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Original article

Diagnostic Accuracy and Interobserver Agreement of p53 Immunohistochemistry in Endometrial Carcinoma: Correlation with TP53 Mutation by Next-Generation Sequencing

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Abstract p53 immunohistochemistry (IHC) serves as a surrogate marker for TP53 mutation in endometrial carcinoma, but its diagnostic performance requires validation against next-generation sequencing (NGS). This retrospective study evaluated diagnostic accuracy and interobserver agreement of p53 IHC compared with TP53 mutation status in 60 endometrial carcinoma cases (2020-2022) from the Institute of Pathology, Ministry of Public Health, Thailand. Formalin-fixed, paraffin-embedded tissues with WHO-confirmed diagnosis underwent TP53 mutation analysis using targeted NGS (oncomine panel) and p53 IHC (clone DO-7). The resulting IHC slides were then independently interpreted by three blinded pathologists. TP53 mutations were detected in 12/60 cases (20%) by NGS; p53 IHC correctly identified 7/12 mutation-positive and 47/48 wild-type cases, yielding sensitivity of 58.33% (95%CI: 28.6-83.5), specificity of 97.92% (95%CI: 88.9-99.9), positive predictive value of 87.50% (95%CI: 46.7-99.3), and negative predictive value of 90.38% (95%CI: 78.6-96.5). Interobserver agreement was substantial (Fleiss' kappa = 0.71, 95%CI: 0.62-0.80) among the 51 cases deemed interpretable by all pathologists. Notably, all eight abnormal cases achieved perfect consensus, while all disagreements occurred within wild-type patterns. We conclude that p53 IHC represents a reliable rule-in test given its high specificity and substantial reproducibility; however, its moderate sensitivity necessitates confirmatory molecular testing for wild-type or ambiguous staining.

***Keywords*:** **endometrial carcinoma; p53 immunohistochemistry; TP53 mutation; next-generation sequencing**

Introduction

Endometrial carcinoma is one of the most common gynecologic malignancies, with a rising global incidence[1,2]. In recent years, molecular classification has emerged as a pivotal tool in stratifying endometrial cancers into prognostically and biologically distinct subgroups. Among these, the TP53-mutant (copy-number high/p53-abnormal) subtype is associated with aggressive behavior, poor prognosis, and distinct therapeutic considerations[2-7].

The TP53 gene encodes the p53 protein, a critical tumor suppressor that prevents cells with damaged DNA from dividing. Mutations in TP53 result in loss of this protective function and are a defining feature of high-risk endometrial carcinomas requiring intensive therapy[2-4,6,7]. Therefore, accurate identification of TP53 mutation status is essential for appropriate patient management[2,4,5-7].

p53 immunohistochemistry (IHC) has been widely adopted as a surrogate marker for TP53 mutation due to its accessibility, cost-effectiveness, and rapid turnaround time compared to next-generation sequencing (NGS)[4,6,7]. The principle is that TP53 mutations typically cause abnormal p53 protein expression patterns detectable by IHC. Normal (wild-type) expression shows variable, weak-to-moderate nuclear staining, while mutations result in either overexpression (strong, diffuse staining in >80% of cells), complete absence (null pattern), or other abnormal patterns including cytoplasmic and subclonal staining[4-7].

Despite its practical advantages, p53 IHC has documented limitations. Previous studies report sensitivity ranging from 75-95% and specificity from 80-100% when compared to molecular testing. Discrepancies between IHC patterns and TP53 mutation status can arise from several factors: certain mutation types may not produce detectable protein changes, technical issues such as tissue fixation can affect staining quality, and interpretation variability exists particularly for ambiguous cases. These limitations raise concerns about reliability as a standalone diagnostic tool[4-7].

Next-generation sequencing remains the gold standard for detecting TP53 mutations, offering high sensitivity and specificity for identifying point mutations and small indels[3,4,6-8]. However, its implementation is often limited by cost and infrastructure requirements, particularly in resource-constrained settings. Therefore, evaluating the diagnostic accuracy of p53 IHC against NGS and assessing interpretation consistency among pathologists is essential to establish its clinical utility[2,4,6,7].

