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ORIGINAL ARTICLE

Mismatch repair status in high-grade endometrial carcinomas of endometrioid and non-endometrioid type

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Summary

Purpose: *To evaluate mismatch repair (MMR) status in a series of high-grade endometrial carcinomas and correlate it with several clinicopathological characteristics and with survival.*

Methods: *One hundred and one patients with high-grade endometrial carcinoma, both of endometrioid and of non-endometrioid type were included in the study. The expression of MLH1, MSH2, MSH6 and PMS2 was evaluated by immunohistochemistry.*

Results: *In our cohort, 41 women had an endometrioid and 60 women a non-endometrioid carcinoma. Endometrioid histotype was statistically more frequent in deficient MMR (dMMR) tumors (73.3%), while non-endometrioid carcinomas in proficient (pMMR) cases (73.8%) (p<0.001). When analyzing the group of endometrioid and non-endometrioid carcinomas separately, only dMMR endometrioid cancers were found to be statistically related to deep myometrial invasion, lymph-node metastases and advanced stage (p=0.035, p=0.011 and p=0.028, respectively). Univariate and multivariate analysis revealed no relation between MMR status and progression-free survival (PFS) or overall survival (OS). Adjuvant treatment was not found to influence the course of the disease. When MMR proteins were studied separately, MLH1/PMS2 loss was related to deep myometrial invasion (p=0.019 and p=0.036, respectively) and MSH6 loss to lymph-node metastases (p=0.04).*

Conclusions: *In our group of high-grade endometrial carcinomas, MMR deficiency was statistically more frequent in endometrioid than in non-endometrioid cancers. Furthermore, only dMMR endometrioid type grade 3 carcinomas were found to be related with features indicative of aggressive behavior. Considering some unique relation of each MMR protein with distinct clinicopathological features, the assessment of all four proteins is proposed.*

Key words: *endometrial cancer, immunohistochemistry, mismatch repair deficiency*

Introduction

Endometrial carcinoma represents a heterogeneous group of tumors with distinct epidemiological, morphological and biological characteristics. Nevertheless, when considering high grade endometrial cancers, there is considerable histological overlapping and interobserver disagreement in defining the specific sub-type, which is critical for decision making concerning the therapeutic approach and for designing type-specific clinical trials [1-3].

Within the group of high-grade endometrial carcinomas, serous cancers and grade 3 endometrioid cancers are the most difficult to distinguish, even though several immunohistochemical bio-

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markers implicated in the carcinogenic process of each different lineage are widely used [4,5]. As for clear cell carcinomas, it was demonstrated that they constitute a histologically and genetically heterogeneous group with varying outcomes [6]. Finally, the group of high-grade endometrial carcinomas comprises malignant mixed mullerian tumors (MMMT), dedifferentiated carcinomas and unclassified/carcinomas with ambiguous features [7]. Nevertheless, a great heterogeneity in clinical outcome is observed among women with the same grade and histotype category. This could result from the irreproducibility of histotype and grade assignment [8] but also from molecular events associated with other oncogenic pathways.

A tremendous progress in tumor classification has been made by The Cancer Genome Atlas (TCGA), which proposed a 'novel classification system' of endometrial cancer, suggesting four distinct molecular groups that corelated with PFS [9]. One of those groups is characterized by high microsatellite instability (MSI), as a result of defects in the post-replicative DNA mismatch repair (MMR) system [10].

The MMR system is a strand-specific DNA repair mechanism with a role to maintain genomic integrity by correcting base substitution mismatches and small insertion-deletion mismatches that are generated by errors during DNA replication. There are several MMR genes identified, but four are of most clinical interest—MLH1, MSH2, MSH6, and PMS2 [11,12].

DNA MMR gene mutations have been thought to be crucial to the tumorigenesis of endometrial cancers. Loss of MMR function has been reported in approximately 20 to 30% of endometrial cancers. Germline mutations account for 3 to 5% of the cases, while the remainder arise due to epigenetic methylation of the MLH1 promoter region causing MSI [11].

