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Mismatch repair deficiency as a predictive marker for response to adjuvant radiotherapy in endometrial cancer

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HIGHLIGHTS

- MMR-deficiency is a common feature of grade 3 endometrioid endometrial cancer (EEC).
- Radiotherapy improved survival in patients with MMR-deficient EECs.
- Patients with MMR-proficient ECs did not experience improved survival after radiotherapy.
- MMR status could be used to select patients that benefit most from adjuvant radiotherapy.

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ABSTRACT

Background. Mismatch repair (MMR) deficiency is found in 20 to 40% of endometrial cancers (ECs) and was recently identified as a discerning feature of one of the four prognostic subgroups identified by The Cancer Genome Atlas. There is accumulating evidence that MMR proteins are involved in the DNA repair processes following radiotherapy. We investigated the predictive value of MMR status for response to adjuvant radiotherapy in patients with stage IB/II, grade 3 endometrioid endometrial cancer (EEC).

Methods. A retrospective multicenter cohort study was performed to compare patients with histopathologically confirmed stage IB/II grade 3 EEC with and without adjuvant radiotherapy. Patients were classified according to the Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE) identifying ECs as either MMR-deficient, POLE, p53abn or p53wt. Multivariable Cox regression analysis explored associations between adjuvant treatment and outcome.

Results. A total of 128 patients were analyzed, including 57 patients (43.0%) with MMR-deficient EECs. Baseline characteristics were comparable, except a higher proportion of MMR-deficient EECs were stage II (36.8% vs. 15.5%, p = 0.006). Eighty-two patients (64.1%) received adjuvant radiotherapy (external beam [n = 55], vaginal brachytherapy [n = 27]). In multivariable analysis, adjuvant radiotherapy was associated with improved disease-specific survival in patients with MMR-deficient EECs (hazard ratio 0.19, 95%-CI 0.05–0.77), but not in patients with MMR-proficient EECs (hazard ratio 0.92, 95%-CI 0.37–2.31).

Conclusion. Adjuvant radiotherapy improved survival in patients with MMR-deficient EECs. MMR status could be used as a predictive biomarker to select patients that benefit most from adjuvant radiotherapy.

1. Introduction

The mismatch repair (MMR) system promotes DNA repair by means of an excision and resynthesis mechanism during DNA replication, increasing replication fidelity [1]. MMR deficiency is a common feature of endometrial cancer (EC) and is present in approximately 20 to 40%

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of cases [2–6]. MMR deficiency may be inherited or acquired and can be assessed by immunohistochemical loss of one or more of the MMR proteins, including MLH1, PMS2, MSH2 and/or MSH6, or through detection of microsatellite instability (MSI).

MSI status was identified as a discerning feature of one of the four prognostic subgroups identified by The Cancer Genome Atlas (TCGA) [7]. In addition to ECs with MSI, molecular profiling in the TCGA also identified an "ultramutated" subgroup of ECs strongly associated with mutations in the exonuclease domain of *polymerase-ε* (*POLE*) with an excellent prognosis; a "copy-number high" subgroup characterized by *p53* mutations and a generally unfavorable outcome; and finally, the copy number-low subgroup. More recently, pragmatic clinically applicable molecular classification systems have evolved that recapitulate TCGA prognostic subgroups but use low-cost methodologies on standard formalin-fixed paraffin embedded (FFPE) hysterectomy or diagnostic endometrial biopsy material [4,5,8–10]. Specifically, ProMisE (Proactive Molecular Risk Classifier for Endometrial Cancer) evaluates MMR immunohistochemistry (IHC), sequencing of the exonuclease domain of *POLE* and p53 IHC. ProMisE has been developed and validated according to the Institute of Medicine guidelines for the development of biomarker assays, improving consistency of categorization of ECs, providing prognostic information for clinicians and patients, but its predictive ability has not yet been determined [4,5,11].

Recent literature suggests differential outcomes and response to chemotherapy within MMR-deficient ECs [6,12]. However, the predictive value of MMR status for response to adjuvant radiotherapy remains unclear. In vitro data suggest increased radiosensitivity in cell lines of MMR deficient cancer i.e. colorectal cancer, however, results of recent observational studies investigating the predictive value of MMR status for radiotherapy in EC were equivocal [2,6,12–16].

