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Review

Discordance Between p53 Immunohistochemistry and *TP53* Mutational Analysis in Endometrial Cancer

Mousa Mobarki

Department of Basic Medical Sciences (Pathology), Faculty of Medicine, Jazan University, Jazan 45142, Saudi Arabia; dr.mobarki@gmail.com or mamobarki@jazanu.edu.sa

Abstract

Molecular classification of endometrial cancer has become necessary to determine treatment options for these patients. p53 is assessed by immunohistochemistry, which can reveal a wild-type or abnormal expression, consisting of overexpression, absence of expression, cytoplasmic expression, or subclonal expression. Given that DNA polymerase epsilon (POLE) will often be sequenced in panels including *TP53*, some discordance between the immunohistochemical expression of p53 and the mutational status of *TP53* can be observed and lead to confusion regarding the correct molecular classification and thus treatment options. Thus, the aim of this review is to present studies exploring this question and provide evidence on how to interpret this discordance.

Keywords: NGS; immunohistochemistry; p53; *TP53*; discordance; interpretation; endometrial

1. Introduction

The *TP53* gene, located on chromosome 17p13.1, is the prototypical tumor suppressor gene, often called the "guardian of the genome", and its mutations occur in more than 50% of all human cancers [1,2]. The p53 protein is expressed in almost all human cells and protects them from cancer through many processes, such as cell cycle arrest, apoptosis, autophagy, senescence, ferroptosis, DNA repair, metabolism, and tumor microenvironment control [1]. It is composed of 393 amino acids and has five distinct domains: the transactivation domain, which acts as the binding region of several regulatory proteins and regulates the transcription of several genes; the proline-rich domain, which regulates cell cycle arrest and cellular death; the central DNA-binding domain, which is responsible for p53 binding to the DNA; the tetramerization domain, which is responsible for the tetramerization of p53, since p53 acts as the tetramer in DNA binding; and the C-terminal regulatory domain, which acts as a regulator of p53 [1]. p53 inactivation mainly occurs due to *TP53* mutations, and in contrast to most tumor suppressor genes, most of these mutations are missense, while nonsense mutations, frameshift mutations, and deletions are uncommon [1,2]. They often occur in the DNA-binding domain; their most common locations, also called hotspots, are G245, R249, R248, R282, R273, Y220, and R175 [1]. Missense mutations of the *TP53* tumor suppressor gene can lead to cancerogenesis because the mutant protein acquires a gain-of-function ability and dominant-negative potential over the normal allele under heterozygous conditions [2]. The mutant p53 protein often accumulates in the nuclei of tumor cells, which has initially led to the belief that *TP53* is

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an oncogene [3]. However, *TP53* missense mutations usually result in a protein that resists degradation and accumulates in the nuclei [3], while under normal conditions, p53 is maintained at low levels by the negative interaction with MDM2 (mouse double minute 2), which promotes its degradation [2]. On the other hand, splice site and stop-gain mutations are associated with the complete absence of p53 from cells [3]. Mutations in the C-terminal domain can disrupt the nuclear localization and lead to p53 accumulation in the cytoplasm [3].

Thus, these types of mutations can correspond to different types of p53 immunohistochemical expression that have been established as the main abnormal immunohistochemical patterns of p53 expression, in contrast to the "normal" expression pattern of p53 which consists of mild expression by some tumor cells [3]:

(1) Overexpression, corresponding to a strong nuclear p53 expression by most tumor cells, and often associated with missense *TP53* mutations (Figure 1);
(2) Complete absence of expression by tumor cells (null-type), despite nearby normal cells (internal control) expressing p53 in low levels, often corresponding to splice site and stop-gain mutations (Figure 2);
(3) Cytoplasmic p53 expression often corresponding to C-terminal domain mutations (Figure 3).

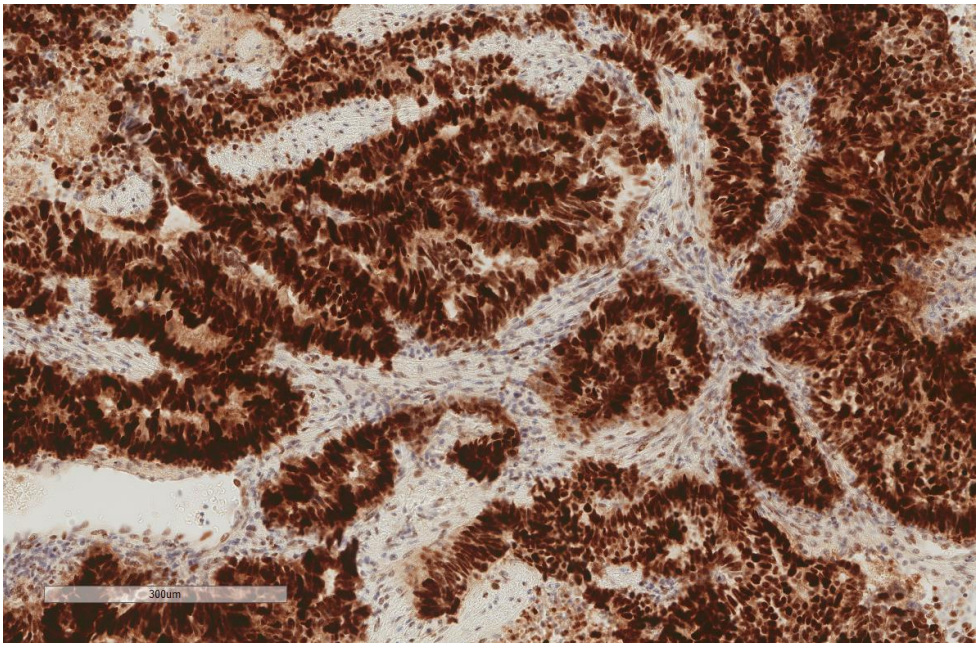


Figure 1. Strong p53 nuclear expression by all tumor cells (mutated pattern of expression).

