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P53 and MMR IHC assessment in D&C samples in patients with uterine cancer. Does it reliably capture their status compared to hysterectomy matched specimens analysis? Could early knowledge guide treatment decisions?

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Abstract

Purpose: International guidelines strongly suggest assessment of POLe, MMR, p53 in patients with early stage endometrial cancer. MMR and p53 are commonly assessed with IHC after hysterectomy (+/-BSO). The main objective of this analysis is to test for the concordance of P53 and MMR status in D&C and hysterectomy matched samples, suggesting that a reliable determination in D&C samples may drive surgical treatment modalities and fertility sparing decision. A secondary objective of the analysis is to test whether there is association between the P53 or the MMR status at the D&C specimens with the depth of invasion or the LVSI status.

Methods: In this single center study 73 matched D&C and hysterectomy samples in patients with clinically early stage endometrial cancer were collected and p53 and MMR status was assessed with IHC. Samples were obtained by gynaecologists and gynaecological oncologists and independently assessed by two expert in gynaecological oncology pathologists at REA hospital (Athens-Greece). Immunohistochemistry was performed using Ventana Benchmark Ultra. P53 was grouped in two mutually exclusive groups, that is mutant or wild type. Similarly, MMR status was grouped in two mutually exclusive groups, that is pMMR and dMMR To determine MMR status, sections were scored visually for loss or intact expression of the proteins MSH6, MSH2, MLH1 and PMS2.

Results: There was a 100% accordance between p53 assessment in D&C and hysterectomy specimens. Discrepancy in MMR result was observed only in 1 case which stained negative for MLH1 in D&C but positive in hysterectomy, yielding an accordance of 98,6% between D&C and hysterectomy specimens. Absolute accordance in histology and grade characterization was observed in all matched specimens. No association was found between p53 and MMR status with LVSI and depth of myometrial invasion.

Conclusions: p53 & MMR status can be accurately assessed with IHC in D&C samples. Repeat assessment after hysterectomy may not be necessary. Early knowledge of the molecular imprint of the disease on D&C samples may drive treatment decisions regarding surgical procedures, fertility preservation and further treatment plans.

Keywords: Uterine cancer; P53; MMR

Background

International guidelines strongly suggest assessment of POLe, MMR, p53 in

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patients with early stage endometrial cancer [1,2] according to the molecular classification system based on The Cancer Genome Atlas genomic subgroups [3].

The Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE) project developed a hierarchical pathway of molecular testing starting with an NGS based POLe assessment. If POLe turns to be wild type, a IHC MMR testing should be followed. If all 4 proteins PMS2, MLH1, MSH2, MSH6 are expressed suggestive of pMMR then testing is completed with IHC p53 assessment [4].

It is however speculated that in low resource countries, POLe assessment may not be feasible due to NGS dependent testing. Moreover, many national authorities -Greece included- and private insurance companies still do not reimburse NGS-POLe testing.

Early knowledge of p53 and MMR status may drive the selection of the appropriate surgical modality and may have an impact on fertility preservation decision. Talhouk et al [5] reported a high concordance of molecular classification rate between diagnostic samples and final hysterectomy specimens, whereas other authors support that hysteroscopy guided biopsy offers a more representative sample in the diagnosis of endometrial cancer [6].

In this study, we prospectively assessed p53 and MMR with ICH in matched D&C and hysterectomy specimens of patients with early endometrial cancer. The main objective of this analysis was to test for the concordance of P53 and MMR status in D&C and hysterectomy matched samples. A secondary objective of the analysis was to test whether there was association between the P53 or the MMR status at the D&C specimens with the depth of invasion or the LVSI status.

Patients, Materials and Methods

In this single center study 73 matched D&C and hysterectomy specimens in patients with clinically early stage endometrial cancer according to FIGO staging 2009 system were collected [7]. Dilation and curettage were obtained by both trained gynaecologists and gynaecological oncologists, whereas curative surgeries (hysterectomy with or without bilateral salpingo-oophorectomy and sentinel lymph node assessment or lymph node dissection) were performed only by certified gynaecological oncologists at REA hospital in Athens, Greece. The study was carried out within January 1st -December 1st 2023.

Tissues including endometrial curettage and hysterectomy specimens fixed in 10% buffered formalin and processed as previously described.

P53 was grouped in two mutually exclusive groups, that is mutant or wild type. Similarly, MMR status was grouped in two mutually exclusive groups, that is pMMR and dMMR. Immunohistochemistry was performed using Ventana Benchmark Ultra and sections 4 μm thick were incubated with the following antibodies: anti-MSH6 rabbit primary antibody (clone SP93, Ventana Roche), anti-PMS2 monoclonal mouse antibody (clone A16-4, , Ventana Roche), anti-MLH1 monoclonal mouse antibody (clone M1, Ventana Roche) and anti-MSH2 monoclonal mouse primary antibody (G219-1129, Ventana Roche). All sections were counterstained with Hematoxylin II (Ventana) before dehydration and mounting.

