HJOG An Obstetrics and Gynecology International Journal

Review

HJOG 2023, 22 (4), 149-157 | DOI: 10.33574/HJOG.0537

Mucinous differentiation of endometrioid endometrial carcinoma: Impact on pathology features and survival outcomes

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Abstract

Objective: Mucinous differentiation of endometrioid adenocarcinoma refers to the presence of a mucinous component that does not exceed 50% of the surface of the tumor. It has been associated with improved survival outcomes. In the present systematic review, we summarize the evidence to provide a robust result concerning the prognostic significance of this histologic variant.

Methods: We systematically searched Medline, Scopus, Clinicaltrials.gov, EMBASE, Cochrane Central Register of Controlled Trials CENTRAL and Google Scholar databases in our primary search along with the reference lists of electronically retrieved full-text papers.

Results: Four retrospective observational studies were included in the present meta-analysis that involved 1.501 patients. Patients with mucinous differentiation of endometrioid carcinomas had similar odds of deep myometrial invasion compared to patients with endometrioid carcinoma (OR 1.00, 95% CI 0.62, 1.59) as well as of developing lymphovascular space invasion (OR 1.00, 95% CI 0.59, 1.71) or lymph node metastases (OR 0.89, 95% CI 0.39, 2.05). Recurrence free survival of these patients (OR 0.59, 95% CI 0.03, 10.42) were also similar to those of patients with endometrioid endometrial carcinoma.

Conclusion: Mucinous differentiation of endometrioid endometrial carcinoma does not appear to be associated with significantly increased risk of lymph node metastases, lymphovascular space invasion or deep myometrial invasion. Concurrently, there is no evidence to support its association with decreased progression free or overall survival rates.

Key words: mucinous, endometrioid, carcinoma, systematic review, meta-analysis

Introduction

Endometrioid endometrial cancer is the most common gynecologic malignancy with an estimated worldwide prevalence that exceeds 417,000 cases and an accompanying mortality that reaches 97,000 deaths.[1] The most frequent histologic subtype encountered refers to endometrioid carcinomas which compose more than 80% of cases. The last decades endometrioid carcinomas are subgrouped in two distinct subtypes, namely type I tumors that are considered to be low grade carcinomas that are estrogen-dependent and mainly appear in women of younger age and type II tumors that behave aggressively, are independent of hormonal parameters and are associated with mutations of the p53 gene.[2] Typically, the disease is diagnosed at early stages as abnormal/postmenopausal uterine bleeding is the main symptom and appears early in the course of the disease.[3]

Mucinous endometrial cancer is an unusual histologic variant that is encountered in approximately 1-4% of endometrial adenocarcinomas and is defined by the presence of mucinous differentiation in an extent that exceeds 50% of the surface of the tumor. In most cases these patients present at early stages and the survival outcome is excellent without the need of adjuvant therapy following surgical resection of the disease.[4,5] However, a large population-based cohort from the Surveillance, Epidemiology, and End Results (SEER) program revealed that these patients are more likely to present with positive lymph nodes, although this did not affect their outcomes compared to patients with endometrioid histology.[6]

Several articles investigated the last years the association of mucinous differentiation of endometrioid adenocarcinoma with other histology parameters that influence patient survival, including deep myometrial invasion, presence of lymphovascular invasion (LVSI) and presence of lymph node metastases. Contrary to the traditional form of mucinous endometrial cancer, mucinous differentiation of endometrioid endometrial adenocarcinoma is associated with a smaller proportion of the mucinous component. The purpose of the present study is to evaluate the prognostic significance of this histologic variant.

Methods

Study design and registration

The present meta-analysis was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[7] The study was based in aggregated data that have been already published in the international literature. Patient consent and institutional review board approval were not retrieved as they are not required in this type of studies. The study's protocol was published in PROSPERO (International prospective register of systematic reviews) prior to the conduct of this review (Registration number: CRD42023402546).