These expression patterns have been established in ovarian cancer [4,5] but have then been accepted in other malignancies [6]. In pathology practice, p53 immunohistochemical expression has been used in several settings, mostly as a diagnostic or prognostic tool, such as in the diagnosis of ovarian high-grade serous carcinoma [7], vulvar dysplasia [8], gastric/esophageal neoplasia [9,10], neuroendocrine neoplasia [11,12], and myeloid neoplasms [13].

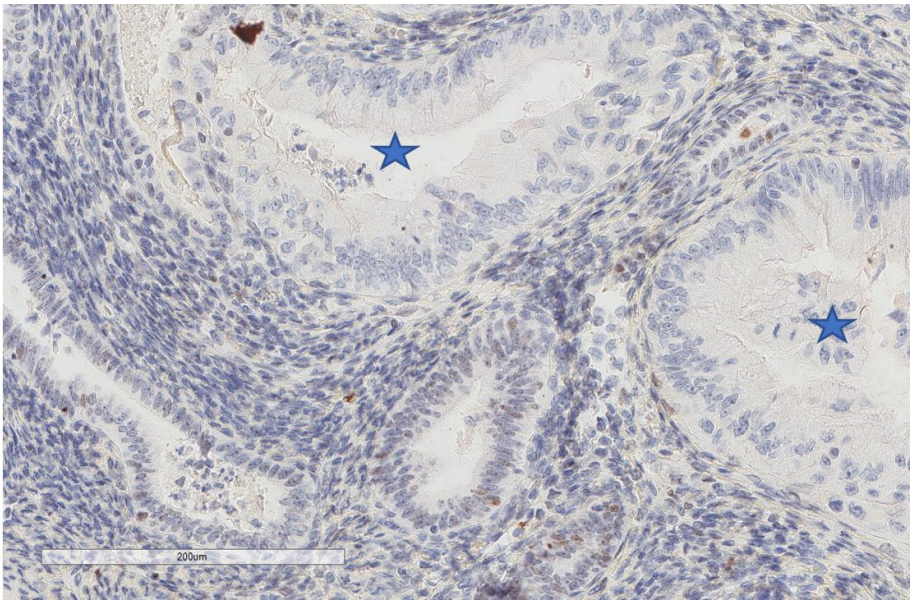


Figure 2. Complete absence of p53 expression (mutated type of expression) by tumor cells (stars) compared to stromal and normal glandular cells (bottom).

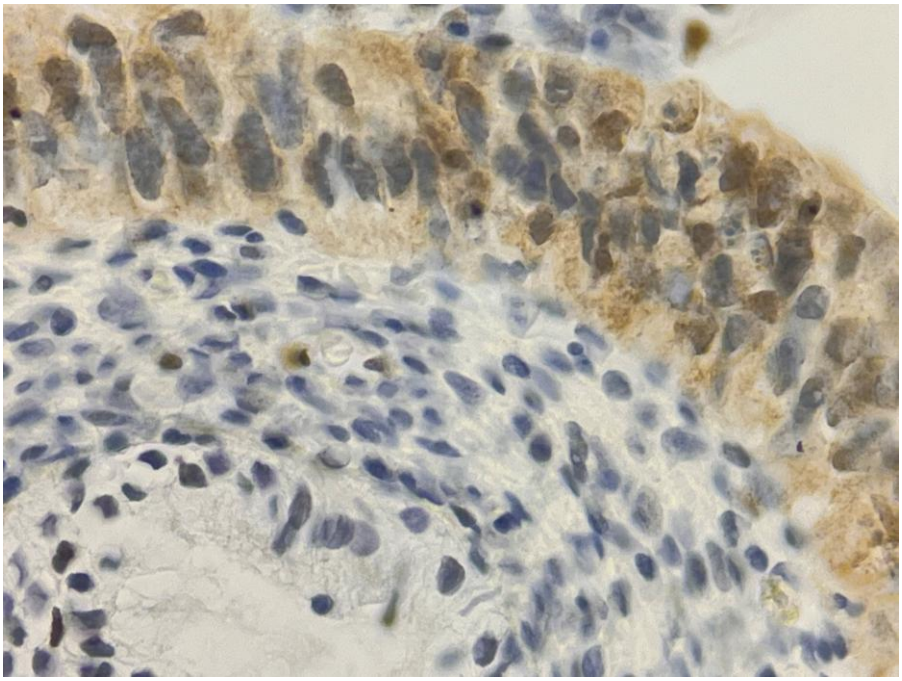


Figure 3. Cytoplasmic p53 expression by tumor cells (mutated type of expression).

