Published in final edited form as:

Gynecol Oncol. 2014 October ; 135(1): 81–84. doi:10.1016/j.ygyno.2014.07.100.

Lynch Syndrome in patients with clear cell and endometrioid cancers of the ovary

Koah R. Vierkoetter[a,*], **Asia R. Ayabe**[a], **Maya VanDrunen**[b], **Hyeong Jun Ahn**[c], **David M. Shimizu**[a], and **Keith Y. Terada**[b]

[a]Department of Pathology, John A. Burns School of Medicine, University of Hawaii, Honolulu, HI, USA

[b]Department of Obstetrics, Gynecology, and Women's Health, John A. Burns School of Medicine, University of Hawaii, Honolulu, HI, USA

[c]Biostatistics Core, John A. Burns School of Medicine, University of Hawaii, Honolulu, HI, USA

Abstract

Objective—Patients with Lynch Syndrome are at an increased risk for a variety of malignancies, including ovarian cancer. Ovarian cancers associated with Lynch Syndrome are predominantly clear cell or endometrioid in histology. Lynch Syndrome is characterized by germline mutations in mismatch repair (MMR) genes. The current study aims to assess the prevalence of loss of MMR expression in patients with endometrioid and clear cell ovarian carcinoma.

Methods—A retrospective review identified 90 patients with endometrioid and/or clear cell carcinomas. Slides made from tumor tissue microarray blocks were evaluated using immunohistochemical stains with antibodies against MLH1, PMS2, MSH2, and MSH6. Statistical analysis was performed.

Results—Seven of the 90 cases (7.8%) had loss of MMR expression. The mean age of patients with loss of MMR expression (47 years) was significantly younger than those with retained MMR expression ($p = 0.014$). Loss of MMR expression was present in 20% of patients under the age of 53 with clear cell or endometrioid cancers. Genetic studies found that 3 of the 5 patients with loss of MMR expression carried mutations consistent with Lynch Syndrome; acquired hypermethylation of MLH1 was noted in one patient. Six of 7 patients (86%) whose tumors lacked MMR expression had synchronous or metachronous primary malignancies, a significantly greater prevalence than those with retained MMR expression ($p < 0.001$).

Conclusion—Patients under the age of 53 with clear cell or endometrioid ovarian carcinomas are at a clinically significant risk for loss of MMR expression and Lynch Syndrome; routine screening with immunohistochemical staining should be considered.

[*]Corresponding author at: John A. Burns School of Medicine, University of Hawaii, Department of Pathology, 651 Ilalo Street MEB #411E, Honolulu, HI 96813 USA. Fax: +1 808 692 1256. koah@hawaii.edu (K.R. Vierkoetter).

Conflict of interest statement

There are no conflicts of interest.

Keywords

Lynch Syndrome; Ovarian cancer; Microsatellite instability; Mismatch repair; Endometrioid ovarian carcinoma; Clear cell ovarian carcinoma

Introduction

The role of genetic evaluation in patients with ovarian cancer has historically focused on BRCA testing in patients with serous cancers of the ovary [1,2]. Women with Lynch syndrome (hereditary non-polyposis colorectal carcinoma), however, are also at increased risk of ovarian cancer [3]. Commonly associated with an increased risk of colon and endometrial cancer, Lynch syndrome may also be associated with ovarian, urothelial, and pancreatic malignancies [4,5]. The risk of ovarian cancer in women with Lynch Syndrome is estimated at 7–12% [6,7]. These malignancies are primarily non-serous in histology, and the majority are clear cell or endometrioid [8–15]. Lynch syndrome is characterized by loss of expression of mismatch repair (MMR) genes. The four clinically significant MMR genes are MSH6, MSH2, MLH1, and PMS2 [16–18]. Immunohistochemical staining can be performed on fixed tumor tissue to assess for loss of MMR expression [19–22]. Although women with serous ovarian cancers are often referred for BRCA testing, women with clear cell or endometrioid ovarian cancers are not routinely screened for Lynch Syndrome [23]. The current study was undertaken to assess the prevalence of Lynch Syndrome in patients with clear cell and endometrioid cancers of the ovary. A high prevalence of MMR deficiency in this population would support routine screening for Lynch Syndrome.