The association between loss of MMR function and outcome has been widely examined in colorectal carcinomas (CRC) [13]. In contrast to CRC, the association between MMR status and clinical outcome in endometrial cancer remains unclear. It has been suggested that MSI acts as a negative prognostic factor only in early-stage disease [14]. Others reported that loss of MMR function may be associated with distinct tumor characteristics, such as histopathologic type, higher grade and advanced stage [15-18].

Finally, a metanalysis of 23 trials and a recently published large population-based study revealed no difference between MMR status and DFS or OS [14,15]. Since in most of these studies, endometrial cancers of all grades were evaluated, we aimed to focus on the immunohistochemical expression of MLH1, MSH2, MSH6, and PMS2 in a series of high-grade endometrial carcinomas, both of endometrioid and non-endometrioid type and correlate it with several clinicopathological characteristics and with survival.

Table 1. Clinicopathological features related to the study group (N=101)

Variables	
Age, years	
Mean	64.96
SD	9.967
Min-Max	31-85
Histologic type, n (%)	
Endometrioid	41 (40.6)
Serous	36 (35.6)
MMMT	8 (7.9)
Clear cell	4 (4)
Unclassified	5 (5)
Mixed	7 (6.9)
Location (n=94), n (%)	
Fundus	40 (42.6)
Body	44 (46.8)
Lower uterine segment	10 (10.6)
Myometrial invasion, n (%)	
Ia	58 (57.4)
Ib	43 (42.6)
Stage, n (%)	
I	49 (48.5)
II	9 (8.9)
III	35 (34.7)
IV	8 (7.9)
MMR status, n (%)	
pMMR	71 (70.3)
dMMR	30 (29.7)
Lymph node metastasis, n (%)	
Negative	71 (70.3)
Positive	30 (29.7)
Lymphovascular space involvement, n (%)	
No	72 (71.3)
Yes	29 (28.7)
Recurrence (N=77), n (%)	
No	57 (74)
Yes	20 (26)
Death (N=77)	
No	64 (83.1)
Yes	13 (16.9)

SD: standard deviation, MMMT: malignant mixed mullerian tumor, MMR: mismatch repair, dMMR: deficient mismatch repair, pMMR: proficient mismatch repair

Methods

This was a population-based retrospective cohort study comprising patients who were diagnosed with high grade endometrial adenocarcinoma, both of endometrioid and of non-endometrioid type, during the period between June 2001 and November 2017 in IASO Women's Hospital, Athens, Greece. From the files of the Pathology Department of the Hospital, 165 cases were identified. Of these, 6 women were previously diagnosed with breast cancer while 57 women were not surgically staged and were not included in the study. The final population of our study consisted of 101 women who were fully staged. Surgical staging included total hysterectomy, bilateral salpingo-oophorectomy and pelvic±paraaortic lymphadenectomy. Omentectomy was performed on selected cases. Twenty-four women were lost to follow-up. Of the remaining 77 patients, 66 received adjuvant therapy. Twelve women were treated with chemotherapy and brachytherapy, 18 with chemotherapy and radiotherapy, 3 with brachytherapy and radiotherapy, 3 with chemotherapy, radiotherapy and brachytherapy, 17 with chemotherapy alone, 8 with brachytherapy alone and 5 with radiotherapy alone.

The hematoxylin-eosin (H&E) and all immunohistochemically stained slides were reviewed by two pathologists (PY and AN) specialized in gynecological pathology who were unaware of the diagnosis. In cases of disagreement the slides were re-evaluated by a third pathologist (KP). The histological type was determined according to World Health Organization criteria while tumors with ambiguous or overlapping morphological and immunohistochemical features that could not be characterized as endometrioid or serous histology were considered as "unclassifiable". The most representative formalin-fixed paraffin-embedded tissue block was selected for the immunohistochemical evaluation of MSH6, MSH2, MLH1 and PMS2 expression. Surgical staging was determined using the standards of the International Federation of Obstetrics and Gynecology (FIGO 2009).

