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POLISH GYNECOLOGY
GINEKOLOGIA POLSKA
ORGAN POLSKIEGO TOWARZYSTWA GINEKOLOGICZNEGO
THE OFFICIAL JOURNAL OF THE POLISH GYNECOLOGICAL SOCIETY

ISSN: 0017-0011

e-ISSN: 2543-6767

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DOI: 10.5603/gpl.101983

Article type: Research paper

Submitted: 2024-08-07

Accepted: 2025-01-05

Published online: 2025-02-15

Articles in "Ginekologia Polska" are listed in PubMed.

ORIGINAL PAPER / GYNECOLOGY

The impact of mismatch repair (MMR), p53, and LCAM-1 immunohistochemical expression on prognosis in low-risk endometrial cancer

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ABSTRACT

Objectives: To investigate the relationship between mismatch repair (MMR) deficiency, *TP53*, and L1 cell adhesion molecule (L1CAM) immunohistochemical staining and their impact on progression-free survival (PFS) and overall survival (OS) in low-risk endometrial cancer.

Material and methods: A total of 253 low-risk endometrial cancer patients were retrospectively screened. Immunohistochemical stains were applied to tumor tissue samples to assess MMR deficiency, *TP53*, and L1CAM expression, and survival analysis were performed.

Results: The expected PFS time was 78.6 months for the MMR-proficient group and 70.3 months for the MMR-deficient group (p = 0.011). OS was 71.6 months for the MMR-proficient group and 68.2 months for the MMR-deficient group (p = 0.755). L1CAM overexpression was associated with a poorer PFS, 62.7 months compared to 77.7 months (p = 0.039). However, there was no statistically significant difference in OS, 58.5 months versus 72.1 months, respectively (p = 0.242). p53 abnormal (p53-abn) staining was associated with a worse prognosis in terms of PFS, 62.8 months versus 77.7 months (p = 0.035), and OS, 43.4 months versus 73 months, respectively (p < 0.001), compared to patients with wild-type staining.

No significant statistical relationship was observed in survival times concerning tumor diameter, grade, and lymphadenectomy status. In a multivariate analysis, MMR deficiency emerged as an independent poor prognostic factor for PFS, while p53-abn was identified as an independent poor prognostic factor for OS.

Conclusions: p53-abn staining was associated with a poor prognosis for both PFS and OS in low-risk endometrial cancer patients. Meanwhile, MMR deficiency and L1CAM positivity were found to be associated solely with a poorer prognosis for PFS.

Keywords: low-risk endometrial cancer, mismatch repair, *TP53*, L1CAM

INTRODUCTION

Patients with endometrial cancer are typically diagnosed through surgery following preoperative biopsy and imaging. Subsequent adjuvant treatment is determined based on their relapse risk classification. The low-risk category includes patients with grade 1 or 2 endometrioid-type tumors confined to the uterus, with less than half myometrial invasion and minimal or no lymphovascular invasion. These patients generally have a high life expectancy and long disease-free survival, and adjuvant therapy (radiotherapy or chemotherapy) is often unnecessary [1]. Although early-stage endometrial cancer is reportedly associated with survival rates of 85% to 95%, there remains a slight risk of recurrence, and the therapeutic success rates of approximately 40% can negatively impact overall survival (OS) [2–5].

The growing use of molecular classification in clinical practice has enhanced clinicians' understanding of why some patients with low-risk endometrial cancer develop relapse. According to this classification, the low-risk group may include subcategories such as *POLE*-

mutated, mismatch repair (MMR)-deficient, *TP53*-mutated, and those with a nonspecific molecular profile, each at varying rates [6, 7]. However, routine molecular profiling for every patient can be expensive. While next-generation sequencing offers detailed insights, immunohistochemical (IHC) studies are a more cost-effective alternative. The Proactive Molecular Risk classification tool for Endometrial cancers (ProMisE) reduces costs by using IHC staining for MMR and *TP53*, while still providing comparable survival data [7].

