Does mismatch repair (MMR) deficiency have prognostic significance in low-risk endometrioid endometrial cancers?

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BACKGROUND

- The mismatch repair (MMR) system is DNA repair mechanism that corrects base substitution mismatches that occur during DNA replication
- Loss of MMR occurs in 20-40% of endometrial cancers, and this MMR deficiency can be detected via immunohistochemistry (IHC) as loss of MMR protein expression
- Only 5-10% of endometrial cancers with MMR deficiency are due to Lynch Syndrome, due to autosomal dominant mutations in *MLH1*, *MSH2*, *MSH6*, or *PMS2*
- Our previous work has demonstrated that in women with advanced endometrial cancer receiving adjuvant treatment, MMR deficiency is associated with better overall and progression-free survival as well as lower recurrence rates; this is theorized to be secondary to heightened response to adjuvant therapy
- It remains uncertain whether MMR deficiency is prognostic or predictive of outcomes, as most patients in these studies had received adjuvant therapy
- To determine the prognostic value of MMR deficiency**, we looked at a subgroup of women with low-risk endometrioid endometrial cancer, for which there is usually no adjuvant therapy given after surgery

OBJECTIVE

To compare recurrence and survival outcomes in women with MMR-deficient endometrial cancers compared to those with MMR-proficient cancers, specifically among those with low risk disease (Stage IA, grade 1 and 2, endometrioid histology)

HYPOTHESIS

By comparing low-risk MMR-deficient vs. MMR-proficient endometrioid endometrial cancers, we can better elucidate the **prognostic value** of MMR deficiency

METHODS

- Study Design**
- Retrospective population-based cohort study
- Patient Cohort**
- Low-risk endometrial cancer cases (Endometrioid type, stage IA, grades 1 or 2 only using ESMO classification)
 - Treated surgically from 2011 to 2016
 - All evaluated for MMR deficiency via IHC (4 MMR proteins evaluated: *MLH1*, *MSH2*, *PMS2*, *MSH6*)
 - Total of 475 patients identified with 6 months of follow up
- Data Analysis**
- Demographics and clinical characteristics compared between patients with MMR-deficient and those with MMR proficient tumors
 - Fisher's exact test for categorical data
 - Wilcoxon rank-sum test for continuous data
 - Recurrence rates reported per 100 person-years
 - Progression free survival (PFS) and overall survival (OS) compared using Kaplan-Meier curves and log-rank tests
 - Cox proportional hazards regression to estimate difference in PFS and OS after covariate adjustment

RESULTS

TABLE 1. CLINICOPATHOLOGIC CHARACTERISTICS

	TOTAL (475)	MMR- PROFICIENT (344)	MMR- DEFICIENT (131)	P-VALUE
AGE AT DIAGNOSIS (MEDIAN AND IQR)	60 (53-68)	59 (53-66)	62 (55-69)	0.005
BMI (MEAN)	35 (+/- 11)	36 (+/- 11)	32 (+/- 8)	0.008
POSTOPERATIVE GRADE:				<0.0001
I	310 (65%)	244 (71%)	66 (50%)	
II	165 (35%)	100 (29%)	65 (50%)	
LYMPHADENECTOMY	42 (8.8%)	19 (5.5%)	23 (17.6%)	<0.0001
LYNCH SYNDROME	14 (2.9%)	0 (0%)	14 (10.7%)	<0.0001
MMR DEFICIENCY MLH1/HYPERMETHYLATION MSH2 MSH6 PMS2			102 (78%) 13 (10%) 14 (11%) 2 (2%)	
ADJUVANT THERAPY	30 (6.3%)	14 (4.1%)	16 (12.2%)	0.002
BRACHYTHERAPY	10 (2.1%)	7 (2.0%)	3 (2.3%)	1.00
PELVIC RADIOTHERAPY	13 (2.7%)	3 (0.9%)	10 (7.6%)	0.0003
ADJUVANT CHEMOTHERAPY	13 (2.7%)	6 (1.7%)	7 (5.3%)	0.053

FIGURE 1. MMR STATUS AND PROGRESSION FREE SURVIVAL (LEFT) AND OVERALL SURVIVAL (RIGHT) IN LOW-RISK ENDOMETRIAL CANCER
P value is from log-rank test. MMR-proficient=red, MMR-deficient=blue. The shaded area indicates the 95% CI.

SUMMARY/CONCLUSIONS

- Women with MMR deficient tumors are older with lower BMI
- Women with MMR deficient tumors are more likely to have undergone lymphadenectomy, and more likely to have lymphovascular space invasion identified in the tumors (18% vs 6%, $p<0.0001$)
- Women with MMR deficient tumors had higher recurrence rates (3.56p100py) compared to those with MMR proficient tumors (1.21p100py) with $p=0.008$
- Absolute recurrences were low, with 11 out of 131 in MMR-deficient and 14 out of 344 MMR-proficient groups
- After adjustment for age, LVSI status, adjuvant therapy, and post-operative grade, MMR-deficient status remained associated with a higher risk of recurrence (HR 3.56, 95% CI 2.01-5.95)**
- Median follow-up was 23.4 months (11.7-40.6mo)
- MMR deficiency may have adverse *prognostic* value in low-risk endometrial cancers, as demonstrated by higher recurrence rates
- In contrast, MMR deficiency has been found to be a favorable *predictive* marker for response to adjuvant therapy as demonstrated by our previous study
- Worse outcomes associated with MMR deficiency may be related to dysregulation of estrogen and progesterone receptor