However, its expression has probably never been as important as in endometrial cancer, where not only does it offer diagnostic and prognostic information but will also impact on the treatment chosen. The Cancer Genome Atlas project defined four distinct molecular subtypes of endometrial cancer [14]: the ultramutated subtype, associated with polymerase epsilon (*POLE*) mutations; the hypermutated subtype, associated with microsatellite instability; the high-copy-number subtype, associated with *TP53* mutations; and the low-copy-number subtype, showing no specific molecular alterations. Despite these subtypes being known for years, it was in 2023 that the new FIGO (International Federation of Gynecology and Obstetrics) staging system was published and revolutionized staging systems, since it considered, for the first time, not only anatomical but also histological and molecular data in defining the stage of disease and thus treatment [15].

This 2023 FIGO classification system recognizes four disease stages (I to IV). Stage I disease contains cases with non-aggressive histology, limited to the endometrium or polyp (IA1), or invading less than 50% (IA2) or 50% or more (IB) of the myometrium, associated with no or only focal lymphovascular space invasion. It also contains an IC stage corresponding to an aggressive histological type without any myometrial invasion. Interestingly, under certain conditions, simultaneous uterine and ovarian involvement is also considered stage I disease (IA3). Stage II includes low-grade histotypes infiltrating the cervix (IIA), or with substantial lymphovascular involvement (IIB), or aggressive histotypes with any myometrial invasion (IIC). Stage III includes invasion of the serosa and/or adnexa (IIIA), of the vagina and/or parametria or pelvic peritoneum (IIIB), and cases with lymph node metastasis (IIIC), while stage IV corresponds to locally advanced tumors invading the bladder or rectal mucosa (IVA) and distant metastasis (IVB).

Despite some criticism when this FIGO classification appeared [16], it was incorporated by the European Society of Gynaecological Oncology (ESGO), the European Society of Radiotherapy and Oncology (ESTRO), and the European Society of Pathology (ESP) guidelines, which defined risk groups of endometrial cancer and their corresponding treatment [17]. A retrospective study of 712 consecutive patients with endometrial cancer compared the FIGO 2009 and FIGO 2023 classifications, showing an improvement in the C-index from 0.712 to 0.785 for progression-free survival, and from 0.725 to 0.811 for overall survival [18]. A better discriminative ability of the FIGO 2023 system was also found in another retrospective study of 720 patients [19]. A higher C-index for the FIGO 2023 classification was noted in a retrospective study, including only patients treated for serous endometrial carcinoma [20]. In a retrospective study of 472 patients with FIGO 2009 stage I–II disease, the FIGO 2023 system showed a better risk stratification but only for the non-aggressive histotypes [21]. In a retrospective study of almost 3000 patients, the FIGO 2023 classification improved the prognostic accuracy compared to the FIGO 2009 system [22]. Thus, despite the lack of large prospective studies, it seems that the new FIGO classification offers better prognostic tools.

The ESGO/ESTRO/ESP guidelines consider the molecular classification in the treatment strategy. For example, the IICmp53 abn group, defined as a p53 abnormal endometrial carcinoma confined to the uterine corpus with any myometrial invasion, with or without cervical invasion, and regardless of the degree of lymphovascular space invasion or histological type, is considered a high-risk carcinoma and adjuvant treatment is suggested. By contrast, the IAm*POLE* mut group, defined as *POLE*-mutated endometrial carcinoma, confined to the uterine corpus or with cervical extension, regardless of the degree of LVSI or histological type, is considered a low-risk group and no adjuvant treatment is suggested [17]. Thus, these guidelines reveal the importance of correctly diagnosing the molecular subtype of endometrial cancer. The proposed algorithm to do so is the immunohistochemical study of endometrial carcinoma for the expression of MMR (MisMatch repair) and p53 proteins, and the sequencing of the *POLE* gene [17].

This highlights the importance of correctly interpreting p53 immunohistochemical expression. Furthermore, since *POLE* is often sequenced with next-generation sequencing panels that also include *TP53*, a discordance between p53 immunohistochemical expression and *TP53* mutational status can be seen in routine practice.

How this discordance is interpreted can dramatically change the treatment chosen for the patient, since it can be considered either a p53 normal or p53 abnormal tumor, which will change the treatment as shown above. Thus, the aim of this review is to present studies exploring the discordance between p53 immunohistochemistry and *TP53* molecular analysis in endometrial cancer, to understand the basis of this discordance, and how to interpret it.

2. Studies Comparing p53 Immunohistochemical Expression with *TP53* Mutational Status

Studies comparing *TP53* mutational status with p53 immunohistochemical expression in endometrial cancer are presented in Table 1. One of the first studies responding to this question was by Singh et al. [3], who used 177 endometrial cancer biopsies and the DO-7 DAKO clone for a centralized immunohistochemical study [3]. They considered as normal (wild type) a variable intensity of staining of 1% to 80% of nuclei, and they employed the following four patterns of abnormal p53 expression: the overexpression pattern, where strong expression is seen in at least 80% of tumor cell nuclei; null pattern, where there is complete absence of expression by tumor cells, despite the internal control-positive nuclei; cytoplasmic staining; and subclonal staining (Figures 4–6) [3].