Medical records were reviewed and personal communication with the patients was made for adjuvant treatments and clinical information. None of the cases was treated with pre-operative chemotherapy. DFS was calculated as the period in months from operation to local recurrence, distant metastasis or disease-specific death, while OS the period from operation to death.

The study was approved by the ethics committee of the hospital, while all patients had signed an informed consent during their first submission.

All clinicopathological features related to the study group are presented in Table 1.

Immunohistochemistry

From each representative tissue block, four 4μm tissue sections were cut and were used for the immunohistochemical analysis. For all four markers DAKO FLEX ready-to-use antibodies were used. Specifically, for MLH1 an antihuman monoclonal mouse antibody, clone ES05, for MLH2 an anti-human monoclonal rabbit antibody, clone FE11, for MSH6 an antihuman monoclonal rabbit antibody, clone EP49 and for PMS2 an anti-human monoclonal rabbit antibody, clone EP51. The immunostaining was evaluated in areas with well-preserved tissue morphology and without necrosis or artifacts. For all the four markers detection, a nuclear immunoreaction was considered for evaluation. The lesions were considered as positive for each marker if tumor cells in the interest area showed immunoreactive intensity stronger than or equal to positive controls. The lesions were considered as negative for each marker if tumor cells showed complete loss of immunoreaction. The assignment of immunoreaction was performed independently by two observers (MK and MM), and any discrepancies between them were resolved by conferring over a multiviewer microscope. Cases that at least one of four proteins were judged as negative were assigned to MMR-deficient cases and the remainder cases were assigned to MMR-proficient cases.

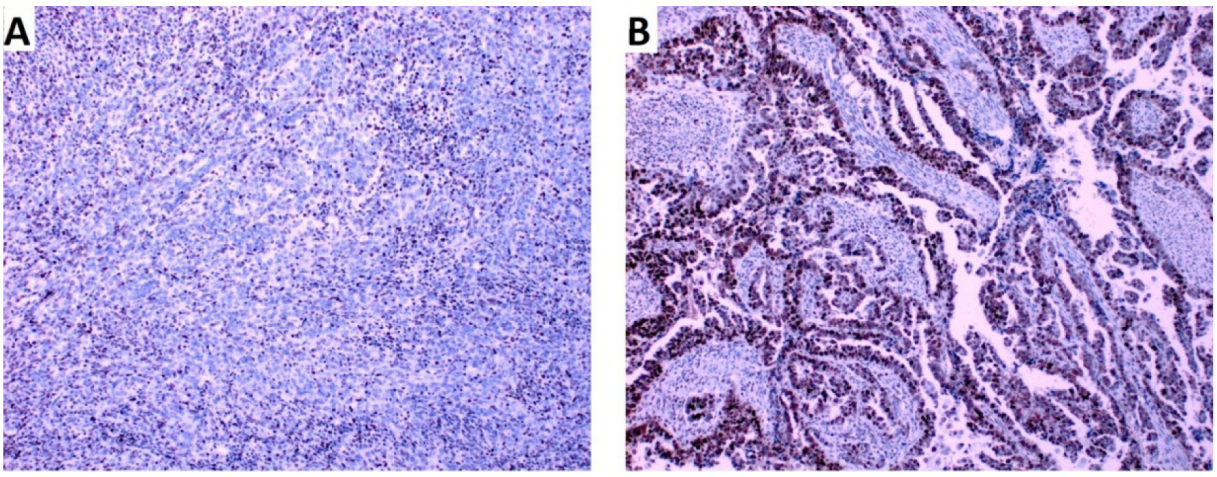

Figure 1. A: dMMR high grade endometrial carcinoma with lymphocytic infiltration as positive internal control (MLH1 x40). **B:** pMMR serous endometrial carcinoma (MLH1 x100). dMMR: deficient mismatch repair, pMMR: proficient mismatch repair.