TP53 regulates the cell cycle, DNA repair, apoptosis, and senescence in response to cellular stress. Loss of p53 function allows cells with genomic damage to survive and divide, promoting tumor formation and progression [8].
The MMR system identifies and repairs DNA replication errors, such as base mismatches and small insertions or deletions, that occur during cell division. MMR is essential for maintaining genome stability. Defects in MMR genes (*e.g.*, *MLH1*, *MSH2*, *MSH6*, and *PMS2*) are associated with microsatellite instability and can lead to colorectal and endometrial cancer [9]. L1 cell adhesion molecule (L1CAM) is a cell adhesion molecule that plays a key role in cell–cell interactions, epithelial-to-mesenchymal transition, and cellular migration. Overexpression of L1CAM is associated with a poor prognosis in patients with endometrial cancer [10–13]. The use of IHC biomarkers such as *TP53*, MMR, L1CAM, estrogen, and progesterone receptors provides useful information in terms of the necessity of adjuvant therapy [14]. Molecular analysis from the PORTEC-3 trial revealed a statistically significant survival benefit for stage I–III endometrial carcinomas with abnormal p53 expression (p53-abn) when treated with combined chemoradiotherapy [15]. However, no clear advantage was observed for MMR-deficient tumors. These tumors are more responsive to immune checkpoint inhibitors due to their high mutational burden and increased production of neoantigens [16]. Although L1CAM expression is associated with a poor prognosis, further research on its impact in low-risk patients is needed.

Studies focused on patients with low-risk endometrial cancer, who typically do not receive adjuvant therapy, are particularly valuable for accurately assessing the prognosis [17]. The present study was designed to evaluate the prognostic value of the IHC markers MMR, *TP53*, and L1CAM in women with low-risk endometrial cancer, in whom the influence of possible confounding factors is minimal.

MATERIAL AND METHODS

Study population

This study involved patients with low-risk endometrial cancer who underwent surgery between January 2017 and December 2022 at Kocaeli University Hospital. The patients were retrospectively screened following approval from the ethics committee of Kocaeli University (Approval number: GOKAEK-2022/23.22). Patients with endometrioid-type endometrial cancers, invasion limited to less than half of the myometrium, grades 1 and 2, and no lymphovascular invasion were included in the study population.

The exclusion criteria were non-endometrioid tumor types (*e.g.*, serous, clear cell), grade 3 tumors, myometrial invasion exceeding half of the myometrium, neoadjuvant chemotherapy or radiation therapy, adjuvant chemotherapy or radiation therapy, concomitant malignancies, and loss to follow-up.

For follow-up, patients were scheduled for physical examinations four times during the first 2 years, twice a year for the next 3 years, and annually thereafter. If recurrence was suspected, further evaluations included serum Ca-125 level monitoring and advanced imaging techniques such as magnetic resonance imaging and positron emission tomography scans. Progression-free survival (PFS) was defined as the time from surgery to the occurrence of recurrence or disease progression. OS was defined as the time from surgery to death, with each death considered an event.

IHC analysis

Four-micrometer sections were prepared from paraffin-embedded, formalin-fixed tissue blocks for each patient. Hematoxylin- and eosin-stained sections were used for histological examination, which was conducted by two experienced pathologists. IHC staining was performed using the following markers: MSH2 (G219-11229, 1:50 dilution; Ventana Medical Systems, Tucson, AZ, USA), MSH6 (SP93, 1:200 dilution; Ventana Medical Systems), PMS2 (A16-4, 1:200 dilution; Ventana Medical Systems), MLH1 (M1, 1:200 dilution; Ventana Medical Systems), *TP53* (DO-7, 1:1000 dilution; DAKO, Glostrup, Denmark), and L1CAM (14.10, 1:100 dilution; BioLegend, San Diego, CA, USA).

MMR deficiency was defined as the complete absence of nuclear staining for at least one MMR protein. L1CAM was considered positive if ≥ 10% of the tumor cells exhibited staining

[11]. *TP53* staining was classified as abnormal (p53-abn) in two scenarios: overexpression, referred to as the “all-type” phenotype, or complete absence of expression, referred to as the “null-type” phenotype.