Methods

This is a retrospective review of cases at the Queens Medical Center in Honolulu diagnosed between January 1, 1995 to April 12, 2013 with clear cell cancer and endometrioid cancer of the ovary. The study was approved by the Institutional Review Board. Patients were identified through the hospital tumor registry and the Pathology Department database. Ninety cases were identified for inclusion. All paraffin-embedded tissue blocks were retrieved for immunohistochemical analysis and patient charts were reviewed for clinicopathologic variables.

A gynecologic pathologist (DS) reviewed hematoxylin and eosin-stained whole-slide sections of the selected cases. Upon confirmation of tumor histologic type per World Health Organization (WHO) guidelines [24], formalin-fixed, paraffin-embedded tissue microarray blocks were constructed from 2.0 mm cores of representative tumor samples. In cases demonstrating mixed endometrioid and clear cell histology, representative areas from each histologic type were selected. Synchronous primary ovarian and endometrial carcinomas were verified as independent primaries using criteria outlined by the WHO [24].

Antigen retrieval was performed with EnVision FLEX Target Retrieval Solution, High pH (Dako, Carpinteria, CA) at 97 degrees C for 20 minutes. Evaluation of MMR protein expression was performed on 4-μm sections of the tissue microarray blocks using antibodies to MLH1 (clone G168-15, 1:75 dilution, Biocare Medical, Concord, CA), PMS2 (clone

A16-4, 1:300 dilution, Biocare Medical), MSH6 (clone BC/44, 1:100 dilution, Biocare Medical) and MSH2 (clone FE11, 1:100 dilution, Biocare Medical). Detection was obtained using the MACH 3 Mouse HRP-Polymer Detection Kit (Biocare Medical). Chromogenic detection was achieved with diamniobenzidine (Dako) and sections were counterstained with hematoxylin (Dako).

Results were evaluated by a gynecologic pathologist experienced in MMR protein immunohistochemical interpretation. Staining of any tumor nuclei was interpreted as positive, with expression by lymphocytes and/or stromal cells considered a positive internal control. Ten tissue microarray results without nuclear staining were then validated with whole-slide sections of the tumor by the aforementioned staining and interpretative procedure. Seven of these cases had validated and confirmed MMR loss of expression.

Clinicopathologic data were obtained via review of electronic medical records, paper charts, and the institutional cancer registry. For all cases, variables collected included age at diagnosis, tumor grade, International Federation of Gynecology and Obstetrics (FIGO) stage, synchronous or metachronous primary malignancies, vital status, disease status, and date of last contact. For cases demonstrating loss of MMR protein expression, results of germline testing DNA sequence analysis, if available, were also obtained (Ambry Genetics, Aliso Viejo, CA; Myriad Genetic Laboratories, Salt Lake City, UT). One case exhibiting loss of MLH1 expression was sent to a reference laboratory for MLH1 promoter hypermethylation PCR analysis (Mayo Medical Laboratories, Rochester, MN).

Statistical analyses were performed using the two sample t-test and Fisher's exact test as appropriate for continuous and categorical variables. Overall survival was assessed and a Kaplan-Meier curve constructed. A p value of <0.05 was considered statistically significant.

Results

At Queen's Medical Center, Honolulu, 438 cases of epithelial ovarian cancer were identified between January 1, 1995 and April 12, 2013. Ninety (20%) had clear cell or endometrioid histology; 53 endometrioid tumors, 33 clear cell tumors, and 4 with mixed clear cell and endometrioid histology. Seven (7.8%) of the tumors demonstrated confirmed loss of MMR expression. Clinical and pathologic characteristics are summarized in Table 1. The mean age of patients with MMR protein loss of expression was 47 years, significantly younger than those with normal expression ($p = 0.014$). Within the subgroup of patients under the age of 53, 7 of 35 (20%) demonstrated loss of MMR expression. A majority of patients with loss of MMR expression (86%) were diagnosed with a synchronous or metachronous primary malignancy, significantly more than those with normal MMR expression ($p < 0.001$). Differences in histology, grade, stage, and overall survival were not statistically significant.