For stage IB/II, grade 3 endometrial carcinoma of endometrioid histological subtype (EEC) radiotherapy is an important element of adjuvant care reported to improve progression-free survival but not disease-specific or overall survival [17–19]. Currently, decisions of whether or not to treat these patients with radiotherapy are made on an individual basis and there is a great need for predictive biomarkers that might select women who can benefit the most from radiotherapy. We therefore investigated the predictive value of MMR status for response to adjuvant radiotherapy in a group of patients with stage IB/II, grade 3 EEC that were classified according to the ProMisE classifier.

2. Material and methods

2.1. Patients

Institutional ethics approval for this study was obtained from each participating study site. This retrospective multicenter study included patients with histopathologically confirmed Federation Internationale de Gynecologie et d'Obstetrique (FIGO) 2009 stage IB or II grade 3 EEC treated between 2005 and 2012 at one of the study sites: British Columbia Cancer Agency (BCCA), Canada; The Gynaecological Oncology Centre South (GOCS), the Netherlands; Tübingen University Hospital, Germany.

All patients underwent at least a hysterectomy and bilateral salpingo-oophorectomy for staging. When pelvic and para-aortic lymph node sampling was performed, lymph nodes had to be negative for inclusion. We included only patients who received adjuvant radiotherapy alone or no adjuvant therapy. Patients receiving adjuvant chemotherapy alone or in combination with radiation were excluded. The study followed the reporting recommendation of tumor marker studies (REMARK) guidelines [20].

2.2. Data extraction

Clinicopathological features were extracted from patient records and included patient characteristics, tumor characteristics, primary surgical treatment and adjuvant treatment and outcomes.

2.3. ProMisE molecular classification

Immunohistochemical methods and scoring criteria for mismatch repair and p53 as well as methods and encompassed exons of the exonuclease domain of *POLE* are given in the Supplemental Methodology. Mismatch repair deficiency (MMR-D) was defined as total loss of nuclear staining of one or more MMR proteins, in presence of an intact internal control. This method has been shown to be highly concordant with MSI-high status [21,22]. Immunostaining for p53 was considered abnormal when there was complete absence of nuclear staining or when more than 80% of tumor cell nuclei showed strong expression (absent p53 protein [IHC score 0] or aberrant increased protein accumulation [IHC score 2+], respectively). *POLE* sequencing for hotspot mutations in the exonuclease domain, including either exons 9 to 14 or exons 9 and 13, was performed using either Sanger or next-generation sequencing approaches (Supplementary Methodology).

2.4. Statistical analysis

Clinicopathological differences between the MMR-proficient and MMR-deficient groups, and between the groups receiving no adjuvant treatment and radiotherapy, were compared with the χ^2 test for categorical data and the Mann-Whitney *U* test for continuous variables. Survival analyses were performed separately for both the MMR-proficient and MMR-deficient group. Kaplan-Meier curves were constructed for overall survival (OS), disease-specific survival (DSS) and progression-free survival (PFS) comparing patients without adjuvant treatment with patients receiving adjuvant radiotherapy. OS was calculated from the date of primary treatment to the date of death or, for surviving patients, to the date of the last follow-up. DSS was calculated from the date of primary treatment to the date of death caused by the disease or, for surviving patients, to the date of the last follow-up. PFS was defined as the length of follow-up, after completion of the primary treatment, during which women survived without any clinical sign of disease recurrence. The log-rank test was used to compare OS, DSS and PFS between these subgroups. Cox proportional hazards regression analysis was used to estimate the association between outcome and adjuvant treatment in patients with MMR-proficient and MMR-deficient EECs, while adjusting for covariates, including stage, LVSI and age. For this purpose, age was dichotomized into <60 and ≥60 [23]. LVSI was analyzed as 'present', 'absent' or 'missing'. Variables that had a p-value <0.200 or were considered clinically relevant were incorporated in a multivariable Cox-regression analysis. The Akaike information criterion (AIC) and Bayesian information criterion (BIC) values were used to compare the relative quality of the different Cox-regression models. A lower AIC of BIC indicated a better fit of the model compared to the other models. Combined with the significance of the variables, the multivariable model with the best fit was chosen. p-Values <0.05 were considered to indicate a significant difference. SPSS version 25 (SPSS IBM, New York, NY, USA) and R (version 3.3.2), with the Survival package (2.43-1) were used.