To determine MMR status, sections were scored visually for loss or intact expression of the MMR proteins: MSH6, MSH2, MLH1 and PMS2.

Positive staining was evaluated as unequivocal nuclear staining in viable tumor cells in the presence of internal positive controls (lymphocytes, fibroblasts, or normal epithelium) in the vicinity of the tumor cells.

Those cases where the loss of one or all proteins was observed were categorized as MMR-deficient, while retained MMR proteins were considered MMR-proficient.

In particular, the interpretation of immunostaining for each protein is classified as: (i) “retained,” when ≥10% of tumor cells show a moderate to strong expression; (ii) “loss,” when no evidence of nuclear expression is seen in cancer cells; (iii) “indeterminate,” if IHC staining in tumor cells is less intense compared to the internal control or expression is retained in <10% of neoplastic cells. If, however, the presence of “indeterminate” immunostaining in one or more proteins is coupled with a convincing loss of expression in at least one protein, the tumor should be interpreted as “dMMR” tumor.

Tumor histology, grade, p53 and MMR were independently assessed by two expert in gynaecological oncology pathologists.

The McNemar test was used to determine if there are differences on the dichotomous dependent variables between the two related groups at the pre-post matched samples design. Fisher exact test was used to determine the relationship between two independent dichotomous variables. Data analysis was performed in SPSS software at a significance level of a=5%.

Results

73 patients with early-stage endometrial cancer participated in the study. Median age was 62,5 years (range 42 – 86). Endometrioid was the most frequent histology with 69 out of the 73 cases (95,8%). Among endometrioid, grade 1 carcinomas were observed in 62 cases (89,8%), grade 2 in 6 (8,7%) and grade 1 in one case (1,4%) respectively. Three out of the 73 cases were diagnosed with serous carcinoma (4,1%) and one case was diagnosed with undifferentiated carcinoma (1,3%). Importantly, absolute accordance in histology and grade characterization was observed in all matched D&C and hysterectomy specimens (Table 1).

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In D&C samples, P53 was mutant in 12 patients (16.4%) and wild type in 61 patients (83.6%). Similarly in hysterectomy, P53 was mutant in 12 patients (16.4%) and wild type in 61 patients (83.6%). Table 2 shows the cross-tabulated data for the paired samples pre and post the hysterectomy intervention. A 100% accordance in P53 status between D&C and hysterectomy was recorded. Mc Nemar's test p-value was 1.000, suggesting no intervention effect on the P53 status.

In D&C samples, MMR was characterized pMMR in 46 patients (63.0%) and dMMR in 27 patients (37.0%). Similarly in hysterectomy specimens, MMR was characterized pMMR in 47 patients (64.4%) and dMMR in 26 patients (35.6%). This difference was attributed to a case staining MLH1 negative in D&C but positive in hysterectomy. Table 3 shows the cross-tabulated data for the paired samples pre and post the hysterectomy intervention. A 98.6% accordance in MMR status between D&C and hysterectomy was recorded. Mc Nemar's test p-value was 1.000, suggesting no intervention effect on the MMR status.

Deep invasion of the myometrium (defined as half or more of the myometrium) was found in 23 patients (31.5%). Less than half of the myometrium invasion was found in 50 patients (68.5%). Table 4 shows the cross-tabulated data of the depth of invasion and the P53 status in D&C samples. Four (33.3%) of the mutant P53 cases had high depth of invasion versus 19 of the wild type P53 cases (31.1%). No significant association between the two factors was detected (p-value=1.000) suggesting no relationship of P53 and depth of invasion.

Table 1: Comparison of results according to the type of pathology specimen

	Dilatation & Curretage (no)	Surgery (no)	Accordance %
Endometrioid grade 1	62	62	100%
Endometrioid grade 2	6	6	100%
Endometrioid grade 3	1	1	100%
Serous	3	3	100%

Table 2: P53 status in D&C and hysterectomy

P53 status	D&C	Hysterectomy
Mutant	12 (16.4%)	0 (0%)
Wild type	0 (0%)	61 (83.6%)

Table 3: MMR status in D&C and hysterectomy

MMR status	D&C	Hysterectomy
pMMR	46 (63.0%)	0 (0%)
dMMR	1 (1.4%)	26 (35.6%)