Clinicopathologic characteristics of the 7 patients with MMR protein loss of expression are displayed in Table 2. Five of the 7 patients with MMR deficient tumors underwent subsequent genetic analysis. Three of these patients were found to carry a deleterious MMR gene mutation consistent with Lynch Syndrome; one patient had hypermethylation of the MLH1 promoter region, and another patient was found to have an MSH6 variant of

uncertain significance. Two patients with loss of MMR expression did not have germline testing, as one woman declined and the other was lost to follow-up.

All endometrial second primary cancers were diagnosed synchronously with the ovarian cancer; all were of endometrioid histology. Two patients had metachronous malignancies; the colorectal cancer was diagnosed prior to the ovarian cancer, and the pancreatic cancer was diagnosed following the diagnosis of ovarian cancer.

Discussion

Although there has been considerable research on the genetic aspects of ovarian cancer, most of the literature is focused on BRCA mutations. Much of the literature regarding Lynch Syndrome has focused on cancers of the endometrium and colon with relatively less attention given to the association of ovarian cancer with Lynch Syndrome. Although ovarian cancer is the fourth most common primary cancer in women with Lynch Syndrome, this still appears to be a relatively uncommon event [5,7]. Previous investigators report that 2–10% of unselected patients with ovarian cancer demonstrate loss of MMR expression [9,25–28]. Lynch Syndrome associated ovarian cancer appears to be mostly of clear cell or endometrioid histology [8–15]. In our institution, 90/438 (21%) of the epithelial ovarian cancers registered over the past 18 years were clear cell or endometrioid carcinomas. The present study found loss of MMR expression in 7 of the 90 (7.8%). All 7 of the MMR deficient ovarian endometrioid and clear cell carcinomas were in patients under the age of 53 years. Thus, the prevalence of MMR deficient ovarian endometrioid and clear cell tumors in patients under the age of 53 was 7/35 (20%); and the 47 mean years of patients with loss of MMR expression was significantly younger than the 58 mean years of patients with retained MMR expression ($p = 0.014$). Besides an earlier age of diagnosis in patients with ovarian endometrioid or clear cell carcinoma with loss of MMR expression compared to those with normal expression, we found no other unique clinical or pathological characteristics. Jensen et al. reported that patients with ovarian cancers demonstrating loss of MMR expression presented with early stage tumors [26], but this was not confirmed in our small study.

Three of the five relatively young patients with loss of MMR expression in their endometrioid or clear cell carcinomas underwent further genetic analysis and were found to have MMR gene mutations consistent with Lynch Syndrome. This suggests that women with MMR deficient endometrioid and/or clear cell carcinomas may be appropriately selected for cancer genetic counseling to consider testing for possible germline mutations. While the present study found MLH1 hypermethylation in the youngest patient in the MMR deficient cohort, a 39 year-old woman with endometrioid carcinoma, the role of acquired hypermethylation of MLH1 in ovarian carcinogenesis remains unclear. Zauber et al. found that 62% of patients with endometrial cancer and loss of MMR expression under the age of 50 had unmethylated tumors, consistent with a germline mutation. Only 17% of similar patients over the age of 50 had unmethylated tumors [29]. This suggests that epigenetic silencing of MLH1 increases with increasing age for endometrial cancer, and that this is a significant factor in endometrial carcinogenesis for older patients. Conversely,

hypermethylation of MLH1 appears to be relatively uncommon in clear cell and endometrioid carcinomas of the ovary.