3. Results

3.1. Patients

A total of 152 patients were identified, of whom 24 were excluded (16.4%) because patients had received adjuvant chemotherapy or chemoradiation ($N = 23$, 15.8%) or no tumor tissue was left for analysis ($N = 1$, 0.7%). A total of 128 patients were included for analysis, including 79 patients from the GOCS (61.7%), 38 patients from BCCA (29.7%) and 11 patients from the University of Tübingen (8.6%). Median follow-up time was 36 months (range, 2 to 271 months), median age was 69 years (range, 44 to 96 years, Table 1). FIGO-stage was stage IB in 96 patients (75.0%) and stage II in 32 patients (25.0%). Radiotherapy was given in 82 patients (64.1%), whereas 46 patients (35.9%) did not receive any adjuvant treatment. Of all patients receiving radiotherapy,

Table 1
Patient baseline characteristics.

	MMR-proficient			MMR-deficient		
	No radiotherapy (n = 25)	Radiotherapy (n = 46)	p†	No radiotherapy (n = 21)	Radiotherapy (n = 36)	p†
Age (y)	70 (44–96)	68 (52–90)	0.228	70 (55–89)	64 (48–86)	0.082
Follow-up (m)	55 (4–163)	37 (2–271)	0.354	26 (2–171)	35 (10–182)	0.167
FIGO stage						
IB	21 (35.0)	39 (65.0)		16 (44.4)	20 (55.6)	
II	4 (36.4)	7 (63.6)	1.000	5 (23.8)	16 (76.2)	0.159
MI						
<50%	4 (50.0)	4 (50.0)		1 (12.5)	7 (87.5)	
≥50%	21 (33.3)	24 (66.7)	0.440	21 (42.9)	28 (57.1)	0.124
LVSI[a]						
Yes	7 (21.9)	25 (78.1)		11 (39.3)	17 (60.7)	
No	13 (44.8)	16 (55.2)	0.099	8 (32.0)	17 (68.0)	0.733
Lymph node status						
Negative	16 (44.4)	20 (55.6)		13 (50.0)	13 (50.0)	
Not sampled	9 (25.7)	26 (74.3)	0.099	8 (25.8)	23 (74.2)	0.059
Radiotherapy						
No	25 (100.0)	0 (0.0)		21 (100.0)	0 (0.0)	
VBT	0 (0.0)	17 (100.0)		0 (0.0)	10 (100.0)	
EBRT	0 (0.0)	29 (100.0)	<0.001	0 (0.0)	26 (100.0)	<0.001

MI, myometrial invasion; LVSI, lymphovascular space invasion; VBT, vaginal brachytherapy; EBRT: external beam radiotherapy.
[a] Data missing in 14 patients.
† p-Value of the Mann-Whitney *U* test for continuous, and χ^2 test for categorical variables.

27 patients (21.1%) received vaginal brachytherapy, whereas 55 patients (43.0%) received external beam radiotherapy (EBRT, with or without brachytherapy).

3.2. ProMisE-classification

The following groups were identified by the classifier (Fig. 1): MMR-deficient in 57 patients (44.5%), *POLE* in 11 patients (8.5%), p53abn in 21 patients (16.3%) and p53wt in 39 patients (30.2%). Three patients had EECs that demonstrated more than one molecular feature, knowing MMR-D and p53abn. The ProMisE algorithm dictates the order of assignment to a specific molecular subtype and therefore the cases demonstrated both MMR-deficiency and p53abn were classified as MMR-D. Patients with *POLE* mutant EECs experienced the most favorable outcome with no events of death from disease (Fig. 1). Patients with MMR-deficient EECs had a similar outcome compared to patients with p53wt and p53abn EECs.

3.3. Adjuvant radiotherapy and MMR status

As shown in Table 1, 57 patients (44.5%) had a MMR-deficient EEC and 71 patients (57.0%) had a MMR-proficient EEC. Patients with MMR-deficient EECs did not differ from patients with MMR-proficient EECs, except that patients with MMR-deficient EECs presented with FIGO stage II more often than patients with MMR-proficient EECs (p = 0.006, Supplementary Table 1). Within these groups, patients that received no adjuvant treatment (21 MMR-deficient; 25 MMR-proficient, Table 1) did not differ from patients that did receive radiotherapy (36 MMR-deficient; 46 MMR-proficient).