Statistics

All data were analyzed using SPSS version 23. Descriptive statistics were done using x^2 test for categorical variables and t-test for continuous variables. Kaplan-Meier method and log rank test were used for survival analyses. Cox regression analysis was used to assess the effects of different variables on patient survival. P<0.005 indicated a significant statistical difference.

Results

Out of 165 women diagnosed with grade 3 endometrial carcinoma between June 2001 and November 2017, 101 were found eligible to enter the study. Immunohistochemical evaluation of all four proteins revealed that 30 cases were dMMR (29.7%) and 71 cases MMR-proficient (pMMR) (70.3%) (Figure 1). Endometrioid histotype was statistically more frequent in dMMR tumors (73.3%), while non-endometrioid carcinomas in pMMR cases (73.8%) (p<0.001). Deep myometrial invasion was statistically more frequent in dMMR (n=18/30, 60%) than in pMMR tumors (25/71, 35.2%) (p=0.021). While tumors located in the lower uterine segment (LUS) were twice more frequent in the dMMR (n=5/30, 16.7%) as opposed to the pMMR group (n=5/64,

Table 2. Correlation of MMR status with clinicopathological features under evaluation

Variables	*dMMR (N=30) n (%)*	*pMMR (N=71) n (%)*	*p value*
Age, years			
Mean	63	66	
SD	10	10	
Min-Max	42-78	31-85	
Histologic type			<0.001
Endometrioid	22 (73.3)	19 (26.8)	
Non endometrioid	8 (26.7)	52 (73.8)	
Serous	3 (10)	33 (46.5)	
MMMT	1 (3.3)	7 (9.9)	
Clear cell	1 (3.3)	3 (4.2)	
Unclassified	1 (3.3)	4 (5.6)	
Mixed	2 (6.7)	5 (7)	
Myometrial invasion			<0.021
Ia	12 (40)	46 (64.8)	
Ib	18 (60)	25 (35.2)	
Location			0.378
Fundus	13 (43.3)	27 (42.2)	
Body	12 (40)	32 (50)	
Lymph node	5 (16.7)	5 (7.8)	
metastasis			0.319
No	19 (63.3)	52 (73.2)	
Yes	11 (36.7)	19 (26.8)	
LVSI			0.25
No	19 (63.3)	53 (74.6)	
Yes	11 (36.7)	18 (25.4)	
Stage			0.935
I-II	16 (53.4)	42 (59.2)	
III-IV	14 (46.6)	29 (40.9)	
Recurrence			0.193
No	17 (85)	40 (70.2)	
Yes	3 (15)	17 (29.8)	
Death			0.165
No	19 (95)	45 (78.9)	
Yes	1 (5)		12 (21.1)

dMMR: deficient mismatch repair, pMMR: proficient mismatch repair, SD: standard deviation, MMMT: malignant mixed mullerian tumor, LVSI: lymphovascular space invasion

7.8%) (p=0.378) the above difference did not reach any statistical significance. There were no significant differences in age distribution, lymph-node metastasis, LVSI and FIGO stage between the two groups. Median follow-up was 55 months (range 12-178), which was similar for both groups. Death and recurrence rates were higher in patients with pMMR tumors, but of no statistical significance (p=0.165 and p=0.193, respectively).

Statistical results relating MMR status to the different clinicopathological features under evaluation are shown in Table 2.

Univariate analysis (Cox method) showed no association between MMR protein expression and PFS (p=0.21). There was a tendency for longer OS in the dMMR group, although it did not reach statistical significance (p=0.056) (Kaplan-Meier, log rank test) (Figure 2). Multivariate analysis revealed no statistically significant results.