Statistical analysis

All statistical analyses were conducted using SPSS 20.0 (IBM Corp., Armonk, NY, USA). The assumption of normality was assessed using the Kolmogorov–Smirnov and Shapiro–Wilk tests. Continuous variables, presented as median (interquartile range), were used because of the non-normal distribution of the data. Categorical variables were summarized as counts and percentages. The Mann–Whitney U test was employed to compare continuous variables between groups, and the chi-square test was used to examine associations between categorical variables. Kaplan–Meier survival analysis with the log-rank test was applied, and multivariate analysis was performed using Cox regression analysis. A p value < 0.05 was considered statistically significant.

RESULTS

The study enrolled a total of 253 patients with low-risk endometrial cancer for whom both survival data and pathological specimens were accessible. The clinical and pathological characteristics of these patients are summarized in Table 1. The median follow-up time was 38 months. The median PFS was 77.5 months, and the median OS was 71.9 months. Survival analyses for both PFS and OS are presented in Figures 1 and 2.

Of the 253 patients, 72 (28.5%) were found to have at least one MMR deficiency. The distribution of MMR deficiencies was as follows: 20 (7.9%) patients with MSH2 deficiency, 11 (4.3%) with MSH6 deficiency, 56 (22.1%) with MLH1 deficiency, and 52 (20.6%) with PMS2 deficiency. Among the MMR-deficient group, there were four (5.6%) relapses, while in the MMR-proficient group, there was only one (0.5%) relapse. The expected PFS was 78.6 ± 0.3 months (95% CI: 77.8–79.3) in the MMR-proficient group and 70.3 ± 1.7 months (95% CI: 66.8–73.8) in the MMR-deficient group ($p = 0.011$).

In terms of OS, there were 6 (8.3%) deaths in the MMR-deficient group, whereas 18 (9.9%) deaths occurred in the MMR-proficient group ($p = 0.875$). The expected OS was 71.6 ± 1.6

months (95% CI: 68.4–74.8) in the MMR-proficient group and 68.2 ± 2.2 months (95% CI: 63.8–72.5) in the MMR-deficient group (p = 0.755).

In the multivariate analysis, MMR deficiency was identified as an independent poor prognostic factor for PFS (HR: 20.654; 95% CI: 1.738–245.475; p = 0.017) (Tab. 2).

Nine (3.6%) patients exhibited p53-abn staining, while the remaining patients had wild-type p53 expression. Among the patients with p53 wild-type expression, four (1.6%) relapses were observed, while in patients with p53-abn staining, one (11.1%) relapse occurred. The expected PFS was 77.7 ± 0.6 months (95% CI: 76.5–78.9) for p53 wild-type patients and 62.8 ± 6.6 (95% CI: 49.8–75.9) for those with p53-abn staining (p = 0.035).

In terms of OS, 19 (7.8%) deaths occurred in the p53 wild-type group, while five (55.6%) deaths occurred in the p53-abn group. The expected OS was 73 ± 1.3 months (95% CI: 70.5–75.5) for p53 wild-type patients and 43.4 ± 8.7 months (95% CI: 26.2–60.6) for those with p53-abn staining (p < 0.001). In the multivariate analysis, p53-abn staining was identified as an independent poor prognostic factor for OS (HR: 7.342; 95% CI: 2.615–20.612; p < 0.001) (Tab. 3).

L1CAM staining was positive in 12 (4.7%) patients. Among the L1CAM-negative group, four (1.7%) relapses occurred, while the L1CAM-positive group had one (8.3%) relapse. The expected PFS was 77.7 ± 0.6 months (95% CI: 76.5–78.9) for L1CAM-negative patients and 62.7 ± 5.8 months (95% CI: 51.2–74.2) for L1CAM-positive patients (p = 0.039).