Table 4: P53 status at D&C and depth of invasion

P53 status	Deep myometrium Invasion (Yes)	Deep myometrium Invasion (No)	Total
Mutant	4 (33.3%)	8 (66.7%)	12 (100%)
Wild type	19 (31.1%)	42 (68.9%)	61 (100%)

Table 5: P53 status at D&C and LVSI

P53 status	LVSI (Yes)	LVSI (No)	Total
Mutant	6 (50.0%)	6 (50.0%)	12 (100%)
Wild type	16 (26.2%)	45 (73.8%)	61 (100%)

Table 6: MMR status at D&C and depth of invasion

MMR status	Depth of Invasion (Yes)	Depth of Invasion (No)	Total
pMMR	13 (28.3%)	33 (71.7%)	46 (100%)
dMMR	10 (37.0%)	17 (63.0%)	27 (100%)

Table 7: MMR tatus at D&C and LVSI

MMR status	LVSI (Yes)	LVSI (No)	Total
pMMR	11 (23.9%)	35 (76.1%)	46 (100%)
dMMR	11 (40.7%)	16 (59.3%)	27 (100%)

High LVSI was measured for 22 patients (30.1%) and low for 51 patients (69.9%).

The following Table 5 shows the cross-tabulated data of LVSI and the P53 status at the D&C stage. Six (50.0%) of the mutant P53 cases had high LVSI versus 16 of the wild type P53 cases (26.2%). No significant association between the two factors was detected (p-value=0.165) at the significance level of a=5% suggesting no relationship of P53 and LVSI.

Thirteen (28.3%) of the pMMR cases had high depth of invasion versus 10 of the dMMR cases (37.0%). Table 6 shows the cross-tabulated data of the depth of invasion and the MMR status in the D&C specimens. No significant association between the two factors was detected (p-value=0.448) suggesting no relationship of MMR and depth of invasion.

Eleven (23.9%) of the pMMR cases had high LVSI versus 11 of the dMMR cases (40.7%). The following table 7 shows the cross-tabulated data of LVSI and the MMR status in the D&C specimens. No significant association between the two factors was detected (p-value=0.187) at the significance level of a=5% suggesting no relationship of MMR and LVSI.

Discussion

The molecular characterization of endometrial cancer is of paramount importance, a fact which has been reflected in the newer 2023 FIGO staging system which includes the molecular imprint of the tumor and provides more accurate prognostication [2].

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Despite the lack of prospective randomized trials based on the molecular characterization in the early stage setting, PORTEC-3 trial provided valuable information on the prognosis of patients with high risk disease treated with adjuvant radiotherapy or chemo-radiotherapy. Particularly, it showed a substantial relapse free survival benefit with the addition of chemotherapy to radiotherapy in patients with p53 mutation and an excellent outcome for the POLe ultramutation group, regardless chemotherapy was administered or not [8]. RAINBO is an ongoing study designed to offer tailored to the molecular imprint treatment and is expected to shed light on the impact of the personalized treatment in early stage endometrial cancer [9]. In the metastatic disease the presence of dMMR-MSI-H has proved to be strong biomarker of response to immune checkpoint inhibitors. Numerous randomized double-blind trials studying the role of different immune checkpoint inhibitors, either anti-PD1 or anti-PDL1, added to chemotherapy and offered as maintenance treatment in locally advanced, recurrent and first line disease showed dramatic improvement of PFS, particularly for dMMR/MSI-H cases [10-13]. For instance, MMR deficiency due to methylation did not have an adverse effect on pembrolizumab efficacy in the GYO-018 study [11]. Interestingly, in an exploratory analysis of the RUBY trial, all molecular subgroups derived a PFS with the addition of Dostarlimab to chemotherapy except for the POLe subgroup [14].

It is however speculated that in low-income countries POLe testing with next generation sequencing may not be feasible and the ProMisE pathway would be difficult to follow [15]. Missing the POLe testing would pose few patients with POLe mutation to adjuvant overtreatment. For instance, in PORTEC-3 study 12% of the high risk patients were classified as POLe mutated.

On the other hand, IHC testing of MMR and p53 could be generalized to all patients with early endometrial cancer. Discrepancies in assessing and reporting the p53 status, could be overcome by following specific guidelines on p53 assessment in order to get a uniform and clinically useful pathology result [16,17]. Testing only for p53 and MMR would spare p53 wild type patients with early-stage disease from receiving adjuvant chemotherapy and encourage patients with deficient MMR be screened for Lynch syndrome [18-20]. Taking into consideration the phenomenon of multiple classifiers, remote testing for POLe of patients with p53 mutation could be regarded as a mirrored ProMisE pathway and could be applied in healthcare settings where POLe testing is expensive and not reimbursed. For instance, in a cohort study a 3.6% of the cases were classified as POLEmut-p53abn [21]. Although this pathway should not substitute the ProMisE one, it could however be an alternative strategy that may fit better to real world practice, particularly in low resource countries.