The recurrence rates were 28.1% and 40.0% for MMR-deficient and MMR-proficient cases, respectively. As shown in Fig. 2, radiotherapy was associated with an improved OS in patients with MMR-deficient EECs (hazard ratio [HR] 0.36, 95%-confidence interval [CI] 0.14–0.92, p = 0.032, Table 2), however no benefit was seen in patients with MMR-proficient EECs (HR 1.00, 95%-CI 0.45–2.19, p = 0.997). Radiotherapy was associated with an improved DSS in patients with MMR-deficient EECs (HR 0.31, 95%-CI 0.10–0.97, p = 0.045), whereas no benefit in DSS from radiotherapy was observed for patients with MMR-proficient EECs (HR 0.73, 95%-CI 0.30–1.76, p = 0.478). In both patients with MMR-deficient EECs and MMR-proficient EECs, improvement in PFS was seen from radiotherapy (HR 0.31, 95%-CI 0.11–0.83, p = 0.020; and HR 0.47, 95%-CI 0.23–0.97, p = 0.042). No difference in outcomes was seen between patients treated with vaginal brachytherapy compared to EBRT (data not shown).

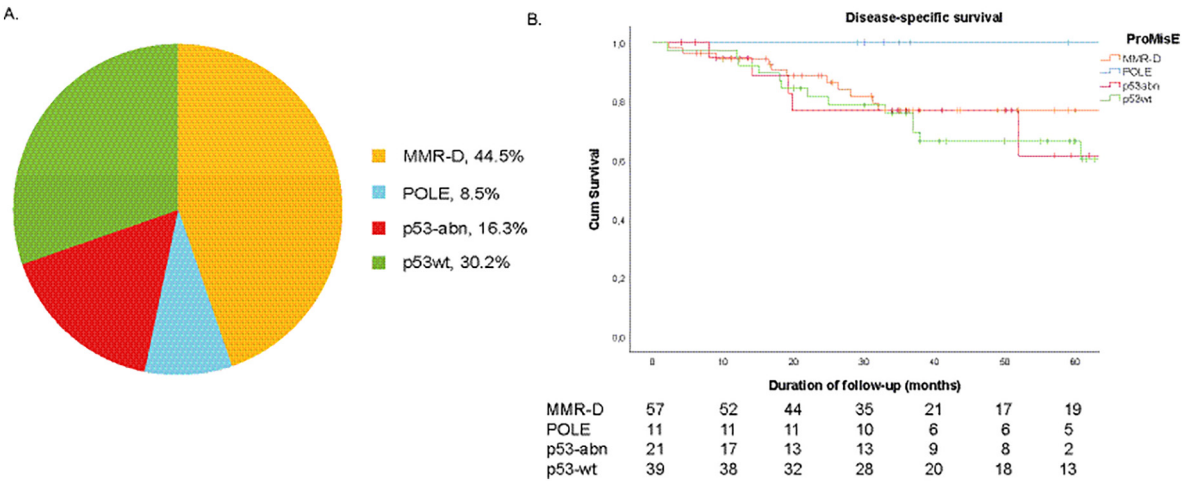

Fig. 1. (A) Distribution of patients according to the ProMisE subgroups (MMR-D 44.5%; POLE 8.5%; p53 abn 16.3%; p53 wt 30.2%). (B) Disease-specific survival (DSS) by ProMisE subgroup.