This study aimed to assess the diagnostic performance of p53 immunohistochemistry in endometrial carcinoma by comparing IHC results to TP53 mutation status determined by NGS. Additionally, interobserver agreement among three pathologists interpreting p53 IHC was analyzed to evaluate reproducibility in a real-world diagnostic setting.

Materials and Methods

Study Design and Sample Size

This was a retrospective, observational study conducted at the Institute of Pathology, Department of Medical Services, Ministry of Public Health, Thailand. Sample size was determined based on available cases with complete molecular profiling during the study period. All endometrial carcinoma cases with successful TP53 mutation analysis by NGS between January

2020 and December 2022 were included (n=60), representing consecutive cases rather than a calculated sample size. Based on an expected TP53 mutation prevalence of 20% and assuming 90% sensitivity and 95% specificity of p53 IHC, this sample size provides 80% power to detect a difference with α=0.05. The inclusion of all available NGS-tested cases minimizes selection bias and represents real-world diagnostic scenarios.

Inclusion and Exclusion Criteria

Cases were included in the study if a confirmed histopathological diagnosis of endometrial carcinoma had been established according to the World Health Organization (WHO) classification[9]. Inclusion also required the availability of adequate tumor tissue for both immunohistochemical and molecular analysis, and the presence of viable, non-necrotic tumor areas within the histologic sections that were suitable for evaluation.

Cases were excluded if the tissue blocks were depleted or contained insufficient tumor material. Specimens with pre-analytical artifacts, such as sub-optimal fixation or decalcification, which compromised specimen integrity, were also excluded. In addition, cases in which DNA extraction failed due to inadequate DNA quality were excluded from molecular analysis.

Sample Preparation

All cases were processed using standard histopathological protocols. Representative tumor tissue was selected by a pathologist for both p53 immunohistochemistry and DNA extraction. For IHC, 4-µm-thick sections were cut from formalin-fixed, paraffin-embedded (FFPE) blocks and mounted on charged slides. For NGS, corresponding unstained sections were obtained from the same blocks, ensuring a tumor cell content of at least 20% in the selected areas. DNA was extracted using a commercially available kit, following the manufacturer's instructions.

p53 Immunohistochemistry and Interpretation

p53 immunohistochemistry was performed on 4-µm sections using mouse monoclonal anti-p53 antibody (clone DO-7, Dako/Agilent, 1:200 dilution) with polymer-based detection, diaminobenzidine (DAB) chromogen, and hematoxylin counterstain. External and internal controls (benign endometrial elements) were included in each run.

Three board-certified gynecologic pathologists with more than 5 years of experience (T.P., N.P., S.K.) independently evaluated digital whole-slide images on calibrated monitors under standardized conditions without time restrictions, blinded to TP53 mutation status and colleagues' interpretations. Using structured reporting forms, each pathologist documented primary pattern (wild-type, abnormal, or uninterpretable), specific abnormal subtype if present, percentage of positive cells, staining intensity (0-3+), and confidence level (high/intermediate/low). Wild-type pattern showed variable weak-to-moderate nuclear staining in scattered tumor cells; abnormal patterns included overexpression (strong diffuse nuclear staining in >80% of tumor cells), null pattern (complete absence of staining with preserved internal control), cytoplasmic pattern (diffuse cytoplasmic staining in >80% of cells), and subclonal pattern (distinct tumor populations showing different staining patterns)[4-7]. Ambiguous cases required documentation of challenging aspects such as heterogeneous staining, borderline percentage positivity, or technical artifacts.

For diagnostic performance analysis, all 60 cases

were assigned final classifications through consensus review when initial interpretations varied or when any pathologist deemed a case uninterpretable. For interobserver agreement analysis, Fleiss' kappa was calculated only for cases where all three pathologists provided definitive binary classifications (wild-type or abnormal), excluding cases where at least one pathologist indicated the pattern was uninterpretable, as the statistic requires complete categorical data from all raters.