In the L1CAM-negative group, 22 (9.1%) deaths occurred, while 2 (16.7%) deaths were observed in the L1CAM-positive group. The expected OS was 72.1 ± 1.3 months (95% CI: 69.5–74.8) in the L1CAM-negative group and 58.5 ± 6.7 months (95% CI: 45.3–71.7) in the L1CAM-positive group (p = 0.242).

For Grade 1 patients, the PFS was 78 ± 0.6 months (95% CI: 76.7–79.3), while for Grade 2 patients, the PFS was 73.8 ± 1.2 months (95% CI: 71.4–76.2). However, the difference in PFS between Grade 1 and Grade 2 patients was not statistically significant (p = 0.307).

In terms of OS, Grade 1 patients had an OS of 70.7 ± 1.7 months (95% CI: 67.2–74.2), while Grade 2 patients had an OS of 71.3 ± 1.8 months (95% CI: 67.7–74.9). Similarly, no statistically significant difference in OS was observed between Grade 1 and Grade 2 patients (p = 0.273).

No relapses were observed in patients with a tumor diameter of ≤ 2 cm, whereas five relapses occurred in patients with tumors of >2 cm (p = 0.143). Patients with a tumor diameter of ≤ 2 cm had an OS of 73.4 ± 1.7 months (95% CI: 69.9–76.8), while those with tumors of > 2 cm had an OS of 70.4 ± 1.7 months (95% CI: 66.9–73.9). However, this difference in OS between the two groups was not statistically significant (p = 0.115).

From the perspective of the lymphadenectomy status, no relapses were observed in patients who had never undergone lymphadenectomy. There were four relapses in patients who had undergone only pelvic lymphadenectomy, and one relapse was observed in those who had undergone both pelvic and paraaortic lymphadenectomy. When comparing groups based on lymphadenectomy status—pelvic lymphadenectomy versus no lymphadenectomy (p = 0.335), pelvic and paraaortic lymphadenectomy versus no lymphadenectomy (p = 0.450), and pelvic and paraaortic lymphadenectomy versus pelvic lymphadenectomy (p = 0.522) — no significant statistical differences were found in terms of PFS.

The expected OS in patients who had never undergone lymphadenectomy, those who underwent pelvic lymphadenectomy, and those who underwent pelvic and paraaortic lymphadenectomy were 68.9 ± 2.0 months (95% CI: 64.8–73), 70.8 ± 1.9 months (95% CI: 67–74.7) (p = 0.402), and 69.7 ± 2.2 months (95% CI: 65.3–74.1) (p = 0.563), respectively. Similarly, no significant differences in OS were observed between patients who underwent pelvic lymphadenectomy and those who underwent pelvic and paraaortic lymphadenectomy (p = 0.667).

DISCUSSION

Molecular classification and potential cost-effective alternatives, such as ProMisE, have introduced repeatable innovations in the prognostication of endometrial cancer compared with classical histopathological classification. However, relapses, albeit rare, may still occur in low-risk groups. Although IHC studies involving *TP53*, MMR, and L1CAM in early-stage endometrial cancers have been documented in the literature, these studies often include heterogeneous patient groups, such as those with non-endometrioid histologies, Grade 3 tumors, lymphovascular invasion, and those who received adjuvant therapy. Adjuvant therapy may obscure whether MMR deficiency is prognostic or predictive of outcomes [18].

In a population-based study involving 475 patients with endometrioid endometrial cancers, those with MMR deficiency exhibited worse PFS than those with MMR-proficient tumors (median of 24 vs. 27 months, respectively) [17]. Multivariate analysis further revealed that MMR deficiency was associated with a higher risk of relapses. However, no significant difference in OS was observed between the MMR groups. A key aspect of this study was the inclusion of 42 (8.8%) patients with lymphovascular invasion and 30 (6.3%) patients who received adjuvant therapy. In the subgroup of patients without lymphovascular invasion and who did not receive adjuvant therapy, a similar relationship between MMR deficiency and recurrence could not be demonstrated ($p = 0.16$). Additionally, because the lymphadenectomy rate in this study was only 9%, some tumors may have been under-staged.