A number of studies have reported on microsatellite instability (MSI) in ovarian cancer [12,30–32]. Microsatellites are short repetitive sequences of DNA distributed throughout the genome and are susceptible to replication errors. With loss of MMR function, these errors accumulate and result in MSI [33]. The National Cancer Institute outlines a panel of five mononucleotide and dinucleotide microsatellite markers, which can be detected by polymerase chain reaction [34]. The current study did not specifically address MSI testing in clear cell and endometrioid tumors. Previous studies, however, have demonstrated excellent correlation between MSI and MMR protein loss of expression by immunohistochemistry for ovarian malignances [15,25]. Immunohistochemical staining for loss of MMR expression is readily available and relatively inexpensive, and for most pathology laboratories will be preferable to MSI testing as a screen for Lynch Syndrome [35].

Previous studies regarding young patients with ovarian cancer have noted a possible role for conservative surgery and fertility preservation [36]. Zanetta et al. reported that a conservative approach might be feasible for young patients, even in the presence of high-grade tumors [37]. The current study found that four of seven patients with loss of MMR expression had synchronous primary endometrial cancers. Aysal et al. found five of seven patients with MMR deficient endometrioid ovarian cancer presented with a primary MMR deficient endometrial cancer [38]. This would suggest that young ovarian cancer patients with loss of MMR expression are not acceptable candidates for fertility preservation. Again, consideration should be given to routine screening for MMR expression in young patients with clear cell or endometrioid ovarian cancer. Unlike BRCA testing, screening for MMR expression can be readily performed on fixed tumor tissue [19–22]. Those demonstrating loss of expression can then be referred for germline testing or genetic counseling [35].

In conclusion, 20% of patients under the age of 53 with clear cell or endometrioid cancers of the ovary have MMR deficient tumors. Of the five patients with MMR deficient tumors who had genetic testing, three were found to carry germline mutations consistent with Lynch Syndrome. There is a significant risk of a second synchronous or metachronous primary malignancy in this population. Immunohisto-chemical staining for MMR expression is recommended for all patients under the age of 53 with endometrioid or clear cell carcinomas of the ovary. Patients with MMR deficient tumors are candidates for cancer genetics counseling to consider germline testing and careful surveillance for second primary malignancies.

The biostatistician collaborator was partially supported by grants from the National Institute on Minority Health and Health Disparities U54MD007584 and G12MD007601 from the National Institutes of Health. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

References

1. Folkins AK, Jarboe EA, Roh MH, Crum CP. Precursors to pelvic serous carcinoma and their clinical implications. Gynecol Oncol. Jun; 2009 113(3):391–6. [PubMed: 19237187]

2. King MC, Marks JH, Mandell JB. New York Breast Cancer Study Group. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. Science. Oct 24; 2003 302(5645):643–6. [PubMed: 14576434]

3. Schmeler KM, Lu KH. Gynecologic cancers associated with Lynch syndrome/HNPCC. Clin Transl Oncol. Jun; 2008 10(6):313–7. [PubMed: 18558577]

4. Koornstra JJ, Mourits MJ, Sijmons RH, Leliveld AM, Hollema H, Kleibeuker JH. Management of extracolonic tumours in patients with Lynch syndrome. Lancet Oncol. Apr; 2009 10(4):400–8. [PubMed: 19341971]

5. Watson P, Vasen HF, Mecklin JP, Bernstein I, Aarnio M, Järvinen HJ, et al. The risk of extra-colonic, extra-endometrial cancer in the Lynch syndrome. Int J Cancer. Jul 15; 2008 123(2):444–9. [PubMed: 18398828]

6. Lynch HT, Casey MJ, Snyder CL, Bewtra C, Lynch JF, Butts M, et al. Hereditary ovarian carcinoma: heterogeneity, molecular genetics, pathology, and management. Mol Oncol. Apr; 2009 3(2):97–137. [PubMed: 19383374]