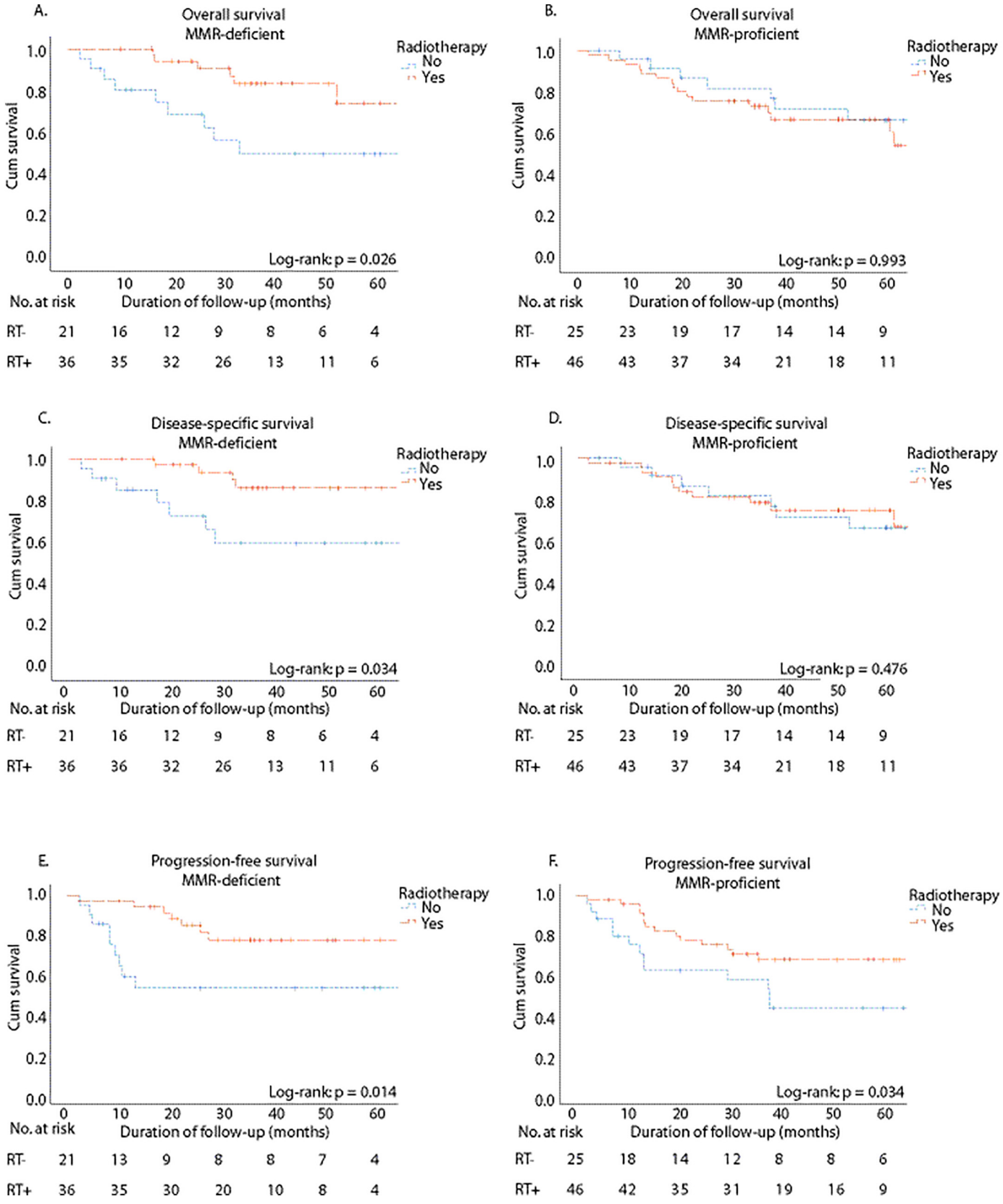

Fig. 2. (A) Overall survival (OS) in patients with MMR-deficient EECs by treatment status. (B) Overall survival (OS) in patients with MMR-proficient EECs by treatment status. (C) Disease-specific survival (DSS) in patients with MMR-deficient EECs by treatment status. (D) Disease-specific survival (DSS) in patients with MMR-proficient EECs by treatment status. (E) Progression-free survival (PFS) in patients with MMR-deficient EECs by treatment status. (F) Progression-free survival (PFS) in patients with MMR-proficient EECs by treatment status.

Table 2
Overall survival (OS) by MMR status in univariable and multivariable analysis adjusted for stage, LVSI and age.

OS	Univariable			Multivariable		
	HR	95% CI	p	HR	95% CI	p
MMR-deficient						
Radiotherapy (ref = no)	0.36	0.14–0.92	0.032	0.28	0.10–0.83	0.021
MMR-proficient						
Radiotherapy (ref = no)	1.00	0.45–2.19	0.997	1.06	0.47–2.40	0.890

Table 4
Progression-free survival (PFS) by MMR status in univariable and multivariable analysis adjusted for stage, LVSI and age.