TP53 Mutation Analysis

Genomic DNA was extracted from FFPE tissue specimens using the cobas® DNA Sample Preparation Kit (Roche Diagnostics, USA) in accordance with the manufacturer's protocol. Tumor-rich regions were identified and selected by a pathologist to ensure a minimum tumor cell content of at least 20% in the extracted material. DNA quality was assessed using the TaqMan™ Copy Number Assays (Thermo Fisher Scientific, USA).

Mutation analysis of TP53 was performed using next-generation sequencing (NGS) with the Oncomine Tumor-Specific Panel on the Ion GeneStudio™ S5 System (Thermo Fisher Scientific, USA). Data analysis was carried out using Ion Reporter™ Software version 5.20, and variant classification was manually reviewed in accordance with the American College of Medical Genetics and Genomics (ACMG) guidelines[10].

Only variants classified as pathogenic or likely pathogenic were considered positive for TP53 mutation; synonymous variants, intronic variants not affecting splice sites, and variants of uncertain significance (VUS) were classified as negative. This NGS-determined TP53 mutation status served as the reference standard for evaluating p53 immunohistochemistry performance.

Statistical Analysis

Diagnostic performance of p53 IHC was evaluated against TP53 mutation status (NGS reference standard) using standard 2×2 contingency tables. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated with 95% confidence intervals (CIs) using the Wilson method[11].

Interobserver agreement among the three pathologists was assessed using Fleiss' kappa (κ) statistic with 95%CIs. Kappa values were interpreted according to Landis and Koch criteria: <0.00=poor, 0.00-0.20=slight, 0.21-0.40=fair, 0.41-0.60=moderate, 0.61-0.80=substantial, 0.81-1.00=almost perfect agreement[12,13].

All statistical analyses were performed using IBM SPSS Statistics Version 20.0 (IBM Corp., Armonk, NY, USA) with significance set at p-value of less than 0.05.

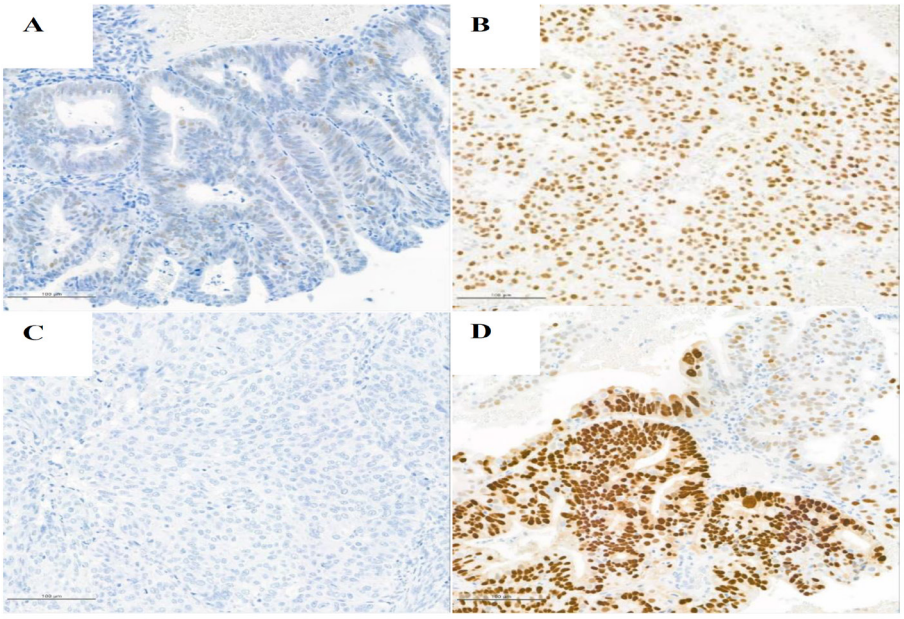
Results

Diagnostic Performance of p53 Immunohistochemistry

TP53 mutations were detected by NGS in 12 of 60 cases (20%). By consensus interpretation, p53 IHC classified 8 cases as abnormal and 52 as wild-type. Representative staining patterns are shown in Figure 1.

