






Evaluation of the Prognostic Value of Peritoneal Cytology in Patients with Endometrial Cancer: A Protocol for a Systematic Review and Meta-Analysis

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ABSTRACT

Background: In 1988, a new conception for endometrial cancer staging was introduced by Fédération Internationale de Gynécologie et d'Obstétrique (FIGO). In addition to pathologic development, peritoneal cytology played an important role in the staging. The goal of peritoneal cytology was to identify hidden and microscopic extensions outside the uterus. In 2009, the system was reviewed; one of the changes was removing the peritoneal cytology. The aim of this review is to evaluate the effect of peritoneal cytology on the survival of patients with endometrial cancer.

Methods: This protocol is reported based on the PRISMA-P guideline. We will search "endometrial cancer," "peritoneal washing," and any other relevant words on PubMed, Cochran, EMBASE, and Scopus databases. The eligibility criteria are: All original studies performed on patients with endometrial cancer, evaluated survival, and performed peritoneal washing cytology. Only one of the non-English studies with the same respect will be included according to the research team's opinion. Also, the most recent paper among multiple articles about a single study is chosen. It should be noted that there will not be any restrictions regarding the language and publication date. For quality assessment, we will use the quality in prognosis (QUIPS) tool. If possible, a meta-analysis will also be performed using a random effects model, and overall survival rates and confidence intervals will be reported. Heterogeneity will be tested by using the I^2 index and Cochrane's Q test. Subgroup analysis will be performed to handle the heterogeneity. The publication bias will be assessed in the presence of 10 or more relevant articles. If there is no chance of meta-analysis, the result will be reported qualitatively.

Discussion: The resulting review will provide valuable information regarding the prognostic value of peritoneal cytology in patients with endometrial cancer.

Keywords: Endometrial cancer, Peritoneal washing, Prognosis, Systematic review, Meta-analysis

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Introduction

The uterus's cancer is the fourth and the seventh most common female cancer in developed and developing countries, respectively, with an annual incidence rate between 15 and 20 per 100000 women in Europe and 23 per 105 women per year in the USA. Endometrial cancer, mostly as corpus uteri cases, is diagnosed in postmenopausal women with an average age of 60 [1-5]. There are important clinical and pathologic prognostic factors for endometrial cancer, such as age, stage, histologic type, Lymphovascular space invasion, and tumor size. The



most important prognostic factor in endometrial cancer is its stage. Via staging, patients are divided into comparable groups, which are different in prognosis and treatment [1, 6-8]. An optimal staging system demonstrates patterns of spread, therapeutic decision, and allowing perfect anticipation. Since staging systems are dynamic and will change by the time, the endometrial cancer staging is changed. One part of endometrial staging is the collection of peritoneal washing in the abdomen and pelvis. The purpose of this collection is to identify the occult disease and spread of microscopic dissemination. However, peritoneal washing has some problems, such as false negativity in early stages and false positivity in the benign form of the disease.

Although positive peritoneal cytology is known as a negative prognostic factor in some malignancies, its role in endometrial cancer is still controversial [9-14]. In 2001, Yasou Hirai et al. published an article in which they concluded that malignant endometrial cells in peritoneal washing usually would disappear by time and have low malignancy potential, but they couldn't deny its prognostic value in endometrial cancer[14]. As a result, in 2009, the system was reviewed; one of the changes that took place was the removal of peritoneal cytology from the staging system. According to the new system, Stage IIIA was changed to lower stages, such as 2, IA, and IB[15, 16]. There are also some other researches indicating positive peritoneal washing might be a negative prognostic factor for endometrial cancer [17-20]. In this study, we will review articles to evaluate the impact of positive peritoneal cytology on the survival of patients with endometrial carcinoma.

Materials and Methods

We wrote this protocol based on the PRISMA-P checklist 2015[21, 22], and the main systematic review article will be written based on the PRISMA checklist 2009[23, 24].

After approval by Consultation Center for Secondary Researches, Data mining and knowledge

transfer in health and medical sciences of Shahid Sadoughi University of Medical Sciences, Yazd, Iran; this protocol was registered in the international register of systematic reviews (PROSPERO; registration number: CRD42018103587). If we need to modify this protocol, we will provide the date of each amendment and explain the change and provide the logic.

Eligibility criteria

Inclusion criteria: We will include all original studies on patients with endometrial cancer (P) which evaluated the survival (O), and performed the peritoneal washing cytology (I).