When analyzing the group of endometrioid and non-endometrioid carcinomas separately, dMMR endometrioid cancers were found to be statistically related to deep myometrial invasion, lymph-node involvement and advanced stage (p=0.035, p=0.011 and p=0.028, respectively) (Table 3). No relation with any of the parameters under evaluation was found for non-endometrioid carcinomas (data not shown). Survival analysis could be performed only for endometrioid carcinomas since in the group of dMMR non-endometrioid cancers no recurrence or death were recorded. Univariate analysis revealed no association between MMR status and PFS (p=0.8) or OS (p=0.83) (data not shown). Multivariate analysis also did not show any statistical association.

Loss of MMR protein expression in the dMMR group of tumors was as follows: combined MLH1 and PMS2 loss (n=12), combined MSH2 and MSH6 loss (n=9), solitary PMS2 loss (n=4) and solitary MSH6 loss (n=9). There were 4 cases with concurrent loss of MSH6 and PMS2 expression.

When analyzing each protein expression separately in the group of endometrioid carcinomas, MSH6 loss was statistically related to lymph-node

Table 3. Correlation of MMR status of endometrioid type carcinomas with the clinicopathological features under evaluation

Variables	*dMMR (N=22/41, 53.7%) n (%)*	*pMMR (N=19/41, 46.3%) n (%)*	*p value*
Age, years			
Mean	61	59	
SD	10	12	
Min-Max	42-78	31-84	
Myometrial invasion			**0.035**
Ia	9 (40.9)	14 (73.7)	
Ib	13 (59.1)	5 (26.3)	
Location			1.0
Fundus and body	18 (81.8)	16 (84.2)	
Lower uterine segment	4 (18.2)	3 (15.8)	
Lymph node metastasis			**0.011**
No	13 (59.1)	18 (94.7)	
Yes	9 (40.9)	1 (5.3)	
LVSI			0.44
No	15 (68.2)	15 (78.9)	
Yes	7 (31.8)	4 (21.1)	
Stage			**0.028**
I-II	10 (45.5)	15 (78.9)	
III-IV	12 (54.5)	4 (21.1)	
Recurrence			1.0
No	13 (81.2)	12 (80)	
Yes	3 (18.8)	3 (20)	
Death			1.0
No	15 (93.7)	14 (93.3)	
Yes	1 (6.3)	1 (6.7)	

