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Survival of endometrial cancer patients with lymphatic invasion and deficient mismatch repair expression

Keith Y. Terada [a,*], Michael Black [b], Laura H. Terada [b], James Davis [c,1], David M. Shimizu [b]

[a] University of Hawaii School of Medicine, Department of Obstetrics and Gynecology, Honolulu, Hawaii, USA
[b] Queens Medical Center Department of Pathology, Honolulu, Hawaii, USA
[c] University of Hawaii Cancer Research Center, Honolulu, Hawaii, USA

HIGHLIGHTS

- Endometrial cancer patients with lymphatic invasion appear to have a better survival when mismatch repair expression is deficient.
- Mismatch repair expression affects survival for patients with stage 3C endometrial cancer.

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ABSTRACT

Objective. This study examines patients under the age of 70 with endometrial cancer and lymphatic invasion or lymph node metastases. Survival of patients with loss of tumor mismatch repair expression is compared to survival of patients with normal mismatch repair expression.

Methods. This is a retrospective review of patients treated from 1998–2009 for carcinoma of the endometrium. All patients with lymphatic invasion, including lymph node metastases, had immunohistochemical staining of the primary tumor for loss of expression of the mismatch repair genes MLH1, PMS2, MSH6, and MSH2. Overall survival and disease specific survival were compared using Kaplan–Meier plots.

Results. Sixty-six patients were identified for inclusion; 26 demonstrated loss of mismatch repair expression and 40 demonstrated normal mismatch repair expression. Overall survival and disease specific survival were significantly better in the group with defective mismatch repair expression. Subgroup analysis of FIGO stage 3C patients also showed significantly better survival in patients with deficient mismatch repair expression.

Conclusion. For patients with endometrial cancer and lymphatic invasion, patients demonstrating loss of mismatch repair expression in the primary tumor appear to have a significantly better survival than patients with normal mismatch repair expression. Further investigation appears warranted to examine a possible role of mismatch repair expression as a prognostic marker for high risk patients with endometrial cancer.

Introduction

Endometrial cancer is the most common gynecologic cancer in the United States. There are well recognized clinical features associated with this malignancy, ie. obesity, diabetes, nulliparity, and anovulation. Recently, however, there has been a growing body of literature associating endometrial cancer with specific genetic profiles. Inherited or acquired defects in specific pathways are now known to drive endometrial carcinogenesis. These pathways include the phosphatidylinositol 3-kinase (PI3K)-AKT and PTEN pathway, the TP53 pathway, and the mismatch repair (MMR) mechanism [1]. Recent literature has indicated that endometrial malignancies associated with MMR deficiency present with a distinctive phenotype. These patients appear to have a normal body mass index (BMI), and high grade tumors with tumor infiltrating lymphocytes, lymphovascular space invasion, and a high risk of lymph node metastases [2].

There are four MMR genes of clinical interest, MLH1 on chromosome 3, PMS2 on chromosome 7, MSH2 on chromosome 2, and MSH6 on chromosome 2. These genes maintain genomic integrity by correcting errors in base pairing during DNA replication. MSH2 and MSH6 recognize and bind to mismatched nucleotides, MLH1 and PMS2 are then recruited to excise the mismatched nucleotides. Presumably, loss of MMR function leads to increased genomic instability, impairment of critical pathways, and carcinogenesis. Approximately 20–30% of endometrial cancers appear to be associated with loss of MMR expression [3]. 5–10% appears attributable to a germline mutation (Lynch Syndrome), and the remainder

* Corresponding author at: 1329 Lusitana St. # 703, Honolulu, Hawaii 96813, USA. Fax: +1 808 528 3671.
E-mail address: kterada@aloha.net (K.Y. Terada).
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arise due to acquired hypermethylation of the MLH 1 promoter region and consequent loss of function [4].

Loss of MMR function is also associated with an increased risk of colorectal cancer; and there is convincing evidence that the clinical behavior of these tumors differs from sporadic colorectal cancer [5]. Approximately 15% of colorectal cancers are associated with loss of MMR function [6]. Pooled data from over 10,000 patients indicates that overall survival and progression free survival are significantly improved for patients with MMR deficient tumors [5]. Other studies indicate that survival for MMR deficient stages 2 and 3 colon cancer is improved when treated by surgery alone, but not when treated with adjuvant 5 FU [7]. The current study was undertaken to explore a possible relationship between MMR deficient tumors, treatment outcome, and survival for endometrial cancer patients with lymphatic invasion.

Methods

Institution Review Board Approval was obtained from the Queens Medical Center in Honolulu, Hawaii. Patients under the age of 70 with adenocarcinoma of the endometrium from 1998–2009 were identified. A total of 699 patients underwent surgery for endometrial cancer over this 12 year period. All patients in this series were treated by a single gynecologic oncologist (KYT) and all pathology was reviewed by a single gynecologic pathologist (DMS). Patients with lymphatic invasion were identified; patients with FIGO stages I–IIIA were included if lymphovascular invasion was found on the hysterectomy specimen. Patients with FIGO stage IIIC and IV were included if lymph node metastases were present and biopsy confirmed. Lymphovascular space invasion and lymph node metastases are recognized as a prognostic marker for a higher risk of metastases and poor survival. Age 70 was used as an upper age boundary to minimize the impact of advanced age and medical co-morbidities on overall survival. All adenocarcinomas were included, including papillary serous, clear cell, and carcinosarcoma; pure sarcomas were excluded. All patients underwent an initial hysterectomy, bilateral salpingoopherectomy, and pelvic lymphadenectomy. Regional lymphadenectomy was performed unless contraindicated for medical or technical reasons; four patients did not undergo pelvic lymphadenectomy. Sixty-six patients were identified for inclusion.