Exclusion criteria: If there are several articles in different languages on a single study, we will include only one of them according to the research team's opinion, and the rest of the studies will be excluded. Also, if there are multiple articles available on a single study, we will include only the most recent one, and the rest will be excluded. It should be noted that there will be no restrictions in the language and publication date.

Information sources

1-To find the articles, we will search online databases including "PubMed," "Cochran," "EMBASE," and "Scopus". In search of each database, we will use the specific search strategy. After searching each database, an alert will be created. If a new article become published during the study, the article will be entered and evaluated. Also, for gray literature, we will search relevant databases such as "WorldCat," "World Health Organization," and "Agency for Healthcare Research and Quality."

2-We will review the references of the included articles and will select relevant studies (Hand searching).

3- Finally, if necessary, we will contact the authors of the articles in order to provide us with other researches on this subject if there are any.

4- We started our research on October 30, 2018.

Search strategy**PICOD model keywords will be:**

[Endometrial Neoplasms[MeSH Terms] OR Endometrial cancer OR Endometrial Carcinoma OR Carcinoma, Endometrial OR Carcinomas, Endometrial OR Endometrial Carcinomas OR Cancer, Endometrial OR Cancers, Endometrial OR Endometrial Cancers OR Endometrium Cancer OR Cancer, Endometrium OR Cancers, Endometrium OR Cancer of the Endometrium OR Carcinoma of Endometrium OR Endometrium Carcinoma OR Endometrium Carcinomas OR Cancer of Endometrium OR Endometrium Cancers OR Carcinoma, Endometrioid[MeSH Terms] OR endometrial adenocarcinoma OR Carcinomas, Endometrioid OR Endometrioid Carcinoma OR Endometrioid Carcinomas OR Adenocarcinoma, Endometrioid OR Adenocarcinomas, Endometrioid OR Endometrioid Adenocarcinomas OR Endometrioid Adenocarcinoma OR Endometrial Neoplasm OR Neoplasm, Endometrial OR Neoplasms, Endometrial OR endometrial tumor or endometrium tumor or uterine endometrium carcinoma]AND[peritoneal lavage[MeSH Terms] OR Peritoneal Irrigation OR Lavage, Peritoneal OR Lavages, Peritoneal OR Peritoneal Lavages OR Irrigation, Peritoneal OR Irrigations, Peritoneal OR Peritoneal Irrigations OR Peritoneal cytology OR Peritoneal washing OR Positive peritoneal washing OR Positive peritoneal cytology OR Peritoneal lavage cytology OR Peritoneal washing cytology OR irrigation, peritoneum OR lavage, peritoneum OR peritoneum irrigation OR peritoneum lavage OR peritoneum rinsing OR cytology, peritoneum OR peritoneum cytology]

The example of searching in "PubMed" is available in the **supplementary Online Table 1**.

Data management

After completing the search, we will import all the articles found into a citation management software (Endnote, version: 20, USA) , and we will delete duplicates.

Selection process

Two individuals will independently Search and review articles, and a third person will solve the disagreement. Then two researchers will evaluate the titles and abstracts based on inclusion and exclusion criteria. If the title and abstract are not clear, we will review the full text.

Data collection process

We will use a pre-designed form to extract information from articles (**supplementary Online Table 2**). Two researchers will collect the data separately. For the purpose of homogenization of the information extraction, as a pilot, we will review ten articles. If there is a discrepancy between the two researchers, the third person's opinion will be decisive. Also, if the content of the article is unclear, we will send 3 Emails within a period of 2 weeks to the contact author. If we do not receive any response within this period, the article will be deleted from the study. Finally, if there is more than one article about a study, we will choose the most recent article.

Data items

After selecting the articles, we will extract the following information from the articles:

Items related to bibliography

Title of the article; First author's name; Year of publication of the article; Journal's name

Items related to the design characteristic

Year of study; Country of the study; Type of study; Inclusion and exclusion criteria; Variables

Participants' characteristics

Number of participants; distribution of participants' age; distribution of Stage of disease and staging methods; distribution of tumor grade; distribution of patients' tumor histological types; duration of treatment; matching items between case and control group; the proportion of baseline sample available for analysis; attempts to collect information on participants who were dropped out; reasons and potential impact of subjects lost to follow-up; the proportion of data on prognostic factor available for analysis

Items related to interventions and comparisons

Standard procedure for peritoneal washing; number of patients with positive peritoneal cytology; number of patients with negative peritoneal cytology; the type of treatment and medications

Items related to the outcome

Overall survival rate; disease-free survival rate; 2,5,10 years survival rates; the duration of the follow-up; statistical survival calculation method; outcome and prognostic factor information on those lost to follow-up

Outcomes and prioritization

The main outcome of this study is the overall survival rate, which is the duration from the date of surgery until the death of the patient from any cause or last visit.