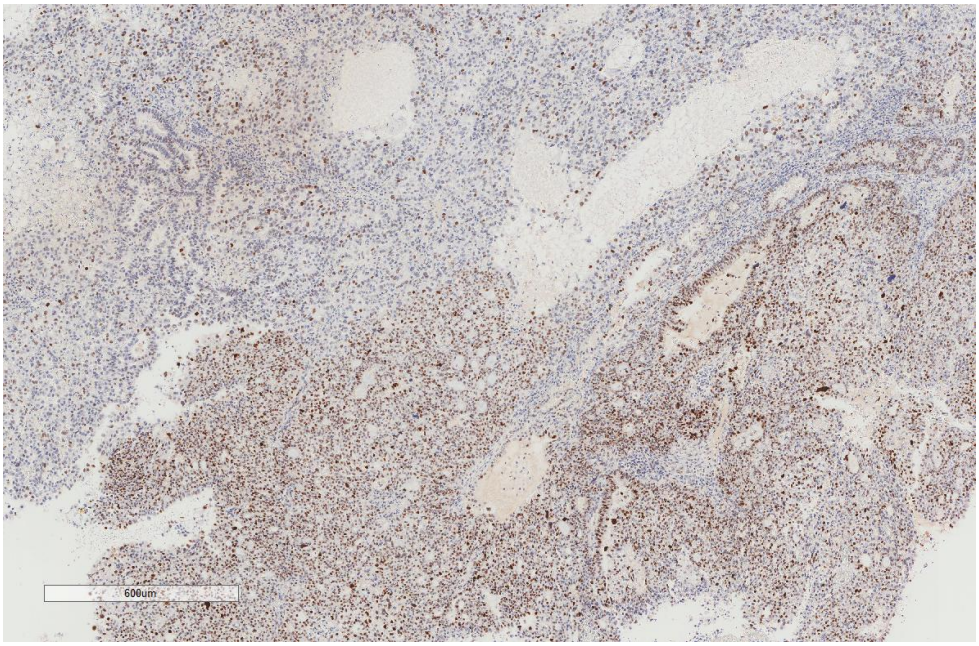


Figure 4. Compared to Figures 1–3, where the same expression pattern is seen all over the tumor cells, this tumor shows some positive and negative foci and could erroneously be considered wild-type.

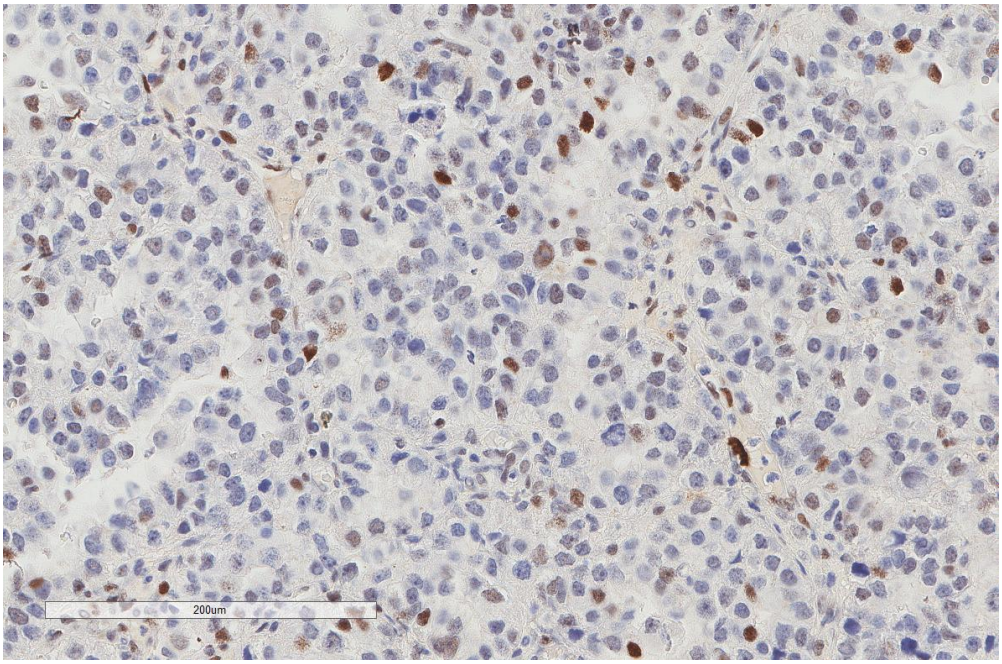


Figure 5. The same tumor as in Figure 4 showing foci of "normal" p53 expression corresponding to few tumor cells showing mild to moderate expression.

