more likely to have pelvic lymph node involvement than those with tumor grades 1–2.[13] A high nuclear grade was also the only histologic feature that correlated with p53 overexpression.[5,14]

This study highlights that LVSI, Grade 3 tumors, and myometrial invasion are associated with LNM. Interestingly, tumor size did not show this association, which is similar to another local study by Bagadiong.[13] p53 alterations have been found to be more commonly found in patients with LVSI (38%) than tumors without LVSI (18.5%).[5]

P53 Mutation-type Expression in Endometrial Carcinoma

The TP53 gene encodes the (wild type) p53 protein, which plays a central role in human carcinogenesis by acting as a transcription factor. It primarily mediates cell cycle arrest and apoptosis. Consequently, aberrations in p53 expression result in the unregulated proliferation of cells. Although several mutations in the TP53 gene have been identified, the most common are the missense mutations within its DNA-binding domain.[15,16] Next-Generation Sequencing (NGS) assays best document TP53 mutations, but Singh and colleagues (2019) have demonstrated that p53 immunohistochemistry studies can serve as a surrogate biomarker and are concordant with TP53 mutation studies, even with only a biopsy specimen of endometrial carcinomas.[6] Our study showed that majority

of this early-stage EC demonstrate the p53wt pattern, while the p53abn pattern has higher prevalence in the non-endometrioid histology or Bokhman Type II EC. This is consistent with the study by Nakamura et al. wherein the prevalence of p53-positive cases varies between 17% and 45% across different histological types of EC. Specifically, type I EC exhibit rates ranging from 10% to 44%, while type II EC display higher levels of p53 expression, ranging from 30% to 86%.[17]

P53 mutant-type expression is rarely found in low-grade EC, however, there have been reports showing p53 mutation-type immunoreactivity in these EC and even in the metastatic carcinomas in their lymph nodes.[18,19] However, in our study, none of the patients with metastatic lymph nodes exhibited p53abn. This observation may be limited by the small number of cases with p53abn. This abnormal p53 expression is attributed to missense mutations in TP53, resulting in p53 protein accumulation in the cell nucleus, detectable through immunohistochemistry. Conversely, null immunoreactive p53 expression results from frameshift/nonsense TP53 mutations.[17]

p53 as Prognostic Factor for Endometrial Cancer

Recent studies have shown that ECs with p53abn expression persistently show poor outcome. Earlier studies done in 2009 have shown that p53 overexpression has inferior 3-year progression-free survival of 52% vs 94% (p=0.02) and disease-specific survival 54% vs 100% (p=0.003).[13] In a study by Laliscia et al (2023) among stage I-II EC patients, there was a significant correlation between LVSI and/or p53abn and pelvic recurrence rate (p=0.002) and distant recurrence rate (p=0.017).[20] Patients with p53abn had a higher risk of local relapse (p=0.041). Substantial LVSI was strongly associated with pelvic recurrence (p=0.001) and distant metastasis (p<0.001).[20] These findings emphasize the critical importance of considering substantial LVSI and/or p53abn in the planning of adjuvant treatment for early-stage EC patients.

Considering p53abn alone, its presence increases the prognostic risk classifications of apparent early-stage patients as seen in the present study. However, it is important to note that for molecular profiling, POLE analysis and IHCs for both MMR and p53 should have been done due to presence of multiple-classifiers EC. This is a distinct subgroup characterized by the presence of multiple molecular features. A study by De Vitis et al. revealed that these cases constituted 9% of the study population, likely due to comprehensive molecular analysis.[21]

CONCLUSION

This study emphasizes the complexity of risk assessment in early-stage endometrial cancer. While p53 immunohistochemical stains show promise in predicting metastasis and has been associated with tumor aggressiveness, IHC alone is not sufficient for predicting metastasis. This should be supplemented with clinicopathological parameters to carry out a more accurate risk stratification of early-stage patients. Accurate surgical staging, considering factors such as tumor grade, myometrial invasion, and LVSI, remains fundamental in predicting LNM and guiding adjuvant therapy decisions.

The study revealed associations between clinicopathological factors and LNM. Tumor grade, myometrial invasion, and LVSI were all significantly associated with lymph node involvement. Notably, histological subtypes exhibited distinct p53 abnormality rates, with non-endometrioid histology, including serous and clear cell types, demonstrating higher rates. This highlights the heterogeneity of endometrial cancer and the need for tailored risk assessment.

Limitations

The sample size, while adequate for the specific objectives, may still limit the generalizability of the findings. Additionally, this study was conducted in a specific clinical setting with its own unique patient population, which may affect the prevalence of certain clinicopathologic factors. Furthermore, the study utilized retrospective data, which can introduce biases and limit the ability to establish causality.

In interpretation of immunohistochemical stains, tissue quality is important, especially when archival specimens are used as was the case in our study. Additionally, the reliability of our findings is contingent upon the quality of tissue processing and is subject to potential interobserver variability. Challenging cases characterized by heterogeneous p53 expression, including those with subclonal p53 expression, present a particular limitation. The influence of sampling on these cases remains inadequately explored in the existing literature, emphasizing the need for further investigations in this domain

Future Directions

Future research should explore the integration of p53 IHC stains into a broader risk assessment framework and investigate their utility in predicting treatment response and long-term outcomes, and also guide in preoperative planning. The study encountered instances where the p53 profile appeared inconsistent with the expected clinical and histological characteristics, particularly in cases with low-grade histology and no apparent high-grade or aggressive features in the final histopathology report. These discrepancies warrant thorough examination and may prompt additional research to elucidate their underlying mechanisms.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Declaration

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