Bold numbers denote statistical significance

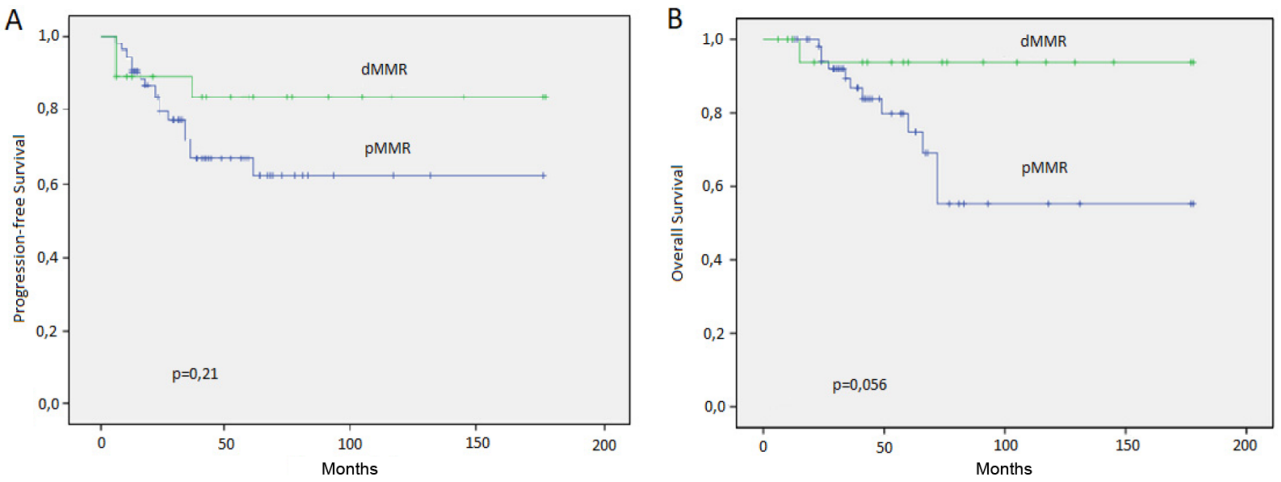

Figure 2. Kaplan-Meier analysis demonstrating absence of statistical significance in **A:** Progression-free survival and **B:** Overall survival between dMMR and pMMR tumors. dMMR: deficient mismatch repair, pMMR: proficient mismatch repair.

involvement (p=0.04), while PMS2 and MLH1 loss to deep myometrial invasion (p=0.011 and p=0.036, respectively). PMS2 loss was related to advanced stage disease but this did not reach any statistical significance (p=0.087). Since no relation was found between the parameters under study and the group of non-endometrioid carcinomas, no further protein analysis for this group was performed.

In order to investigate the contribution of adjuvant treatment among the two groups, univariate analysis was assessed. There was no difference among dMMR and pMMR cases who received adjuvant treatment and PFS (p=0.33) or OS (p=0.13), nor when studying the group of endometrioid carcinomas separately (p=0.9).

Discussion

For many years, the aim of identifying MSI in endometrial carcinomas was restricted to the isolation of Lynch syndrome carriers. Recently, the Food and Drug Administration (FDA) of USA approval of immunotherapy for all microsatellite unstable carcinomas has strengthen the need for more detailed studies in order to highlight the group of endometrial carcinomas that would probably favor from this new therapeutic option [19]. The above agreed with the suggestion by the Cancer Genome Atlas (TCGA) that for endometrial cancers belonging to the microsatellite unstable group, immunotherapy could be considered. Even though in the aforementioned group mostly endometrioid type carcinomas are included, it was found that any histological subtype can also be encountered.

The results of our study indicate that in high grade endometrial carcinomas, dMMR was statistically related to endometroid histology, yet 26.7% of dMMR tumors were of non-endometrioid histology. The issue of MMR deficiency in non-endometrioid tumors, mostly serous carcinomas, is debatable. Some investigators have demonstrated that serous histology was inconsistent with MMR deficiency and suggested that it could also be used as a diagnostic tool for the differential diagnosis within the spectrum of high-grade endometrial carcinomas [20,21]. Nevertheless, the results of [22] indicated that rarely, serous and clear cell carcinomas but also carcinosarcomas can belong to the MMR deficient group. One could hypothesize that in our group of tumors, those characterized by MMR deficiency and belonging to the unclassifiable, mixed or mixed Mullerian tumor histological subtype, could represent endometrioid carcinomas with serous-like or sarcomatous metaplastic features. Such a misclassification could result from the ambiguous morphological features with serous-like atypia that might characterize some dMMR related endometrioid carcinomas [5].Even so, 3 serous and 1 clear cell carcinoma with typical diagnostic features both on morphology and on immunohistochemistry presented loss of one or more of the proteins under evaluation.

When considering the rest of the clinicopathological parameters under evaluation, such as the age of the patients, the location of the tumor, the depth of myometrial invasion, the presence of lymph vascular space invasion, lymph-node metastases and the stage of disease in our total cohort, only deep myometrial invasion was related to dMMR tumors. Nevertheless, a clear trend was observed towards worse recurrence and death rates in the pMMR in comparison to the dMMR group of

tumors, which is in agreement with the results of other investigators [15]. In univariate analysis, although without statistical significance, the dMMR group was found to have longer OS (p=0.056), while in multivariate analysis revealed no relation between MMR status and survival. When isolating only endometrioid carcinomas, dMMR tumors were found to be associated with more features indicative of aggressive behavior, such as lymph-node metastases and higher stage disease. Despite the above findings, there were similar outcomes among the MMR groups. In our study, no woman with non-endometrioid carcinoma and dMMR status died or recurred, so survival analysis for non-endometrioid tumors could not be applied.