Furthermore, it is appreciated that in many countries MMR and p53 are assessed with IHC in hysterectomy specimens, a fact which practically follows the paradigm of the ProMisE confirmation cohort which included only hysterectomy specimens [4]. Knowledge of the molecular imprint of the disease has a clear impact on adjuvant treatment, as clearly depicted in ESGO guidelines [1].

Nonetheless, preoperative molecular assessment could potentially influence surgical procedures. For instance, a more thorough surgical procedure could be followed in cases of a POLe wild type, MMR proficient, p53mutated disease for which lymph node assessment is mandated [22]. Early knowledge of the molecular imprint could have an impact on fertility preservation decision [23]. Cases with p53 mutation carry a less favorable prognosis, a fact that is currently reflected in the newer FIGO 2023 staging system. Specifically, patients with aggressive histology and disease confined to endometrium are allocated to stage Ic, whereas those with p53 mutated disease invading the myometrium are upstaged to IIc [2]. Tanos et al report that alterations in PIK3CA, HER2, ARID1A, L1CAM, FGFR2 and importantly in P53, are considered poor prognostic factors and fertility sparing treatment may not be favored in these cases [24]. However, for patients who have already received fertility preserving treatment the impact of significance of the ProMisE classification has not been proven. The authors concluded that larger prospective studies are needed to elucidate the impact of the molecular imprint in these cases [25].

In our study we performed a matched IHC-based p53 and MMR analysis between specimens obtained by D&C and hysterectomy. The almost absolute accordance of our results is partly attributed to the good quality of specimens with adequate neoplastic cellularity collected by experienced gynaecologists and gynaecology oncologists. Our results are in line with those reported by Abdulfatah et al, in their cohort of 50 biopsies and corresponding hysterectomy specimens [26].

Furthermore, it merits to be mentioned that specimens were all collected and assessed at REA Maternity and Gynaecological Hospital and pathology procedures were double checked independently by two expert in gynaecological oncology pathologists. Preanalytic phase issues, mainly fixation procedures, were strictly followed in all our cases, reflecting to the good quality of the specimens. An MMR result discrepancy between D&C and hysterectomy was observed in only one case of our study. This difference was attributed to a case staining MLH1 negative in D&C but positive in hysterectomy. It may happen that a MLH1 loss expression is not accompanied by a PMS2 loss, as it may form stable heterodimers with other minor MMR proteins such as MSH3 and PMS1. Another described in literature phenomenon refers to cases with indeterminate immunostaining of one MMR protein without a coupled loss of expression in at least one protein [27,28].

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P53 mutation is regarded as a valid prognostic marker of aggressive clinical course. Interestingly, in our study no association was found between p53 status and LVSI or depth of myometrial invasion. It is however reported that subclonal abnormal p53 expression is a strong indicator for POLEmut and/or MMRd. It is essential therefore that MMR and POLe status are assessed following a p53 abnormal result [29]. Moreover, Singh et al (30) reported that the IHC p53 assessment in biopsy specimens, could be regarded as a surrogate test for p53 mutation in endometrial cancer, which is line with our findings.

Importantly, Berg et al [31] not only they identified a substantial agreement of MMR status between preoperative and postoperative specimens, they also showed that high expression of MSH6 and MSH2 proteins were associated with an aggressive behavior. In our study the MMR status was not associated with the lymphovascular invasion status or the depth of myometrial invasion, however, the small number of patients could not allow for extrapolations due to weak statistical significance.

Our results are in line with those reported by other groups [5,6,26,31] which prove that the molecular classification on diagnostic specimens is highly concordant with that at final hysterectomy. Even though our results should be interpreted with caution as they derive from a small number of cases in a single center, they may pave the way to bigger studies which may validate the hypothesis that molecular characterization can safely be performed at D&C specimens.

In this study, we aimed to depict the real-world practice in Greece for newly diagnosed patients with early endometrial cancer. POLe assessment was not part of this study as NGS testing is not reimbursed in Greece. Our next step therefore will be to obtain funding to retrospectively assess POLe in both D&C and hysterectomy specimens in the cases of this study.

Conclusion

The p53 and MMR status may be accurately assessed with IHC in D&C specimens compared to hysterectomy samples. Early knowledge of the molecular imprint of the disease may drive treatment decisions regarding surgical procedures, fertility preservation and further treatment plans.

Conflict of Interest: None

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