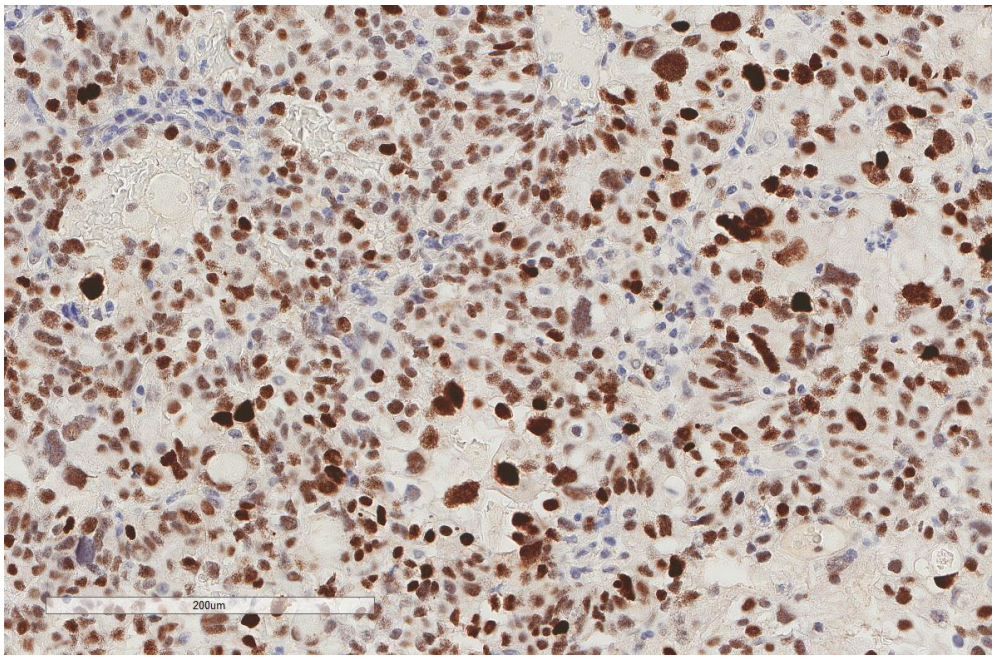


Figure 6. However, the same tumor harbors foci of strong uniform p53 expression. This type of staining is considered a mutated type of expression, the subclonal expression type, which can be easily confounded with wild-type expression.

This was defined as the combination of more than one type of staining in at least 5% of tumor cells [3]. They used tagged amplicon deep sequencing (Tam-Seq) on an Illumina MiSeq or Hiseq 4000 using the PE-150 bp protocol and the Fluidigm 48.48 Access Arrau platform [3]. The discordance rate found was 10%, but after excluding the MMR-deficient (MMRd) and the *POLE*-mutated (*POLE*mut) cases, this discordance was reduced at 5.6% [3].

Indeed, the molecular classification of endometrial carcinoma includes "multiple classifiers", meaning cases that harbor more than one molecular abnormality; these cases are classified according to their driver mutation, meaning *POLE* predominates over MMRd and p53abn, and MMRd predominates over p53abn [17]. This is why when finding *POLE*mut or MMRd in an endometrial carcinoma, this is considered as such even if it harbors p53 abnormalities which are considered secondary [17]. Thus, studies exploring the p53/*TP53* discordance exclude these cases from their analysis. Two years later, Thiel et al. studied 213 endometrial cancer patients with stage III/IV disease or recurrent disease [23]. They used the same DO-7 clone, and a custom Roche Noblemen SeqCap EZ system for sequencing [23]. They found a 12% discordance, reduced by 7% after excluding the MMRd/*POLE*mut cases and the reclassification of some cases, either on immunohistochemistry or molecular analyses [23]. It is worth noting that variants with unknown function were included by the authors [23]. At the same time, Vermij et al. compared the immunohistochemical expression of p53 (DO-7 clone) with the mutational analysis of *TP53* (AmpliSeq Cancer Hotspot Panel version 5, a variant allele frequency of at least 10%, and only mutations with pathogenic or likely pathogenic classification were included) in 344 hysterectomy patients from the international PORTEC-3 study (high-risk patients) [24]. They used the same four abnormal p53 patterns of expression (overexpression, null, cytoplasmic, and subclonal) [24]. However, the subclonal pattern was defined as any abrupt

and regional abnormal p53 expression in less than 80% of tumor [24]. The initial discordance was 9.3%, reduced at 1.7% after excluding MMRd/*POLE*mut and reclassified cases [24]. In 2023, Matsumoto et al. examined 43 high-grade endometrial carcinomas, finding 100% concordance between the immunohistochemical expression of p53 (DO-7 clone) and mutational analysis (FoundationOneCDx) [25]. The abnormal p53 staining patterns were the overexpression, null, and cytoplasmic one [25]. The authors found no subclonal pattern in their cases, and their cohort includes a *POLE*mut case and five MMRd cases, but in all of them, concordance of p53/*TP53* was found [25]. Jamieson et al. in 2023 used the DO7 antibody and the Imagia Canexia Health Find It V5.0 amplicon-based NGS (Next-Generation Sequencing) gene panel after sequencing on Illumina MiSeq of 164 cases [26]. The variant allele fraction (VAF) threshold was set at 5% but cases with a VAF of 1% to 5% were reviewed on a case-by-case basis [26]. Regarding the p53abn group (no *POLE*mut/MMRd cases), the discordance was at 1.2% [26]. A year later, Jamieson et al. examined 545 cases and found 2% discordance for p53/*TP53*, while Huvila et al. examined a cohort of 957 with a special interest in subclonal staining and found a 7.8% discordance [27]. More recently, Machuca-Aguado et al. examined 386 cases, finding a discordance of 11.4% reduced by 3.3% after excluding *POLE*mut/MMRd cases and reviewing immunohistochemical slides [28]. In this study, no percentage of subclonal staining is used, with any percentage of abnormal staining being considered as subclonal abnormal expression [28]. Finally, Yang et al. examined a 103-cohort sample harboring a single missense *TP53* mutation and compared its p53 immunohistochemistry (MX008 clone) and its four abnormal patterns [29]. They found a 17% discordance [29]. It is not clear whether *POLE*mut/MMRd cases were included [29]. In addition, the authors included variants of uncertain significance in their analysis [29].

Table 1. Studies comparing p53 immunohistochemical expression with *TP53* mutational status.