7. Aarnio M, Sankila R, Pukkala E, Salovaara R, Aaltonen LA, de la Chapelle A, et al. Cancer risk in mutation carriers of DNA-mismatch-repair genes. Int J Cancer. Apr 12; 1999 81(2):214–8. [PubMed: 10188721]

8. Ketabi Z, Bartuma K, Bernstein I, Malander S, Grönberg H, Björck E, et al. Ovarian cancer linked to Lynch syndrome typically presents as early-onset, non-serous epithelial tumors. Gynecol Oncol. Jun 1; 2011 121(3):462–5. [PubMed: 21388660]

9. Lu FI, Gilks CB, Mulligan AM, Ryan P, Allo G, Sy K, et al. Prevalence of loss of expression of DNA mismatch repair proteins in primary epithelial ovarian tumors. Int J Gynecol Pathol. Nov; 2012 31(6):524–31. [PubMed: 23018216]

10. Pal T, Permuth-Wey J, Kumar A, Sellers TA. Systematic review and meta-analysis of ovarian cancers: estimation of microsatellite-high frequency and characterization of mismatch repair deficient tumor histology. Clin Cancer Res. Nov 1; 2008 14(21):6847–54. [PubMed: 18980979]

11. Murphy MA, Wentzensen N. Frequency of mismatch repair deficiency in ovarian cancer: a systematic review. Int J Cancer. Oct 15; 2011 129(8):1914–22. [PubMed: 21140452]

12. Gras E, Catasus L, Argüelles R, Moreno-Bueno G, Palacios J, Gamallo C, et al. Microsatellite instability, MLH-1 promoter hypermethylation, and frameshift mutations at coding mononucleotide repeat microsatellites in ovarian tumors. Cancer. Dec 1; 2001 92(11):2829–36. [PubMed: 11753956]

13. Cai KQ, Albarracin C, Rosen D, Zhong R, Zheng W, Luthra R, et al. Microsatellite instability and alteration of the expression of hMLH1 and hMSH2 in ovarian clear cell carcinoma. Hum Pathol. May; 2004 35(5):552–9. [PubMed: 15138928]

14. Liu J, Albarracin CT, Chang KH, Thompson-Lanza JA, Zheng W, Gershenson DM, et al. Microsatellite instability and expression of hMLH1 and hMSH2 proteins in ovarian endometrioid cancer. Mod Pathol. Jan; 2004 17(1):75–80. [PubMed: 14631366]

15. Ueda H, Watanabe Y, Nakai H, Hemmi H, Koi M, Hoshiai H. Microsatellite status and immunohistochemical features of ovarian clear-cell carcinoma. Anticancer Res. Jul-Aug;2005 25(4):2785–8. [PubMed: 16080527]

16. Lynch HT, Lynch PM, Lanspa SJ, Snyder CL, Lynch JF, Boland CR. Review of the Lynch syndrome: history, molecular genetics, screening, differential diagnosis, and medicolegal ramifications. Clin Genet. Jul; 2009 76(1):1–18. [PubMed: 19659756]

17. Li GM. Mechanisms and functions of DNA mismatch repair. Cell Res. Jan; 2008 18(1):85–98. [PubMed: 18157157]

18. Peltomäki P, Vasen H. Mutations associated with HNPCC predisposition – Update of ICG-HNPCC/INSiGHT mutation database. Dis Markers. 2004; 20(4–5):269–76. [PubMed: 15528792]

19. Piñol V, Castells A, Andreu M, Castellví-Bel S, Alenda C, Llor X, et al. Gastrointestinal Oncology Group of the Spanish Gastroenterological Association. Accuracy of revised Bethesda guidelines, microsatellite instability, and immunohistochemistry for the identification of patients with hereditary nonpolyposis colorectal cancer. JAMA. Apr 27; 2005 293(16):1986–94. [PubMed: 15855432]