PFS	Univariable			Multivariable		
	HR	95% CI	p	HR	95% CI	p
MMR-deficient						
Radiotherapy (ref = no)	0.31	0.11–0.83	0.020	0.28	0.10–0.79	0.016
MMR-proficient						
Radiotherapy (ref = no)	0.47	0.23–0.97	0.042	0.55	0.26–1.16	0.102

In multivariable analysis, adjusting for FIGO-stage, LVSI and age, adjuvant radiotherapy was associated with improved OS (Table 2, p = 0.021) and DSS (Table 3, p = 0.020) for patients with MMR-deficient EECs. On the contrary, no correlation between adjuvant therapy OS (p = 0.890) and DSS was observed (p = 0.858) for patients with MMR-proficient EECs. In the MMR-deficient group radiotherapy was significantly associated with PFS (Table 4, p = 0.016), whereas in the MMR-proficient group no significant association was found with PFS (p = 0.114). Full data on multivariable analysis are shown in Supplementary Tables 2–4.

Lymphadenectomy was performed in 48.4% of all patients. However, OS, DSS and DFS were comparable between patients who underwent lymphadenectomy compared with those who did not undergo lymphadenectomy (Supplementary Fig. 1).

4. Discussion

In stage IB/II, grade 3 endometrioid endometrial carcinoma, radiotherapy is commonly used to improve local control [17,18]. Even though progression-free survival is improved by adjuvant radiotherapy, clinical trials have so far failed to show any effect on disease-specific and overall survival [19]. In this study, patients with stage IB/II, high grade EEC have been classified according to the ProMisE classifier, resulting in 44.5% MMR-deficient EECs. In this retrospective analysis, we have shown that adjuvant radiotherapy was associated with improved overall, disease-specific and progression-free survival in patients with MMR-deficient EECs, adjusted for stage, LVSI and age. On the contrary, in MMR-proficient EECs no benefit was seen in overall and disease-specific survival and only a trend was seen toward improved progression-free survival. MMR status could be used as a predictive biomarker to select patients that benefit most from adjuvant radiotherapy.

Two previous clinical studies reported on the associations between MMR status and response to adjuvant radiotherapy in EC. A recent large retrospective series included 535 EC patients treated with adjuvant chemotherapy and/or radiotherapy [2]. Even though improved overall survival and progression-free survival in patients with MMR-deficient ECs was found, this association did not remain significant in multivariable analysis. However, there was a trend toward improved progression-free survival associated with MMR-deficiency in the non-endometrioid subgroup. This study was characterized by a heterogeneous study population, including 28.9% of the patients having advanced stage (stage III or IV) disease. In addition, adjuvant treatment regime included either radiotherapy or chemotherapy; these modalities were not analyzed separately, hampering comparison with our results. *Resnick* et al. reported on 477 EEC patients of whom 66 received adjuvant radiotherapy [16]. Subgroup analyses revealed improved outcome in patients with non-endometrioid MMR-deficient ECs treated with radiotherapy, compared to those with MMR-proficient ECs. Studies investigating the prognostic value, instead of the predictive value, report conflicting results [6,24,25]. *McMeekin* et al. have shown that, even though MMR-deficient ECs were more frequently high-grade and had lymphovascular space invasion, outcomes were comparable, and the authors suggest a counteractive mechanism from MMR defects [6]. Differences between treatment regimes were seen between both groups, as well as a trend toward significant interaction between MMR-status and adjuvant therapy, suggesting treatment effects could have influenced these results. *Backes* et al. on the other hand have shown worse outcomes of MMR-deficient ECs in high-intermediate risk EC [25]. Both MMR-deficient and MMR-proficient ECs received adjuvant treatment in only a minor fraction of patients. These results by *Backes* et al. could (partly) be attributable to the low rates of radiotherapy in both groups. For future studies, it is important to keep in mind the adjuvant treatment regimes when investigating prognostic value of MMR-status.

Although there are few clinical series investigating radiosensitivity specifically within MMR-deficient ECs, there is accumulating molecular evidence supporting the role of MMR proteins in cellular processes to repair radiation injury. The most lethal form of radiation-induced DNA damage is considered to be double-strand breaks (DSBs), where both strands of the DNA helix are severed [26]. As a response, a highly complex and only partly understood network of DNA repair pathways is activated. Mismatch repair proteins are involved in these pathways both directly and indirectly, including recognition of radiation induced DNA damage by MLH1 and MSH2, mobilization of downstream targets and arrest of the cell cycle at the G2/M phase transition [13,14,27]. In support, MSH2 negative cells fail to mobilize meiotic recombination 11 (MRE11), a DSB repair protein, showing increased cell death after radiation [13]. Importantly, MLH1 and PMS2 have been suggested as target proteins for p53 in human fibroblasts and may influence p53 mediated signaling with regards to entering either cell cycle arrest or apoptosis [27]. Finally, loss of MLH1 decreases activation of nuclear factor κB (NFκB), that is usually activated after radiation induced DNA damage and promotes cell survival by counteracting the p53 apoptotic pathway [15,28]. Summarizing, these data indicate that the MMR proteins may have multiple roles in the damage repair pathways following radiation injury supporting our findings from a biological perspective.