Compared to NGS, p53 IHC demonstrated a sensitivity of 58.33% (95%CI: 28.6-83.5) and a specificity of 97.92% (95%CI: 88.9-99.9), correctly identifying 7 of 12 mutation-positive cases and 47 of 48 wild-type cases, respectively. These

Figure 1 Representative p53 immunohistochemical staining patterns in endometrial carcinoma.



Remark: (A) Wild-type pattern shows variable, weak to moderate nuclear staining in scattered tumor cells with heterogeneous distribution. (B) Overexpression pattern demonstrates strong, diffuse nuclear staining in more than 80% of tumor cells. (C) Null pattern is characterized by complete absence of nuclear staining in tumor cells, with preserved nuclear staining in adjacent benign endometrial glands serving as an internal positive control. (D) Subclonal pattern displays two distinct tumor populations, one with overexpression and the other with wild-type staining features.

results are summarized in Table 1. The positive predictive value was 87.50% (95%CI: 46.7-99.3) and the negative predictive value was 90.38% (95%CI: 78.6-96.5). The wide confidence intervals, particularly for PPV, reflect our limited number of abnormal cases in our cohort.

Interobserver Agreement

Fleiss' kappa was calculated for the 51 cases (85%) where all three pathologists provided definitive binary classifications (wild-type or abnormal), yielding κ=0.71 (95%CI: 0.62-0.80), indicating substantial agreement. Nine cases (15%) had at least one pathologist unable to provide binary classification due to ambiguous staining patterns and were excluded from kappa calculation but retained for the consensus review. As detailed in Table 2, this agreement was

Table 1 Comparison of p53 IHC and TP53 Mutation Status

	TP53 Mutant	TP53 Wild-Type	Total
Abnormal p53 IHC	7 (True Positive)	1 (False Positive)	8
Wild-type p53 IHC	5 (False Negative)	47 (True Negative)	52
Total	12	48	60

Table 2 Distribution of pathologist agreement patterns

Agreement pattern	Cases with binary classification from all pathologists (n=51)		Cases with ≥1 uninterpretable (n=9)	Total (n=60)
	Wild-type (n=43)	Abnormal (n=8)		
Complete agreement (3:0)	36	8	N/A	44
Majority agreement (2:1)	7	0	N/A	7
Uninterpretable by ≥1 pathologist	N/A		9	9

asymmetric: perfect 3:0 concordance was achieved for all eight abnormal cases (100%), while among the 43 wild-type cases, 36 (83.7%) showed complete agreement and 7 (16.3%) showed majority agreement.

Among 16 discordant cases (7 with majority agreement, and 9 uninterpretable), all were classified as wild-type by consensus, yet NGS revealed TP53 mutations in two, representing 40% of our five false-negative results. These misclassified cases displayed borderline staining patterns (30-50% and ~70% positivity) that fell below the 80% threshold required for an overexpression classification.

Discussion

This study evaluated the diagnostic utility and interobserver reproducibility of p53 immunohistochemistry as a surrogate marker for TP53 mutation in endometrial carcinoma. Our findings revealed a notable discordance between sensitivity (58.33%) and specificity (97.92%). Our specificity aligns well with literature values, which range from 94.3% to 100%[4,6,7]. In contrast, our sensitivity is considerably lower than the 90.8% reported by Singh et al[6]. This sensitivity gap is likely multifactorial. Our inclusion of a consecutive, unselected cohort may have captured a broader spectrum of borderline patterns, while our stringent 80% threshold for abnormal classification likely missed mutations causing 50-60% positivity. Furthermore, we speculate that differences in TP53 mutation patterns across populations might contribute to variations in immunohistochemical detection rates. The high PPV (87.50%) confirms that abnormal p53 staining reliably indicates TP53 mutation, while the moderate NPV (90.38%) underscores the risk of false-negative results with wild-type patterns.