20. Baudhuin LM, Burgart LJ, Leontovich O, Thibodeau SN. Use of microsatellite instability and immunohistochemistry testing for the identification of individuals at risk for Lynch syndrome. Fam Cancer. 2005; 4(3):255–65. [PubMed: 16136387]
21. Marcus VA, Madlensky L, Gryfe R, Kim H, So K, Millar A, et al. Immunohistochemistry for hMLH1 and hMSH2: a practical test for DNA mismatch repair-deficient tumors. Am J Surg Pathol. Oct; 1999 23(10):1248–55. [PubMed: 10524526]
22. Lindor NM, Burgart LJ, Leontovich O, Goldberg RM, Cunningham JM, Sargent DJ, et al. Immunohistochemistry versus microsatellite instability testing in phenotyping colorectal tumors. J Clin Oncol. Feb 15; 2002 20(4):1043–8. [PubMed: 11844828]
23. Lancaster JM, Powell CB, Kauff ND, Cass I, Chen LM, Lu KH, et al. Society of Gynecologic Oncologists Education Committee Society of Gynecologic Oncologists Education Committee statement on risk assessment for inherited gynecologic cancer predispositions. Gynecol Oncol. Nov; 2007 107(2):159–62. [PubMed: 17950381]
24. Lee, KR.; Tavassoli, FA.; Prat, J., et al. Pathology and Genetics of Tumours of the Breast and Female Genital Organs. In: Tavassoli, FA.; Devilee, P., editors. Surface Epithelial-Stromal Tumors. Lyon: IARC Press; 2003. p. 117-45.
25. Malander S, Rambech E, Kristoffersson U, Halvarsson B, Ridderheim M, Borg A, et al. The contribution of the hereditary nonpolyposis colorectal cancer syndrome to the development of ovarian cancer. Gynecol Oncol. May; 2006 101(2):238–43. [PubMed: 16360201]
26. Jensen KC, Mariappan MR, Putcha GV, Husain A, Chun N, Ford JM, et al. Microsatellite instability and mismatch repair protein defects in ovarian epithelial neoplasms in patients 50 years of age and younger. Am J Surg Pathol. Jul; 2008 32(7):1029–37. [PubMed: 18469706]
27. Domanska K, Malander S, Måsbäck A, Nilbert M. Ovarian cancer at young age: the contribution of mismatch-repair defects in a population-based series of epithelial ovarian cancer before age 40. Int J Gynecol Cancer. Jul-Aug;2007 17(4):789–93. [PubMed: 17343610]
28. Rosen DG, Cai KQ, Luthra R, Liu J. Immunohistochemical staining of hMLH1 and hMSH2 reflects microsatellite instability status in ovarian carcinoma. Mod Pathol. Nov; 2006 19(11): 1414–20. [PubMed: 16941012]
29. Zauber NP, Denehy TR, Taylor RR, Ongcapin EH, Marotta SP, Sabbath-Solitare M, et al. Microsatellite instability and DNA methylation of endometrial tumors and clinical features in young women compared with older women. Int J Gynecol Cancer. Dec; 2010 20(9):1549–56. [PubMed: 21370598]
30. Sood AK, Holmes R, Hendrix MJ, Buller RE. Application of the National Cancer Institute international criteria for determination of microsatellite instability in ovarian cancer. Cancer Res. Jun 1; 2001 61(11):4371–4. [PubMed: 11389062]
31. Geisler JP, Goodheart MJ, Sood AK, Holmes RJ, Hatterman-Zogg MA, Buller RE. Mismatch repair gene expression defects contribute to microsatellite instability in ovarian carcinoma. Cancer. Nov 15; 2003 98(10):2199–206. [PubMed: 14601090]
32. Singer G, Kallinowski T, Hartmann A, Dietmaier W, Wild PJ, Schraml P, et al. Different types of microsatellite instability in ovarian carcinoma. Int J Cancer. Nov 20; 2004 112(4):643–6. [PubMed: 15382045]
33. Loeb LA. Microsatellite instability: marker of a mutator phenotype in cancer. Cancer Res. Oct 1; 1994 54(19):5059–63. [PubMed: 7923117]
34. Boland CR, Thibodeau SN, Hamilton SR, Sidransky D, Eshleman JR, Burt RW, et al. A National Cancer Institute Workshop on Microsatellite Instability for cancer detection and familial predisposition: development of international criteria for the determination of microsatellite instability in colorectal cancer. Cancer Res. Nov 15; 1998 58(22):5248–57. [PubMed: 9823339]
35. Folkins AK, Longacre TA. Hereditary gynaecological malignancies: advances in screening and treatment. Histopathology. Jan; 2013 62(1):2–30. [PubMed: 23240667]
36. Schmeler KM, Lynch HT, Chen LM, Munsell MF, Soliman PT, Clark MB, et al. Prophylactic surgery to reduce the risk of gynecologic cancers in the Lynch syndrome. N Engl J Med. Jan 19; 2006 354(3):261–9. [PubMed: 16421367]