Stasenko et al. [19] conducted a refined study on ultra-low-risk patients and found no statistically significant difference in recurrence rates between those with and without MMR deficiency. Conversely, a case-control study involving 311 patients with Grade 1 endometrioid endometrial cancer revealed a significantly higher prevalence of MMR deficiency in the relapse group than in the control group [20].

The present study identified MMR deficiency as a worse prognostic factor for PFS and an independent poor prognostic factor for PFS in the multivariate analysis. Moreover, in an earlier study focusing on the low-risk group, we found that MMR deficiency was associated with ovarian metastasis and synchronous gonadal involvement [21].

In studies that included patients from all endometrial cancer risk groups, p53-abn was significantly associated with higher risk classifications and poorer outcomes [22, 23]. Two studies specifically evaluating p53-abn in low-risk endometrial cancer reported no significant differences in PFS or OS [19, 20]. By contrast, the current study found a clear association between p53-abn and worse PFS and OS, identifying it as an independent poor prognostic factor for OS.

L1CAM expression has been shown to be an independent predictor of both PFS and OS in patients with endometrial cancer. Zeimet et al. [12] conducted a study of 657 patients with low-grade endometrial cancer, finding L1CAM positivity in 17% of cases. L1CAM was strongly associated with an increased risk of death (HR: 15.00) and recurrence (HR: 16.33). Additionally, L1CAM staining in tissues from the PORTEC-1 and PORTEC-2 study cohorts confirmed a higher incidence of distant and pelvic nodal recurrence in L1CAM-positive patients [10]. In patients with L1CAM positivity, the risk of distant recurrence increased by a

factor of 3.5, while OS decreased by a factor of 2.1. However, in this study, only 26.9% of the patients were classified as low-risk, and 72.6% of the patients received adjuvant therapy, which may have influenced the outcomes.

In a separate study analyzing TCGA data on uterine cancer, L1CAM was identified as an independent prognostic factor for OS [11]. However, the authors could not confirm a worse effect on survival in Stage I subpopulation. In a large study involving 1,199 patients with endometrial cancer, L1CAM expression was linked to poor outcomes even in stage I cancers [13]. Kommos et al. [24] reported significantly worse PFS (71.8% vs 100%, $p < 0.0001$) and OS (63.8% vs 95.3%, $p < 0.0001$) in L1CAM-positive patients. The study identified L1CAM as an independent prognostic factor in low-risk endometrial cancer and recommended revising the ESGO risk classification to consider only L1CAM-negative patients as low-risk.

A common criticism of these studies is the inclusion of heterogeneous patient groups and the use of adjuvant therapy, which may affect the findings. More specifically, a meta-analysis evaluating patients with stage I endometrial cancer and L1CAM positivity reported worse PFS (HR: 4.11) and OS: (HR 3.62) in L1CAM-positive patients [25]. Notably, only one of the five studies included in this review focused exclusively on pure endometrioid endometrial cancer patients, and even that study included patients with Grade 3 tumors.

In terms of survival, we found no significant differences related to grade, tumor diameter, or lymph node status. These findings are consistent with similar studies in the literature, which also reported no significant association between tumor diameter and survival in early-stage endometrial cancers [26, 27].

The strengths of this study lie in its exclusive focus on low-risk patients, the exclusion of adjuvant therapy that could influence prognosis, and the simultaneous evaluation of all MMR subgroups, *TP53*, and L1CAM IHC prognostic markers. This approach ensures a more precise assessment of the independent prognostic value of these markers in a homogeneous patient population.

The lack of *POLE* analysis can be considered a limitation of the study. However, because PFS and OS are generally good in patients with *POLE* mutation, our study aimed to decipher the relationship between relapse and death using only IHC markers. Other limitations include its retrospective design and the relatively small patient cohort because it was a single-center study.

In conclusion, p53-abn staining was associated with poor PFS and OS in patients with low-risk endometrial cancer, while MMR deficiency and L1CAM positivity were found to be associated solely with poorer PFS.