Types of studies and patients

The eligibility criteria for the inclusion of studies were predetermined. Observational studies (prospective and retrospective) that evaluated the impact of mucinous differentiation of endometrioid adenocarcinoma on survival outcomes of patients with endometrial cancer were selected for inclusion. The percentage of the mucinous component among cases was expected to vary, however, cases with mucinous endometrial cancer were excluded from the present meta-analysis. Studies that evaluated the correlation of mucinous differentiation with the presence of LVSI and lymph node metastases were also considered eligible for inclusion, even if they did not report survival outcomes. Tumor stage and grade of differentiation were also considered as potential factors of subgroup analysis, provided that a substantial number of studies and cases were eligible for inclusion. Case reports, experimental studies and conference proceedings were excluded from the present meta-analysis.

Information sources and search methods

We used the Medline (1966–2022), Scopus (2004–2022), Clinicaltrials.gov (2008–2022), EMBASE (1980–2022), Cochrane Central Register of Controlled Trials CENTRAL (1999–2022) and Google Scholar (2004–2022) databases in our primary search along with the reference lists of electronically retrieved full-text papers. The date of our last search was set at March 31, 2022. Our search strategy included the text words "mucinous; endometrial cancer and survival". The process of selection of eligible articles is briefly presented in Figure 1.

Study selection

Studies were selected in three consecutive stages. Following deduplication, the titles and abstracts of all electronic articles were screened by two authors to assess their eligibility. Studies that investigated the impact of histologically confirmed mucinous differentiation of endometrioid cancer with survival outcomes and/or presence of LVSI or lymph node metastases were selected for inclusion. The decision for inclusion of studies in the present meta-analysis was taken after retrieving and reviewing the full

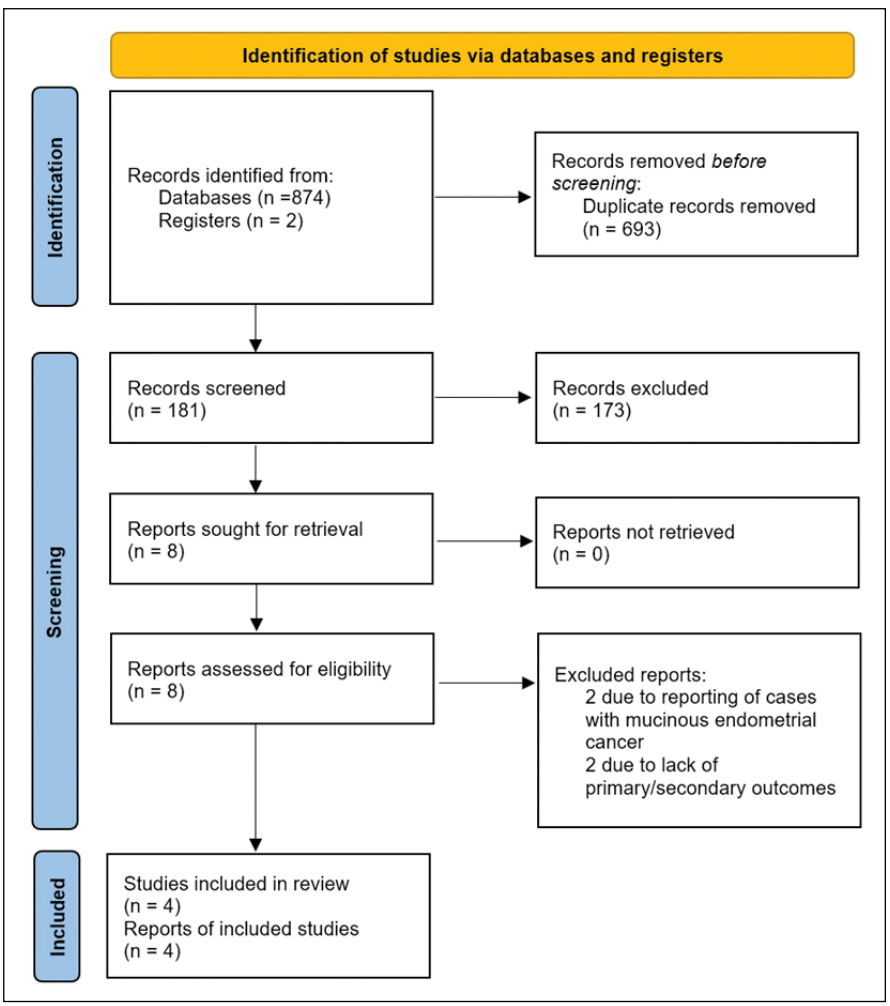

Figure 1. Search plot diagram depicts the process of article retrieval.