Study	Cohort	Discordance	Real Discordance After Reviewing *
Yang 2026 [29]	103 *TP53* missense cohort	18 (17.4%)	18 (17.4%)
Machuca-Aguado 2026 [28]	386	44 (11.4%)	13 (3.3%)
Jamieson 2024 [30]	545	12 (2%)	11 (2%)
Jamieson 2023 [26]	164	3 (1.8%)	2 (1.2%)
Matsumoto 2023 [25]	43	0	0
Huvila 2023 [27]	957	75 (7.8%)	28 (2.9%)
Vermij 2022 [24]	344	32 (9.3%)	6 (1.7%)
Thiel 2022 [23]	213	24 (12%)	15 (7%)
Singh 2020 [3]	177	18 (10.1%)	10 (5.6%)

* MMRd and *POLE*mut cases, as well as cases reclassified after the authors reviewed them.

As we can see from this presentation of relevant studies, the cohorts/designs used are not homogenous, as it is not the definition of subclonal expression, the variants VUS included, or the cutoff of VAFs used. Thus, any conclusion drawn here should be seen with caution. Despite these limitations, we can see that the discordance rate ranges from 2% to 17.4%, and when reviewing the cases/excluding the *POLE*mut/MMRd cases, this ranges from 1% to 17.4%. When gathering all these published cases, there are 2932 endometrial carcinomas studied for p53/*TP53* comparison with an overall discordance of 7.7%, but with a "real" discordance after exclusion/review of 3.5%.

3. Interpretation of the Discordance

It is important to understand how the reported discordance was interpreted (Table 2). Of the 226 discordant cases reported, the authors of each study excluded 110 (48.6%) because their molecular subgroup was the MMRd or the *POLE*mut. This does not really explain the discordance; however, the p53 status is of no clinical significance in these cases. It is also worth noting that in these cases of the *POLE*mut/MMRd subgroups, it is often the subclonal type of staining that is found. A total of 29 cases (some already present in the *POLE*mut/MMRd group), corresponding to 8.4% of the discordant cases, were excluded, because after reviewing by the authors, p53 staining was reclassified or the mutation found was considered a polymorphism.

Table 2. Interpretation of the discordance cases.

Study	Cohort	Discordance	p53abn/ *TP53*wt	p53nor/ *TP53* mut	Reclassification of IHC	Reclassification of Mutation	MMRd, *POLE*mut Excluded
Yang 2026 [29]	103	18	0	18	0	0	0 §
Machuca-Aguado 2026 [28]	386	44	6	38	19	0	21
Jamieson 2024 [30]	545	12	7 **	5	1	0	0 +
Jamieson 2023 [26]	164	3	2	1	0	1 #	0 +
Huvila 2023 [27]	957	75	11	64	0	0	65
Vermij 2022 [24]	344	32	12	16	4	0	10
Thiel 2022 [23]	213	24	7	13	3	1 #	6 *
Singh 2020 [3]	177	18	9	9	0	0	8

p53abn = abnormal immunohistochemical staining; p53nor = normal immunohistochemical staining; *TP53*wt = no *TP53* mutation; *TP53*mut = mutation of *TP53*. * One E1949K *POLE* mutation is not excluded by the authors. § Not specified if *POLE*mut/MMRd cases are present. ** Mixed serous endometroid = sampling error possible for 2. # They were considered polymorphisms. + Molecular subtypes already assigned. Subclonal included in this table (initially excluded by the authors).

Finally, out of the 226 cases, 103 (45.5%) were considered the "real" discordant cases (Table 3). For 63 cases (61.1%), immunohistochemistry revealed a normal p53 staining, while a *TP53* mutation was found. For 40 cases (38.9%), p53 showed an abnormal staining, but no *TP53* abnormality was found. For these 40 cases, two carcinomas were mixed, and the authors suggest that the component sequenced could be that with normal p53 immunohistochemistry. Eight cases (20%%) showed subclonal expression, 12 showed overexpression (30%), and 18 (45%) the null type of abnormal staining.

Table 3. Type of discordance for the "real" discordant cases.

Study	"Real Discordance" *	Type of Mutation and Staining
Yang 2026 [29]	18	18 p53nor = *TP53* missense mutations **
Machuca-Aguado 2026 [28]	13	2 overexpression = no mutation 3 null = no mutilation 8 p53 normal = *TP53* mutation (type not specified)
Jamieson 2024 [30]	11	2 mixed carcinomas (p53abn = no *TP53* mutation) 4 null = no mutation 5 WT = *TP53* mutation (type not specified)
Jamieson 2023 [26]	2	2 null = no mutation
Huvila 2023 [27]	28	3 subclonal = no mutation 2 overexpression = mutation (not specified)

		4 null expression = mutation (not specified) 21 p53 normal = mutation (not specified)
Vermij 2022 [24]	6	1 p53 normal = missense *TP53* mutation 4 overexpression = no mutation 1 subclonal = no mutation
Thiel 2022 [23]	15	4 null = no mutation 3 overexpression = no mutation 8 p53 normal = mutation (4 truncating, 4 VUF)
Singh 2020 [3]	10	2 p53 normal = mutation (1 missense, 1 stop-gain) 1 overexpression = no mutation 3 null = no mutation 4 subclonal = no mutation

VUF = variants of unknown function. * Only the "real" discordant cases presented in Table 2 are included here. ** The authors also find 5 abnormal p53 stainings corresponding to 5 VUS, one p53 normal staining corresponding to a VUS, and 9 p53 normal stainings corresponding to likely benign variants; all these cases were considered concordant.