Article information and declarations

Ethics statement

Ethics committee of Kocaeli University (Approval number: GOKAEK-2022/23.22).

Author contrıbutıons

Ş.G. and B.Y.B. performed the protocol design, and implementation and drafted the manuscript. M.E. and E.B.T. contributed to data analysis, critical revision of the manuscript and final approval.

Fundıng

This study was supported by the Kocaeli University Scientific Research Projects Coordination Unit (Project Num: TSA-2022-2893).

Acknowledgments

None.

Conflıcts of ınterest

The authors have no conflicts of interest to disclose.

Supplementary material

None.

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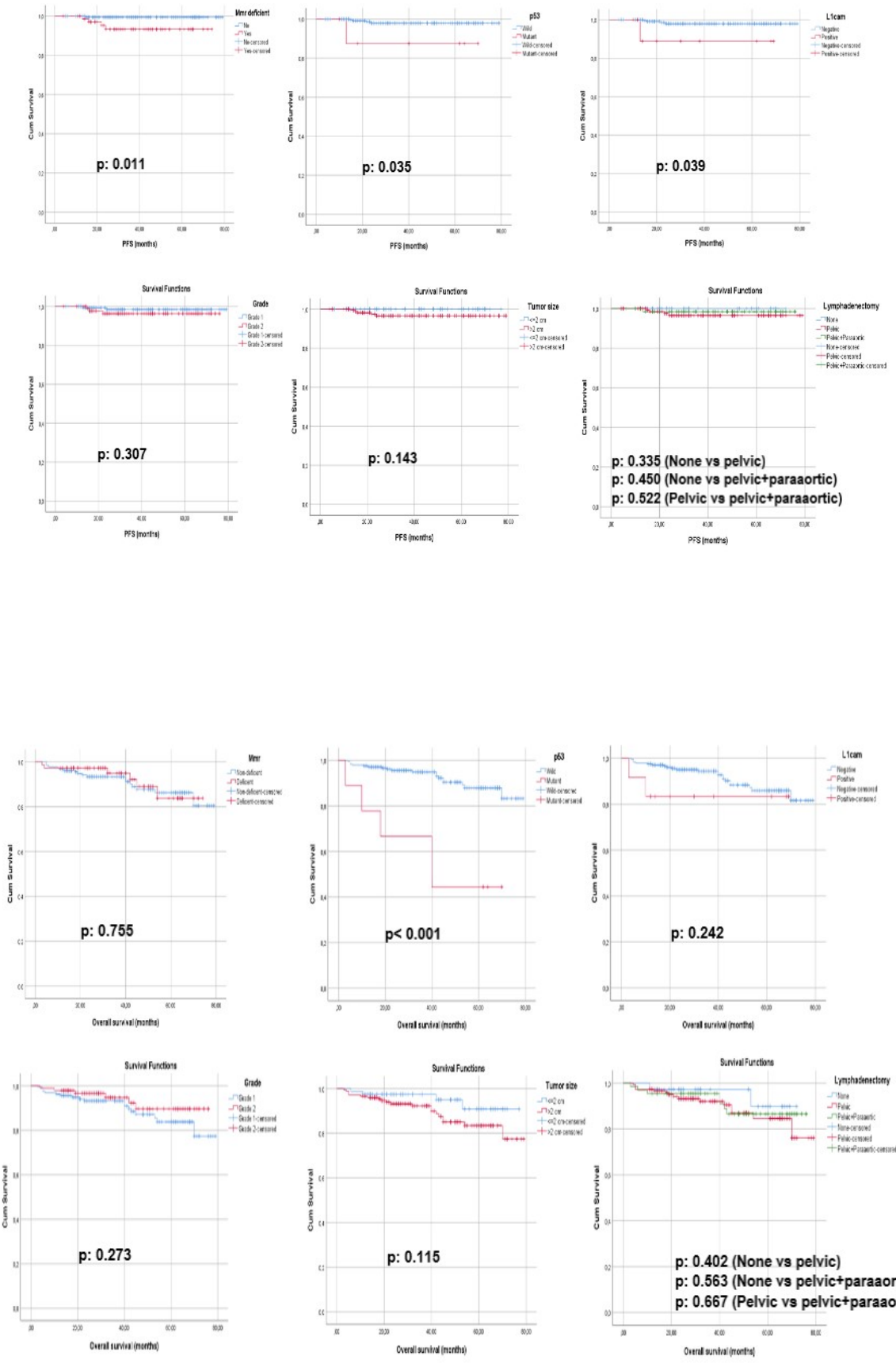