version of articles that were considered potentially eligible. Discrepancies that arose in this latter stage were resolved by consensus from all authors.

Predefined outcomes and data extraction

Investigated outcomes were predefined during the design of the present systematic review. We predetermined as primary outcome the investigation of the impact of the TFD on survival rates, including progression free survival (PFS) and overall survival (OS) of endometrial cancer patients. Differences in the presence of LVSI and lymph node metastases were also evaluated as secondary outcomes.

Aggregated data from included articles were retrieved in the form of odd ratios (OR) and hazard ratios (HR) of survival. Absolute differences in survival rates among the two groups as well as proportions of patients with LVSI and lymph node metastases were also considered for inclusion.

Assessment of risk of bias

The methodological quality of included observational studies was evaluated with the use of the Newcastle-Ottawa score which evaluates the selection of the study groups, the comparability of the groups and the ascertainment of the exposure or outcome of interest.[8] Each quality indicator is assigned points with the maximum score representing the maximum. Comparability of the groups was based on tumor grade and stage of the disease. Studies assigned 6-7 points were considered of moderate methodological quality, studies assigned 8-9 points of high methodological quality and studies assigned <6 points of low methodological quality.

Data synthesis

Statistical meta-analysis was performed with RStudio using the *meta* function (RStudio Team (2015). RStudio: Integrated Development for R. RStudio, Inc., Boston, MA URL http://www.rstudio.com/). Statistical heterogeneity was not considered during the evaluation of the appropriate model (fixed effects or random effects) of statistical analysis as the considerable methodological heterogeneity (Table 1) did not leave space for assumption of comparable effect sizes among studies included in the meta-analysis.[9] Confidence intervals were set at 95%. We calculated pooled odds ratios (OR) and hazard ratios (HR) as well as the respective 95% confidence intervals (CI) with the Hartung-Knapp-Sidik-Jonkman instead of the traditional Dersimonian-Laird random effects model analysis (REM). The decision to proceed with this type of analysis was taken after considering recent reports that support its superiority compared to the Dersimonian-Laird model when comparing studies of varying sample sizes and between-study heterogeneity.[10] Publication bias was not assessed due to the small number of included studies.[11]

The potential presence of small-study effects

Table 1. Study characteristics.

YEAR; AUTHOR	TYPE OF STUDY	NO OF PATIENTS	INCLUSION CRITERIA
2014; Worley	Retrospective observational	Endometrioid:518 MD:137	Grade 1 endometrioid endometrial carcinoma, any stage
2017; Abdulfatah	Retrospective observational	Endometrioid:366 MD:227	Low grade (grade 1 & 2) endometrioid endometrial carcinoma, any stage
2017; Miyamoto	Retrospective observational	Endometrioid:309 MD:31	Endometrioid endometrial carcinoma regardless of grade of differentiation and stage
2022; Saatli	Retrospective observational	Endometrioid:122 MD:97	Endometrioid endometrial carcinoma regardless of grade of differentiation and stage

was planned to be evaluated with Rücker's Limit Meta-Analysis and the possibility of p-hacking with inspection of the results of the p-curve analysis. None of these analyses as the number of studies did not suffice to provide robust results.

Sensitivity analysis was performed evaluating the summary effect using the fixed effects model which assumes that the level of heterogeneity among studies is low. This type of analysis aimed to evaluate the importance of mucinous differentiation on survival outcomes of patients, if studies with similar patient characteristics were available, in order to help designate if further research with predetermined, homogeneous criteria is needed.