There are several possible explanations for the discordance observed between immunohistochemical expression and the mutational profile. First, as suggested by Yang et al. [29], *TP53* mutations, even when considered "oncogenic or likely oncogenic", may not uniformly lead to the loss of function of the mutant allele at the protein level. The authors propose three possible mechanisms to explain this: mutations in the transactivation domain or the tetramerization domain do not disrupt the DNA-binding domain, so the p53 maintains wild-type stability; certain mutations may cause partial rather than complete dysfunction of the protein; cells may possess compensatory mechanisms to maintain the function of the protein [29]. In addition, mutations leading to a late stop codon may result in wild-type expression of a protein that is non-functional; similarly, alterations in non-coding regions resulting in loss of protein expression, but no detectable mutations, can also occur [25]. Furthermore, the null-type staining can be associated with large *TP53* deletions or insertions that remain undetectable by NGS [26,28,30].

Apart from these "real" concordance reasons, more technical explanations can also be hypothesized. Differences in NGS platforms can account for not detecting some *TP53* mutations [25]. Another explanation is that NGS may be more sensitive to detecting subclonal mutations that have been overlooked at the immunohistochemistry slides; also, differences may be found if a different bloc is used for mutational analysis compared to that used for immunohistochemistry [28]. Similarly, such a specimen-based explanation could be supposed if a biopsy over a surgical specimen is used or if a mixed tumor is considered. Indeed, the concordance between matched biopsy and hysterectomy specimens regarding p53 immunohistochemistry is very high but not perfect [31,32].

In addition, interpretation of p53 immunohistochemistry could be difficult for some cases, such as distinguishing between null-type and low wild-type expression (Figure 7); overexpression and high wild-type expression (Figure 8); and cytoplasmic expression and non-specific cytoplasmic blush [28].

In addition, the agreement in the evaluation of p53 immunohistochemistry is high but not perfect [33]. It could also be hypothesized how integrating the *TP53* variants of uncertain significance, and the *TP53* VAFs, as this varied between the different studies, can also impact on concordance with immunohistochemistry.

It is also interesting that some of these studies comparing mutational *TP53* status and p53 expression offer us information on the type of expression corresponding to the type of mutation in endometrial cancer. Most cases with p53 overexpression show that missense mutations, cytoplasmic expression, and absence of expression were associated with

stop-gain mutations/splice site mutations [3,23], and subclonal staining is often seen in the context of a *POLE* mutant or MMR-deficient tumor [3,27,28]. It should be mentioned that these studies did not "implicate" DNA polymerase delta 1 (POLD1). POLD1 is a molecule whose action resembles that of *POLE*, and its mutations can lead to a similar ultramutated phenotype [34]. However, our knowledge on how to interpret *POLD1* mutations is very limited. Which variants are pathogenic, in which context, and its association with *TP53* mutations remains to be elucidated.

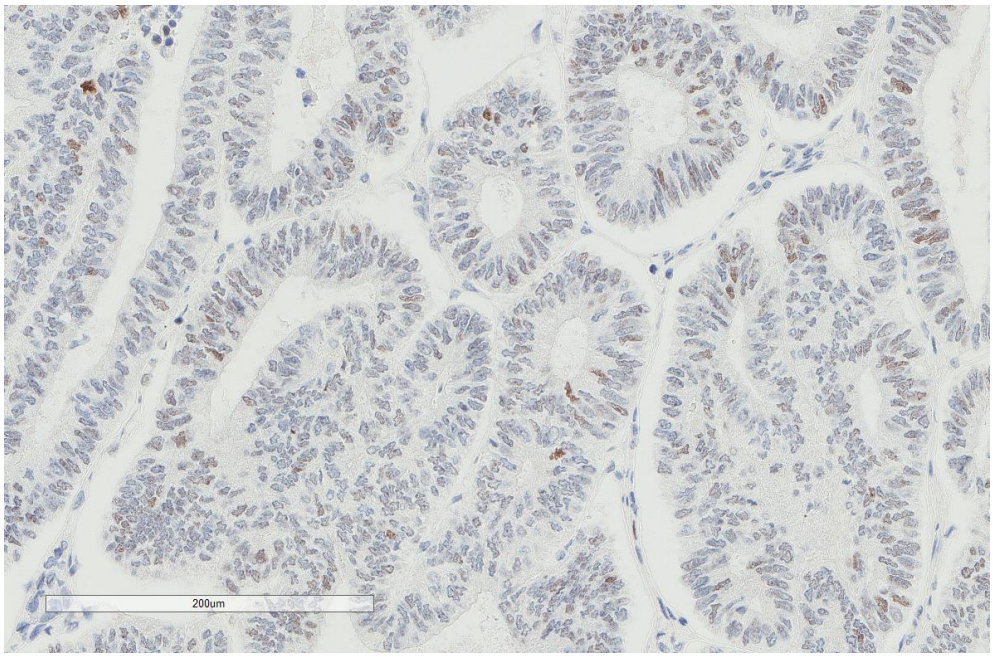


Figure 7. Expression of p53 can be very mild and misinterpreted as a null-type or mutated expression instead of a wild-type expression.