Immunohistochemistry was performed using antibodies to MLH1, MSH6, PMS2 (BD Biosciences, San Jose, CA), and MSH2 (Calbiochem, San Diego, CA). Detection was obtained using diaminobenzidine after a polymer based amplification step (Envision Plus, Dako, Carpinteria, CA) for MLH1 and MSH2 and Mach 2 polymer (Biocare Medical, Concord, CA) for PMS2 for antibodies run on the Dako Autostainer (Dako, Carpinteria, CA). Detection for MSH6 (using the Ventana Benchmark autostainer, Ventana, Tucson, AZ) was obtained using the diaminobenzidine and avidin–biotin complex methodology. Nuclear staining of normal lymphocytes and/or stromal cells in each slide served as an internal control. The current study did not test for hypermethylation of the MLH1 promoter region. MMR deficient was defined as less than 5% of tumor cells staining positive. Lymphovascular space invasion was defined as tumor cells within (not necessarily attached) to endothelial lined vascular spaces.

Survival analysis was performed using Kaplan Meier plots and log rank statistic was used to compare survival. Statistical significance was defined as $p<0.05$.

Results

Sixty-six patients were identified for inclusion. All patients underwent surgery. Fifty-three patients received post-operative chemotherapy with or without radiation. In the earlier years cis-platinum, Adriamycin, and Taxol were utilized; Taxol and Carboplatinum were favored in the later years. Three patients received only radiation after surgery. Six patients did not receive post-operative adjunctive treatment, and post-operative treatment details were not available for four of the patients. Forty patients had normal expression of MMR in tumor tissue. Twenty-six patients had deficient MMR expression; four had deficient MSH6 or MSH2 expression and 22 had deficient MLH1 or PMS2 expression. Clinical findings are summarized in Table 1. Median follow-up for all patients was 32 months.

Overall survival is shown in Fig. 1. The difference between MMR deficient and MMR normal was statistically significant ($p=0.03$); patients with MMR deficient tumors experienced a significantly improved survival. Fig. 2 compares disease specific survival between the two groups. Patients with MMR deficient tumors had a significantly lower risk of cancer death than patients with MMR normal tumors ($p=0.04$).

A subgroup analysis was performed for patients with FIGO stage 3C cancer. Again, patients with MMR deficient tumors were noted to have a significantly improved overall survival ($p=0.01$) and improved disease specific survival ($p=0.04$). This is demonstrated in Figs. 3 and 4. Because of the uniformly poor prognosis noted for patients with stage 4 cancer, additional survival analysis was performed excluding the stage 4 patients. Patients with MMR deficient tumors again had a significantly improved overall survival ($p=0.05$). Although disease specific survival was better for MMR deficient patients, the difference was not statistically significant ($p=0.08$).

Discussion

Various studies have noted that 20–30% of patients with endometrial cancer exhibit deficient MMR expression in tumor cells. There is a growing body of literature to suggest that these tumors are associated with specific histopathologic features [8]. There are relatively few studies, however, examining survival. Cohn [9] and Nout [10] both noted an improved survival in patients with normal MMR expression compared to patients with deficient MMR expression. Both studies, however, compared an unselected group of patients; and both studies note that MMR deficient tumors were associated with poor prognostic findings. The current study, by contrast, selected only patients with lymphatic invasion, i.e. a prognostically high risk group. Survival for this high risk group was compared for patients with MMR deficient tumors and MMR normal tumors. Both overall survival and disease specific survival were better in the MMR deficient patients. In particular, for stage 3C patients, overall survival and disease specific survival were better in patients with MMR deficient tumors.

Loss of MMR expression is also associated with colorectal cancer; approximately 15% of colorectal tumors demonstrate MMR deficiency. Ribic [11], Sargent [7], and others have noted a significantly improved prognosis in stages 2 and 3 colorectal cancers associated with MMR deficient tumors. This improved prognosis, however, appears to extend only to patients treated with surgery alone. Although 5FU appeared to

Table 1
Clinical characteristics of patients with endometrial cancer and lymphatic invasion. Non-endometrioid histology includes clear cell, papillary serous, undifferentiated, and carcinosarcoma. CT = chemotherapy, RT = radiation therapy, n.s. = not significant.

	Mismatch repair deficient	Mismatch repair normal	p value
Number	26	40	
Mean age	54	52	n.s.
Histology			
Endometrioid	21 (80%)	27 (68%)	
Non-endometrioid	5 (20%)	13 (32%)	n.s.
Stage			
I	2 (8%)	5 (13%)	
II	2 (8%)	3 (7%)	
III	20 (76%)	27 (67%)	
IV	2 (8%)	5 (13%)	n.s.
Post-operative treatment			
CT and/or RT	22 (84%)	34 (85%)	
None	2 (8%)	4 (10%)	
Unkown	2 (8%)	2 (5%)	n.s.