

## **MLH1 promoter hypermethylation among mismatch repair deficient, high-intermediate risk, endometrial cancer patients is associated with differences in prognostic factors**

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Topic: Endometrial

### Objectives

To compare prognostic factors in patients with mismatch repair deficient (dMMR), high-intermediate risk (HIR), endometrial cancer (EC) based on MLH1 promoter methylation (MPM) status.

### Methods

Adult women with HIR EC diagnosed between January 1, 2016, and December 31, 2018, were identified from UC San Diego and Kaiser Southern California. MPM, dMMR, patient, and disease characteristics were collected by chart review. Cases were limited to those who underwent hysterectomy with endometrioid histology and pathology confirmed stage 1 disease. HIR disease was defined as the presence of three risk factors if age < 50 years, two risk factors if age ≥50 and < 70 years, and one risk factor if age ≥70 years. Risk factors included tumor grade 2 or 3, the presence of lymphovascular space invasion (LVSI), and ≥50% myometrial invasion as outlined in GOG protocol 249. MPM positive relative risk (RR) of the risk factors were calculated.

### Results

Two hundred forty-four patients with HIR EC were identified; 86 (35.2%) patients were dMMR by immunohistochemistry. Seventy-four (86.1%) patients were MPM positive and 12 (13.9%) were MPM negative. We found no significant differences in age, BMI, race, LVSI, or type of adjuvant treatment received between the MPM positive and negative groups. The MPM positive patients were more likely to have ≥50% myometrial invasion (RR 3.9, 95% CI 1.1-13.9,  $p=0.037$ ), but less likely to have a grade 2-3 tumor (RR 0.9, 95% CI 0.8-0.9,  $p=0.0009$ ).

We found no significant difference in recurrence rates between the MPM positive and negative groups (21.6% versus 16.7%, RR 1.30,  $p=0.70$ ), even when controlling for adjuvant radiation. The mean time to recurrence was 485 days in the MPM positive group ( $n=16$ ) and 724 days in the negative group ( $n=2$ ), which was not statistically significantly different ( $p=0.27$ ). Six cancer-related deaths occurred within the MPM positive group and none in the negative group.

### Conclusions

Despite significantly lower grade, MPM positive dMMR HIR EC patients are at higher risk of deep myometrial invasion. If confirmed in other cohorts, this seemingly contradictory finding may offer insights into how MPM status interacts with conventional prognostic factors. No outcome differences were seen; however, the relatively modest size of the study cohorts increase the chance of type II error. Work is ongoing to more precisely evaluate the interaction of MPM status with prognostic factors and prognosis.

Abstract Table or Graph

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