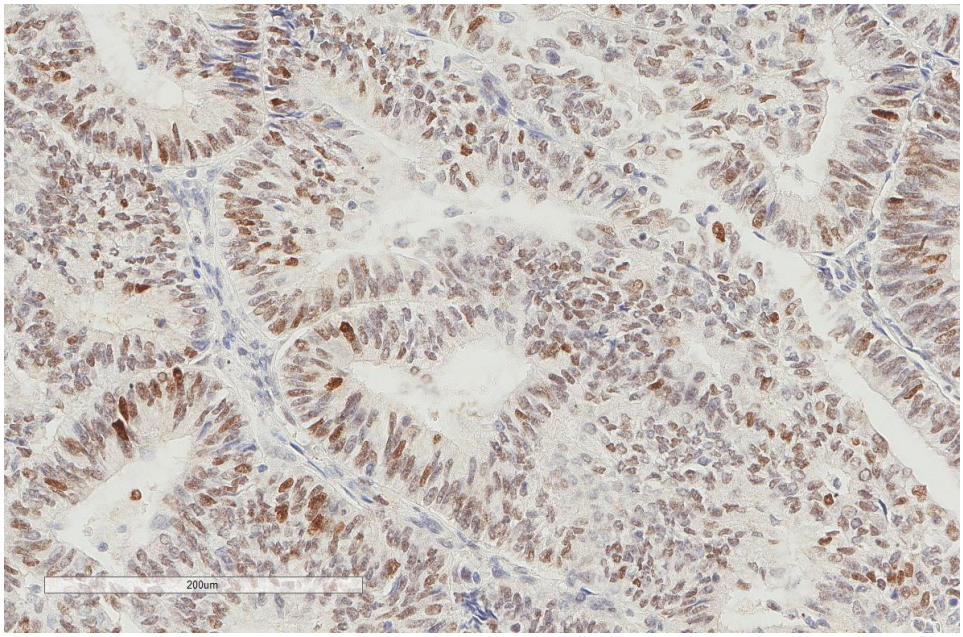


Figure 8. Expression of p53 can be more than mild in most tumor cells and misinterpreted as an overexpression mutated type of expression instead of a wild-type expression.

It should also be noted that, from a practical point of view, p53 immunohistochemistry and *TP53* sequencing have a central role in endometrial cancer pathology, and

pathologists and clinicians should be able to interpret these results, as presented herein. However, from a biological point of view, the role of p53 extends beyond its immunohistochemical expression or its mutations, since p53 has at least twelve isoforms that can independently change p53 activity, even in *TP53* wild-type tumors [35]. Thus, the final result of the p53 function depends on several factors, including the mutational status, allele dominance, protein isoforms, post-translation modifications, and stability of the protein [35]. A study of 37 patients with endometrial serous carcinoma by quantitative real-time PCR of mRNA for different p53 isoforms showed that the gamma isoform was associated with worse progression-free survival [36]. Another isoform, the Δ133p53, was found to have some prognostic significance in ovarian cancer patients [37]. However, the role of p53 isoforms specifically in endometrial cancer has been rarely studied, and relevant future research could be of interest.

4. Conclusions

Concordance between p53 immunohistochemistry and *TP53* mutational status is high. The discordance rate in the literature is about 8%. However, after excluding the other molecular subtypes, where p53 abnormality is not important, and after reviewing case-by-case, this discordance is 3.5%. That means that, first, a strict interpretation of p53 immunohistochemistry/*TP53* variants should be applied (Figure 9). Repeating these techniques on a different bloc could also be useful. If, after assuring this interpretation, there is still a discordance between immunohistochemistry and molecular analysis, in an otherwise non-*POLE*mut/MMRd tumor, this tumor should be regarded as p53/*TP53* abnormal. This will have major consequences especially in an otherwise-low-risk endometrial cancer patient, and discussion in a multi-disciplinary approach is necessary to decide whether adjuvant therapy should be applied in these patients.

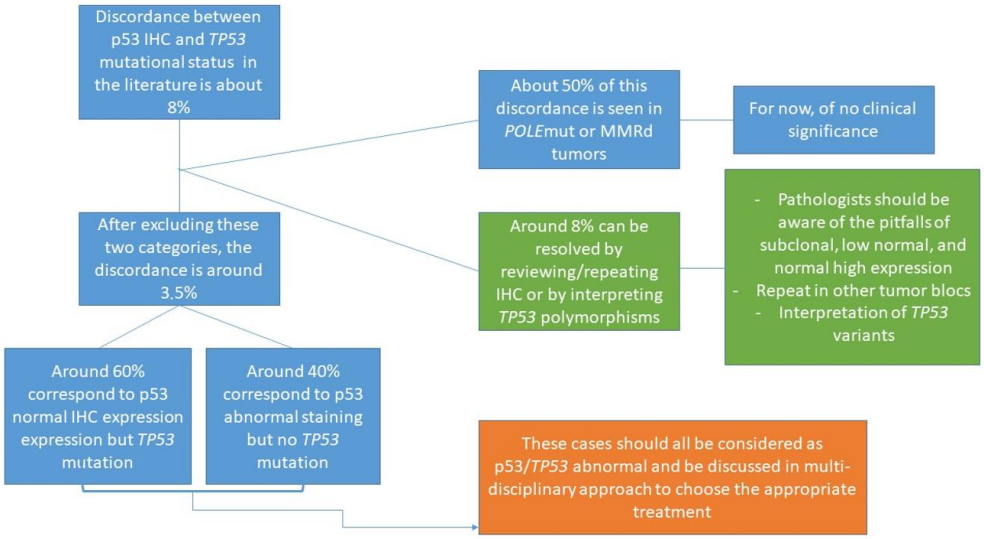


Figure 9. How we can proceed with p53/*TP53* discordance in routine practice (*note IHC = immunohistochemistry*).

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