Prediction intervals

Prediction intervals (PI) were also calculated, using the *meta* function in RStudio, to evaluate the estimated effect that is expected to be seen by future studies in the field. The estimation of prediction intervals considers the inter-study variation of the results and express the existing heterogeneity at the same scale as the examined outcome.

Results

Overall, 4 retrospective observational studies were included in the present meta-analysis that involved 1.501 patients.[12-15] Of those, 186 patients (12.3%) constituted the mucinous differentiation group, whereas the remainder (1.315 patients) had endometrioid endometrial cancer. Two studies.[12,13] involved only patients with low grade disease, whereas the remaining two studies included patients with Gr3 endometrioid differentiation as well[14,15] (Table 1). The stage of the disease did not vary significantly among the two groups, however, given the fact that aggregate data were used subgroup analysis was not possible to detect potential differences among women with mucinous differentiation of endometrioid subtypes compared to those with standard endometrioid endometrial carcinoma (Table 2). The quality assessment of included studies revealed a moderate possibility of bias which primarily accounted in the selection of included patients (Table 3).

Meta-analysis of recurrence free survival revealed that mucinous differentiation of histologically proven endometrioid endometrial carcinoma does not have an impact on the recurrence free survival of these patients (OR 0.59, 95% CI 0.03, 10.42) (Figure 2). The result was similar in the fixed effects sensitivity analysis. Prediction intervals were extremely wide, indicating that the sample size was small to reach

Table 2. Tumor characteristics and survival rates (Mucinous differentiation vs standard endometrioid).

YEAR; AUTHOR	GRADE	STAGE	LVSI	LYMPH NODES
2014, Worley Jr. et al.	All Gr1	I-II: 130 vs 503 III-IV:7 vs 15	12 vs 26	3 vs 8
2017, Abdulfatah et al.	Gr1:47 vs 73 Gr2:180 vs 293	I-II: 150 vs 239 III-IV: 77 vs 127	120 vs 178	65 vs 88
2017, Miyamoto et al.	Gr1:27 vs 195 Gr2:4 vs 63 Gr3:51	NA	10 vs 114	1 vs 31
2022, Saatli et al.	Gr1:66 vs 72 Gr2:26 vs 31 Gr3:3 vs 19	IA:41 vs 63 IB:18 vs 17 II:27 vs 30 III:11 vs 11 IV:1 vs 1	36 vs 44	10 vs 15

Table 3. Newcastle-Ottawa Assessment Scale.

	SELECTION					OUTCOME			
DATE; AUTHOR	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome of interest not present at start of study	**COMPARABILITY**	Assessment of outcome	Adequacy of duration of follow up	Adequacy of completeness of follow up	**TOTAL**
2022; Saatli	√	-	√	-	√√	√	√	√	7
2018; Miyamoto	√	-	√	-	√	√	√	√	6
2017; Abdulfattah	-	-	√	-	√√	√	√	√	6
2014; Worley	√	√	√	-	√√	√	√	√	8

definitive conclusions. Trial sequential analysis revealed that to ascertain the importance of findings a sample size of 11.578 women would be required.

Patients with mucinous differentiation of endometrioid carcinomas had similar odds of deep myometrial invasion compared to patients with endometrioid carcinoma (OR 1.00, 95% CI 0.62, 1.59). Similar results were obtained for the possibility of detecting invasion of the lymphovascular space (OR 1.00, 95% CI 0.59, 1.71) or lymph node metastases (OR 0.89, 95% CI 0.39, 2.05). Sensitivity analyses of all these parameters revealed that the level of statistical significance remained unaffected by the use of fixed effects model. Trial sequential analysis revealed that none of the aforementioned association had an adequate sample size to provide a robust level of statistical significance (Figure 3). Consequently, the prediction intervals were wide enough, although considerably narrower compared to those provided in the recurrence free survival analysis.