37. Zanetta G, Chiari S, Rota S, Bratina G, Maneo A, Torri V, et al. Conservative surgery for stage I ovarian carcinoma in women of childbearing age. Br J Obstet Gynaecol. Sep; 1997 104(9):1030–5. [PubMed: 9307530]

38. Aysal A, Karnezis A, Medhi I, Grenert JP, Zaloudek CJ, Rabban JT. Ovarian endometrioid adenocarcinoma: incidence and clinical significance of the morphologic and immunohistochemical markers of mismatch repair protein defects and tumor microsatellite instability. Am J Surg Pathol. Feb; 2012 36(2):163–72. [PubMed: 22189970]

HIGHLIGHTS

- Women with clear cell/endometrioid ovarian cancer are at risk for Lynch Syndrome.
- Synchronous and metachronous malignancies are more common in these patients.
- Screening for MMR expression is recommended in patients under 53 with these tumors.

Table 1

Clinocopathologic characteristics of ovarian endometrioid and clear cell carcinomas with and without MMR protein loss of expression (LOE).

	MMR LOE (n = 7)	Normal MMR (n = 83)	P value
Age at diagnosis	47 y (39–53 y)	58 y (38–84 y)	0.014
Incidence under age 53			
≤53 y	100% (7)	34% (28)	<0.001
>54 y	0% (0)	66% (55)	
Synchronous or metachronous malignancy			
Other primary malignancy	86% (6)	13% (11)	<0.001
No other primary malignancy	14% (1)	87% (72)	
Histology			
Clear cell	14% (1)	38% (32)	n.s.
Endometrioid	86% (6)	57% (47)	
Mixed	0% (0)	5% (4)	
Tumor grade			
1	29% (2)	20% (17)	n.s.
2/3	71% (5)	80% (66)	
FIGO stage			
I	71% (5)	72% (60)	n.s.
II–IV	29% (2)	28% (23)	
Five year overall survival rate	50%	57%	n.s.

Table 2

Clinicopathologic features of patients with MMR protein loss of expression (LOE).

Case	Age	MMR LOE	Histologic subtype	Grade	FIGO Stage	Synchronous or metachronous primary malignancy	Additional genetic testing
1	39	MLH1	Endometrioid	1	I	Endometrial	MLH1 promoter hypermethylation
2	42	MSH2	Endometrioid	1	I	Endometrial	Deleterious mutation R621X (Lynch syndrome)
3	47	MLH1	Endometrioid	2	II	Colorectal	Deleterious mutation Q426X (Lynch syndrome)
4	48	MSH2	Endometrioid	3	III	None	Not performed
5	51	MSH6	Endometrioid	2	I	Endometrial	Not performed
6	52	MSH6	Endometrioid	3	I	Endometrial	Deleterious mutation E1163X (Lynch syndrome)
7	53	MSH6	Clear cell	3	I	Pancreatic	MSH6 variant of uncertain significance (G1216E)