Table 1. The demographic and clinical characteristics of the patients

Variable	n = 253
Age	58 (53–64)
Age	
< 60	145 (52.3%)
≥ 60	108 (42.7%)
Gravida	3 (2–5)
Parity	3 (2–4)
Body mass index (BMI)	33 (30–37)
BMI	
< 30	60 (23.7%)
≥ 30	193 (76.3%)
Menopausal status	
Premenopause	64 (25.3%)
Postmenopause	189 (74.7%)
Systemic disease	
Hypertension	149 (58.9%)
Diabetes	94 (37.2%)
Grade	
Ⅰ	160 (63.2%)
Ⅱ	93 (36.8%)
Tumor diameter (cm)	3 (2–4)
Tumor diameter	
≤ 2 cm	78 (30.8%)
> 2 cm	175 (69.2%)
Lymphadenectomy status	
None	37 (14.6%)
Pelvic	150 (59.3%)
Pelvic and paraaortic	66 (26.1%)
Pelvic lymph node count	19 (13–26)
Paraaortic lymph node count	5 (2–8)
Total lymph node count	20 (14–26)

Numerical variables that do not correspond to the normal distribution are shown as Median (25.–75. percentile) and the categorical variables are shown as n (%)

Table 2. Factors associated with progression-free survival (PFS) (n = 253)

	Univariate analysis			Multivariate analysis		
	HR	95% CI	p	HR	95% CI	p

Gravida	0.720	0.449–1.153	0.171	0.850	0.583–1.240	0.400
Hypertension	0.184	0.021–1.643	0.130	0.207	0.019–2.300	0.200
Pelvik lymph node count	0.908	0.803–1.027	0.125	1.654	0.275–9.961	0.583
Total lymph node count	0.908	0.810–1.018	0.099	0.496	0.080–3.076	0.452
Mmr deficient	9.943	1.111–88.971	**0.040 ***	20.654	1.738–245.475	**0.017 ***
p53-abn	7.407	0.828–66.289	0.073	14.357	0.960–214.754	0.054

Variables with a p value below 0.2 were included in the univariate analysis, *: $p < 0.05$

p53-abn: overexpressed ("all type" phenotype) or totally unexpressed of *TP53* ("null type" phenotype) with Immunohistochemical analysis.

Table 3. Factors associated with overall survival (OS) (n = 253)

	Univariate analysis			Multivariate analysis		
	HR	95% CI	p	HR	95% CI	p
Age ≥ 60	3.114	1.328–7.304	**0.009***	1.813	0.656–5.005	0.251
Gravida	1.124	1.012–1.249	**0.029***	0.974	0.707–1.348	0.875
Parity	1.188	1.050–1.346	**0.006***	1.111	0.730–1.691	0.623
Hypertension	5.580	1.661–18.750	**0.005***	2.798	0.744–10.520	0.128
Diabetes	2.979	1.318–6.736	**0.009***	1.908	0.794–4.585	0.148
Tumor size ≥ 2 cm	2.311	0.790–6.763	0.126	1.396	0.455–4.285	0.559
p53-abn	6.852	2.549-18.418	< **0.001***	7.342	2.615–20.612	< **0.001***

Variables with a p value below 0.2 were included in the univariate analysis, *: $p < 0.05$

p53-abn: overexpressed ("all type" phenotype) or totally unexpressed of *TP53* ("null type" phenotype) with Immunohistochemical analysis