The 41.67% false-negative rate highlights critical pre-analytical factors that can compromise p53 IHC interpretation. Antigen degradation from delayed fixation, for instance, is thought to cause an artifactual reduction in staining in portions of truly p53-abnormal tumors. This partial loss of staining creates a heterogeneous or weak pattern that mimics wild-type expression, leading pathologists to misclassify mutant cases as normal[7,18]. Such technical artifacts were particularly problematic in our consultation cases with unknown fixation histories. Distinct from technical artifacts, the biology of TP53 mutations themselves contributes to false negatives. Some truncating and splice-site mutations produce non-functional proteins that retain antibody binding capacity, generating wild-type staining patterns despite harboring pathogenic alterations. This inherent

limitation, where mutant protein mimics normal expression, affects all p53 IHC assays regardless of technical excellence, explaining why even optimally processed specimens can yield false-negative results[7].

The interobserver agreement analysis revealed a significant disparity between pattern types, with perfect consensus for all abnormal cases but variable agreement for wild-type patterns. This variability resulted in an overall substantial agreement (Fleiss' $\kappa = 0.71$). While excellent inter-laboratory reproducibility has been reported, with a 95.1% concordance between local and central review[6], our finding that 30.8% of wild-type cases (16/52) showed interpretive disagreement likely reflects our inclusion of consecutive unselected cases and stringent interpretation criteria. This demonstrates that distinguishing true wild-type from weak abnormal expression remains a significant challenge, a variation that is known to occur in practice even when high agreement can be achieved with training[4,6,7]. This overall substantial agreement, however, supports p53 IHC's feasibility in routine workflows, particularly where access to molecular testing is limited by cost or availability constraints.

The clinical implications of p53 IHC depend on context. As a "rule-in" test, its high specificity allows immediate TP53-mutant classification when abnormal patterns are detected. However, our finding that p53 IHC missed 41.67% of TP53 mutations precludes its use as a standalone diagnostic tool for treatment decisions. Instead, p53 IHC functions optimally as a component of the established molecular classification algorithm, which integrates MMR protein IHC and POLE sequencing to achieve prognostic accuracy[14,15]. This is because TP53 mutations frequently co-occur in MMR-deficient and POLE-mutant cases, but in this context, their prognostic significance is superseded by the primary molecular driver[6,8]. For population-level screening, p53 IHC retains utility by efficiently identifying clear-cut abnormal cases, thereby reserving expensive NGS confirmation for wild-type results in clinically high-risk patients.

Several strategies could enhance p53 IHC sensitivity based on emerging evidence. First, a multi-clone antibody approach may improve detection, as studies showing variable concordance rates suggest that single monoclonal antibodies like DO-7 may be unable to recognize mutations affecting specific epitopes[16-18]. Second, adjusting interpretation thresholds substantially impacts sensitivity: while our study used 80% for defining overexpression, research in breast carcinomas showed that a 50% threshold achieved optimal sensitivity (0.90) while maintaining good specificity (0.88)[17]. Lowering the threshold to 50-60% might capture additional true mutations, though this requires validation in endometrial carcinoma. Third, standardizing pre-analytical processing is critical, as delayed fixation causes antigen degradation that creates heterogeneous staining patterns potentially leading to false-negative interpretation[7,18]. Finally, digital pathology with AI integration shows promise for objective assessment, with automated nuclear scoring algorithms achieving high accuracy (0.89) in predicting mutations[17]. These approaches warrant systematic evaluation in endometrial carcinoma cohorts before clinical implementation.

In conclusion, p53 immunohistochemistry demonstrates several strengths as a diagnostic tool for TP53 mutation detection in endometrial carcinoma:

excellent specificity (97.92%) that enables reliable "rule-in" diagnosis, substantial interobserver reproducibility (κ=0.71) supporting feasibility in routine workflows, and cost-effectiveness as a screening modality in resource-limited settings. However, important limitations must be acknowledged: moderate sensitivity (58.33%) with a 41.67% false-negative rate precludes its use as a standalone diagnostic marker, interpretation variability for wild-type patterns requires specialized training, and inherent biological constraints wherein certain mutations produce wild-type staining patterns cannot be overcome by technical optimization alone.