Discussion

Overview of results

The finding of our study suggest that mucinous differentiation of endometrioid endometrial carcinomas should not be considered a parameter

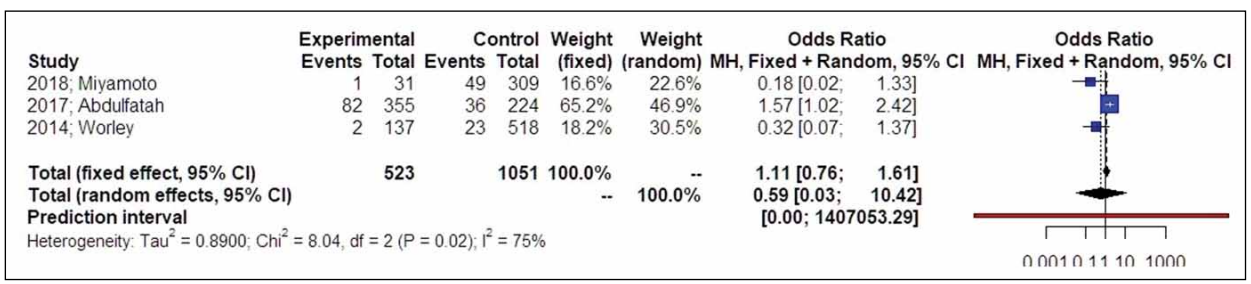

Figure 2. Odds ratio of recurrence free survival. Forest plot analysis: Vertical line = "no difference" point between the two groups. Red squares = odds ratios; Diamond = pooled odds ratios and 95% CI for all studies; Horizontal black lines = 95% CI; Horizontal red line = prediction intervals.