Risk of bias in individual studies

Researchers will use the QUality In Prognosis Studies (QUIPS) tool [25, 26] to measure the bias of articles. In the case of disagreement between the two researchers, they will first discuss the subject, and if it was not effective, they would consult a third investigator.

Data synthesis

After a systematic search, if possible, we will perform a meta-analysis. For the meta-analysis, we will use STATA 14 software to analyze and aggregate findings of selected studies, and forest plots will be provided. We will use hazard ratios and odds ratios as effect size to measure the relationship between positive peritoneal washing and survival. We will use a random-effects model to derive the overall estimates. Then the survival rate and confidence interval will be reported. To report the between-study heterogeneity, Cochrane's Q test and Higgins I² statistic will be reported. According to the values of the I², the heterogeneity will be considered as low, average, and high respectively if heterogeneity be less than 50%, 50%-75%, and more than 75%; and for clinical heterogeneity, we consider the setting of the

study (including follow-up duration and outcome measurement). To handle the high heterogeneity, we will perform subgroup analyses based on probable factors causing heterogeneity. In case of a large number of studies for explaining the heterogeneity by metastasis, we will use Meta-regression or subgroup analysis. If there are enough articles (at least 10), we will examine publication bias by visual examination of asymmetry of funnel plots and testing at the 10% level for asymmetry by using the Egger's test for HR and Peter's test for odds ratios [27]. Articles may not be included in the study for a variety of reasons, such as the inaccessibility of required data in the full text of the study. In this case, researchers will be contacted via email to the corresponding author at least three times. If necessary, we will perform a sensitivity analysis by re-running analyzes without studies that have a high risk of bias. If there is no possibility of the meta-analysis by considering the strength and consistency of results, we will present them qualitatively. According to HR, the strength of association will be defined as weak with HR <1.5, moderate with HR=1.5-2.9, and strong with HR ≥3. For assessing consistency, we will use this schema that uses (Kunath F et al., 2015)[28]:

- Strong evidence of effect: Consistent findings (defined as >75% of studies showing the same direction of effect) in multiple low risks of bias studies
- Moderate evidence of effect: Consistent findings in multiple high risks of bias and/or one study with low risk of bias
- Limited evidence of effect: One study available
- Conflicting evidence: Inconsistent findings across studies
- No evidence: No association between patient expectations and the outcome of interest

Discussion

Prognostic articles are studies that follow patients with a specific start point till the endpoint. Today,

health policymakers pay particular attention to the issue of prognostic studies because, given the spread of various diseases in the world, they will be able to divide health resources among the most profitable people. For decision and policymakers, it is important to know which group of patients get the most benefit from treatment and which group of patients does not have a healing benefit, and taking into account the complications of treatment may be more harmful than intervention [29, 30].

Nowadays, despite the fact that prognostic studies have a significant growth in the world, the quality of these papers is low in terms of design, analysis, and reporting. Selective reporting and publication bias is also evident in these studies, and this lack of quality has prevented the expansion of the prognostic models [30, 31].

One of the issues showing the weakness of studies regarding a prognostic factor is the length of time spent to explore prognostic factor value, which ultimately does not lead to a clear result. This issue is also evident in the topic of the prognostic value of cytological peritoneal fluid [31, 32].

Systematic review studies are the most reliable type of studies if high-quality studies are used. However, unfortunately, prognostic studies in terms of methodology fall into the category of weak studies [30, 31, 33]. Regarding the above, we will also encounter several challenges in reviewing the articles for this study, the most notable of which are the weakness of prognostic articles in terms of methodology. To solve it, as well as minimizing the selective reporting bias, the research team decided that by selecting the minimum inclusion and exclusion criteria as well as removing the keywords provided for Comparison & Outcomes & Design domains and accepting the downturn of the specificity of the initial search to increase its sensitivity; Furthermore, after the initial selection of papers, according to the high prevalence of low-quality studies, the results will be divided into

subgroups based on the risk of bias and type of study to examine the results. We hope the results of the study will be used in staging systems such as FIGO and save resources by allocating them to those patients who make the most benefit. We also hope the adequate treatment will also be available to patients who are in need of it to reduce mortality from endometrial carcinoma.

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Authors' contributions

All authors contributed to this project and article equally. All authors read and approved the final version of the manuscript.

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Conflict of interest

There is no conflict of interest.

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