The literature on the relation of MMR deficiency and the clinical outcome of the tumors is controversial. The largest study published to date [23] included 1024 endometrioid tumors and showed similar outcomes between the dMMR and pMMR groups. Similar results were published by Zighelboirn et al [18]. Studies on both endometrioid and non-endometrioid carcinomas revealed worse progression and mortality rates for pMMR tumors [15,17]. Nevertheless, in a systematic review by Diaz-Padilla et al [14], no association between MMR status and clinical outcome was observed. Finally, Nelson et al [20] in their analysis of 64 high-grade endometrial cancer cases of all subtypes noted worse outcome in advanced-stage disease with dMMR. Those controversial results might be related to the marked heterogeneity observed among those trials, with inter-study variability and use of different methodologies for the detection of MMR deficiency. Moreover, the use of tissue microarray technology by some investigators, neglects the existence of subclonal evolution and is prone to classification errors when considering MMR deficient and proficient tumors.

In order to evaluate the inconsistency between the aggressive prognosticators encountered in our group of high-grade dMMR endometrioid carcinomas and the lack of association with features related to the clinical outcome, the role of the microenvironment should be considered. It has been shown that both tumor infiltrating lymphocytes (TILs) and peritumoral lymphocytes can significantly predict the presence of microsatellite instability in endometrial carcinoma [24,25]. The better-than-anticipated outcomes for women with dMMR tumors could reflect differences in T-cell infiltration and their various immune responses with the host that could balance the effect of high-risk prognosticators [23,26,27]. Another factor that has probably influenced the outcome of those patients is adjuvant therapy. Most of the women in our study group had adjuvant chemotherapy either alone or together with radiotherapy or brachytherapy. A defected MMR system inhibits apoptosis, thereafter it could induce a high sensitivity to platinum-based therapies [7,23]. Moreover, adjuvant brachytherapy was found to improve survival in stage 1A grade 3 endometrial carcinomas [28]. As for the role of radiotherapy, the results of different studies are controversial [29]. In a retrospective population-based cohort study comprising endometrial carcinomas of all histological sub-types for which both chemotherapy and radiotherapy was administered, multivariate analysis revealed no relation between MMR status and PFS or OS [30]. In our study there was no difference in outcome between the dMMR and pMMR cases who received adjuvant treatment. Finally, our study confirms the results of other investigators pointing out that a two-marker panel comprising MSH6 and PMS2 could be used for screening of MMR status [12,20,31], as MSH2 loss was always accompanied by loss of its partner protein MSH6 and MLH1 loss by PMS2 loss. Nevertheless, when analyzing the relation of the parameters under evaluation to the expression of each protein separately, loss of PMS2 and MLH1 was related to myometrial invasion and MSH6 loss but not MSH2 loss to lymph node metastases. Moreover, only PMS2 loss was strongly associated with advanced stage disease. Thereafter, the study of all four proteins could be considered as a valuable tool in predicting the aggressiveness of high-grade dMMR endometrioid tumors.

In conclusion, in our group of high-grade endometrial carcinomas, MMR deficiency was statistically more frequent in endometrioid than in non-endometrioid cancers. Furthermore, only dMMR endometrioid type grade 3 carcinomas were found to be related with features indicative of aggressive behavior despite not presenting a worse clinical course than pMMR tumors. To highlight this inconsistency, the role of the immune system and of adjuvant therapy is discussed. Considering some unique relation of each MMR protein with distinct clinicopathological features, the assessment of all four proteins is proposed.

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Conflict of interests

The authors declare no conflict of interests.

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