Future research should focus on several key areas: first, validating multi-antibody panels to improve epitope coverage and mutation detection; second, establishing optimal interpretation thresholds through systematic evaluation of 50-60% cutoffs versus our 80% threshold; third, developing standardized pre-analytical protocols to minimize fixation artifacts; and finally, integrating digital pathology with artificial intelligence algorithms for objective pattern assessment. Until these enhancements are validated, we recommend p53 IHC be utilized as a valuable but imperfect surrogate within the molecular classification algorithm, requiring NGS confirmation for wild-type patterns in high-grade cases where accurate TP53 status would influence clinical management. This pragmatic approach balances diagnostic accuracy with resource utilization while acknowledging current methodological constraints.

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ความถูกต้องเชิงวินิจฉัยและความสอดคล้องระหว่างผู้สังเกตของการประเมิน p53 โดยวิธีการย้อมอิมมูโนฮิสโตเคมี ในมะเร็งเยื่อบุโพรงมดลูก และความสัมพันธ์กับการกลายพันธุ์ TP53 โดยการหาลำดับเบสรุ่นใหม่

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บทคัดย่อ: การย้อมอิมมูโนฮิสโตเคมี p53 ถูกใช้เป็นตัวบ่งชี้ทดแทนการกลายพันธุ์ TP53 ในมะเร็งเยื่อบุโพรงมดลูก แต่ประสิทธิภาพการวินิจฉัยยังต้องตรวจสอบเทียบกับการหาลำดับเบสรุ่นใหม่ การศึกษาย้อนหลังนี้มีวัตถุประสงค์เพื่อประเมินความแม่นยำและความสอดคล้องระหว่างผู้สังเกตของการย้อมอิมมูโนฮิสโตเคมี p53 เทียบกับสถานะการกลายพันธุ์ TP53 ในผู้ป่วยมะเร็งเยื่อบุโพรงมดลูก 60 ราย (พ.ศ. 2563-2565) จากสถาบันพยาธิวิทยาฯ โดยวิเคราะห์การกลายพันธุ์ TP53 ด้วยการหาลำดับเบสรุ่นใหม่แบบเจาะจงเป้าหมายและย้อมอิมมูโน-ฮิสโตเคมี p53 ซึ่งพยาธิแพทย์ 3 ท่านตีความผลย้อมอิมมูโนฮิสโตเคมีอย่างอิสระแบบปกปิดผลการกลายพันธุ์ ผลการศึกษาพบการกลายพันธุ์ TP53 ใน 12/60 ราย (ร้อยละ 20) การย้อมอิมมูโนฮิสโตเคมี p53 ระบุถูกต้อง 7/12 รายที่มีการกลายพันธุ์และ 47/48 รายที่ไม่มีการกลายพันธุ์ ซึ่งให้ความไวร้อยละ 58.33 (95% CI: 28.6-83.5) ความจำเพาะร้อยละ 97.92 (95% CI: 88.9-99.9) ค่าพยากรณ์บวกร้อยละ 87.50 (95% CI: 46.7-99.3) และค่าพยากรณ์ลบร้อยละ 90.38 (95% CI: 78.6-96.5) ความสอดคล้องระหว่างผู้สังเกตอยู่ในระดับมาก (Fleiss' kappa = 0.71, 95% CI: 0.62-0.80) สรุปได้ว่าการย้อมอิมมูโนฮิสโตเคมี p53 มีความจำเพาะและทำซ้ำได้ดี แต่ความไวที่จำกัดบ่งชี้ว่าต้องมีการตรวจยืนยันด้วยวิธีทางโมเลกุลเมื่อพบการติดสีแบบปกติหรือไม่ชัดเจน

คำสำคัญ: **มะเร็งเยื่อบุโพรงมดลูก; การย้อมอิมมูโนฮิสโตเคมี p53; การกลายพันธุ์ TP53; การหาลำดับเบสรุ่นใหม่**