MMR-deficient tumors are known to be highly immunogenic with upregulation of immune checkpoints including the Programmed Death 1 (PD-1) pathway [29]. Subsequently, MMR-deficient tumors are of great interest for selective pathway blockade with PD-1 inhibitors, and U.S. Food and Drug Administration (FDA) approval was recently obtained for MSI-high or MMR-deficient solid tumors, including EC. Also, recent in vitro data suggest molecular links between the cellular response to radiotherapy and signaling pathways that are usually elicited by viral infections and that could impact the immunostimulatory potential of radiotherapy [30]. In this light, an

Table 3
Disease-specific survival (DSS) by MMR status in univariable and multivariable analysis adjusted for stage, LVSI and age.

DSS	Univariable			Multivariable		
	HR	95% CI	p	HR	95% CI	p
MMR-deficient						
Radiotherapy (ref = no)	0.31	0.10–0.97	0.045	0.19	0.05–0.77	0.020
MMR-proficient						
Radiotherapy (ref = no)	0.73	0.30–1.76	0.478	0.92	0.37–2.31	0.858

increasing number of clinical trials investigate the potential of radiotherapy to increase to efficacy of immune checkpoint blockers [31].

To define MMR status we have used a validated molecular classifier that can be applied to standard formalin-fixed paraffin embedded material using low-cost easily interpretable methodologies [5]. Limitations of this study are inherent to the retrospective character and non-standardized treatment arms e.g., treatment at the discretion of the treating physician. Yet, we have strengthened our study by including a homogenous group of EC patients, limited stage distributions (IB and II) and identical histology (grade 3 EEC). Also, clinicopathological variables between our two cohorts (MMR-deficient and MMR-proficient) appeared to be comparable and no differences in baseline characteristics were found between patients with and without adjuvant radiotherapy. Finally, we have corrected for the most important confounders used to guide adjuvant radiotherapy (LVSI, age, stage) by performing multivariable Cox regression analysis. Another potential weakness of this study was that lymph node status was unknown in a significant proportion (51.6%) of the study cohort. However, lymphadenectomy was performed equally in both MMR-groups and in this series performing lymphadenectomy was not associated with differences in clinical outcomes (data not shown). Thus although there is a risk of 'occult' higher stage cases in this cohort there is no reason to believe those cases would be disproportionately represented in one or the other MMR subgroups. Another potential limitation could be the fact that there were minor differences in molecular approaches between the participating centers, including sequencing of *POLE* exons 9 and 13 in the GOCS region, and sequencing of *POLE* exons 9 to 14 in the BCCA and Tübingen University. Even though the most common hotspot mutations were analyzed in all cases, we cannot rule out the possibility that some mutations may have been missed. Finally, not all patients received external beam radiotherapy (EBRT), a minority received vaginal brachytherapy. However in this respect, the Post-Operative Radiation Therapy for Endometrial Carcinoma 2 (PORTEC-2) trial has shown that vaginal brachytherapy is non-inferior to EBRT with respect to preventing distant metastasis in this patient group, with similar recurrence and survival outcomes [23]. Also in this present study, no difference in outcomes was seen between patients treated with vaginal brachytherapy compared to EBRT.

In conclusion, we have shown that adjuvant radiotherapy may improve survival in patients with MMR-deficient EECs, whereas no benefit was seen in patients with MMR-proficient EECs. MMR status could be a valuable predictive marker for selection of patients who may benefit from adjuvant radiotherapy.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2019.03.097.

Conflict of interest

None declared.

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Author contribution

All authors contributed to the manuscript. CR, HK, LM, JK, JA and JP contributed to the study design. CR, HK, CP, LM, MS, SK, SB, JK, JA and JP contributed to data collection. CR, HK, CP, LM, MS, SK, SB, JK, JA and JP contributed to the data analysis. All authors contributed to writing of the manuscript, have read and have approved the final version of the manuscript being submitted for peer review.

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