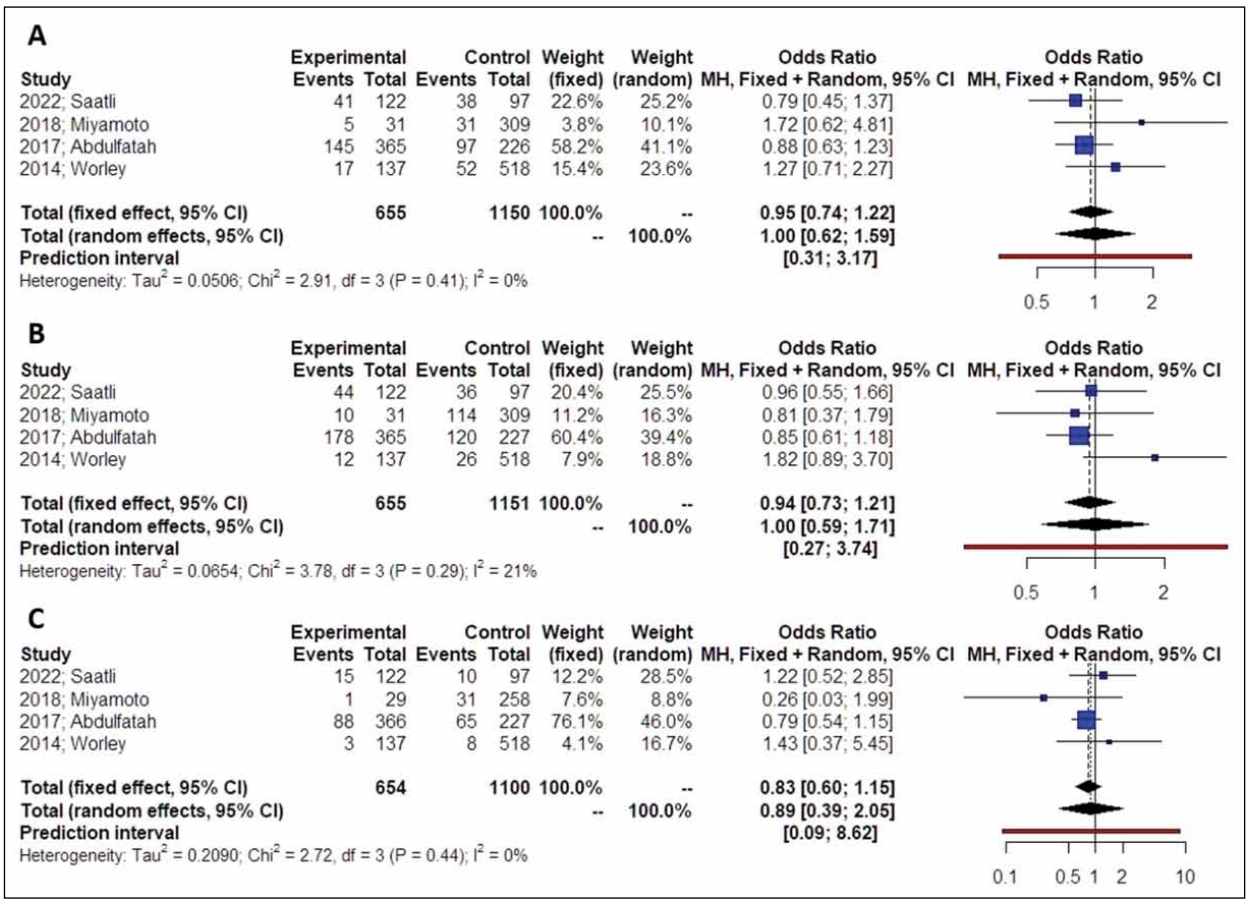

Figure 3. Odds ratio of of a) deep myometrial invasion, b) LVSI involvement, c) lymph node metastases. Forest plot analysis: Vertical line = "no difference" point between the two groups. Red squares = odds ratios; Diamond = pooled odds ratios and 95% CI for all studies; Horizontal black lines = 95% CI; Horizontal red line = prediction intervals.

that positively influences the course of the disease. Neither the rates of recurrences, nor the risk of encountering LVSI or lymph node metastases seems to differ significantly compared to that of patients with classic endometrioid subtypes. However, given the relatively small sample size of included patients and studies, these should be interpreted with caution as future studies may provide further information that may help subclassify these patients.

Comparison to existing literature

Histological patterns of endometrioid adenocarcinomas may vary significantly and certain variants that seem to arise from mucinous metaplastic regions may lead to the occurrence of a microcystic, elongated, and fragmented (MELF) pattern of invasion[16] which is associated with a higher rate of lymph node metastases, lymphovascular and deep myometrial invasion.[17] Mucinous endometrial cancer is generally considered a more aggressive histologic subtype as it has been previously shown that it may influence the risk of lymph node metastases without, however, reducing patient survival.[6] This is in accordance with its immunohistochemical profile as it expresses

a wild-type p53 staining pattern and p16 patchy positivity, rendering its behavior as intermediate and in between that of serous and villoglandular carcinoma.[18] It remains unclear whether the histologic an immunohistochemical profile of the mucinous component of endometrioid carcinomas may have enough penetrance to allow for severe deterioration of patterns of spread, including LVSI and lymph node metastases, let alone to affect survival rates of those patients.

Current recommendations for the staging of patients with endometrial cancer suggest the introduction of molecular classification using analysis for the detection of mutations in the polymerase E (POLE) and p53 genes as well as analysis for microsatellite instability (MSI) of the PMS2, MLH1, MSH2 and MSH6 genes.[19] To date, it remains unclear whether the molecular profile of patients with mucinous endometrial cancer and those with mucinous differentiation of endometrioid adenocarcinoma share common variants as well as how much they differ compared to that of low grade endometrioid carcinoma. This information will be vital as in the era of personalized medicine treatment is expected to be guided by the molecular profile of patients.

Conclusion

Summarizing, mucinous differentiation of endometrioid endometrial carcinoma does not appear to be associated with significantly increased risk of lymph node metastases, lymphovascular space invasion or deep myometrial invasion. Concurrently, there is no evidence to support its association with decreased progression free or overall survival rates; hence, treatment does not need to deviate from that offered to patients with endometrioid carcinoma. In the future molecular profiling of those patients will identify if these patients require specific tailoring and if adjuvant therapy is needed.

Disclosure

The authors report no conflict of interest.

Funding

None to disclose for all authors.

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Received 20-09-23
Revised 25-09-23
Accepted 28-09-23