Original Research

Systematic Review of the Molecular Diagnosis of the Endometrial Carcinoma

Farnoosh Farahbod[1], Elmira Hosseini[2], Sahar Zarrin[3*], Hadise Baghaee[4]

1. Obstetric gynecologist specialist, Isfahan University of medical sciences, Isfahan, Iran. 0000-0003-4285-1180
2. Department of Obstetrics and Gynecology, School of Medicine, Urmia University of Medical Sciences, Urmia, Iran. 0000-0003-0898-2849
3. Gynecology department, Urmia University of medical science, Urmia, Iran. 0000-0002-5537-6107
4. Resident of Obstetrics & Gynecology, Guilan University of Medical Sciences, Rasht, Iran. 0000-0002-6489-1688

***Corresponding Author: Sahar Zarrin,** Gynecology department, Urmia University of medical science, Urmia, Iran. E-mail: sahar.zarrin@gmail.com. Orcid: 0000-0002-5537-6107

Abstract

Background:

Today, the diagnosis and staging of endometrial cancer are surgical and pathological procedures, but other non-invasive diagnostic methods, such as molecular diagnostic methods are being used with caution. So, this study aimed at reviewing current molecular diagnostic methods to clarify available methods for further accuracy analyses.

Methods:

This was a systematic review. PubMed and Scopus databases were queried with relevant. All articles related to the topic were selected. Then, the search results were reviewed based on the relationship between the title of the article and then the abstract and text of the article with the aim of the research. The articles found were published in the period 2008 to 2022. Only qualitative analysis was performed.

Results:

Finally, 11 retrospective studies were found along with a meta-analysis study. CA-125, HE4, Serum-Amyloid-A, Sperm-associated antigen 9, YKL-40, and Visfatin were individual factors assessed as diagnostic or prognostic factors along with some studies evaluating a panel of proteins for the prediction of endometrial cancer. Most studies showed valuable diagnostic features of the evaluated proteins and panels versus being prognostic.

Conclusion:

Advances in molecular biology in recent decades have helped enhance researchers' to predict endometrial cancer and those available choices should be more evaluated for preparation for clinical use.

Keywords: Endometrial Cancer, Endometrial Carcinoma, Molecular biomarker, Visfatin, CA-125, HE4

Submitted: 13 September 2022, Revised: 14 October 2022 , Accepted: 20 November 2022

Introduction

Endometrial cancer is one of the most common female cancers in the Western world, accounting for 6% of all female genital cancers (1). Endometrial cancer begins in the layer of cells that make up the lining of the uterus (2). Other malignancies can develop in the uterus, including uterine sarcoma, but are much less common than endometrial cancer; while differentiation before surgery is challenging (3). Endometrial cancer is often diagnosed in the early stages because it repeatedly causes abnormal vaginal bleeding (4). If endometrial cancer is detected early, surgical removal of the uterus will most often cure endometrial cancer; while endometrial carcinoma might often be asymptomatic, and the symptoms of endometrial cancer might manifest when the tumor has grown and also spreads around the tissue and affects other organs (5). Endometrial carcinoma cells in the uterine can spread to other parts of the body causing metastases. Understanding how a type of cancer grows and metastasizes greatly helps with how well care is provided (6). Most endometrial carcinoma deaths are due to primary tumor metastasis. In other words, metastasis is a very inefficient process, as a result of which most cancer cells die when they leave the main tumor (7). The lack or inadequacy of screening programs is considered an important factor in the late diagnosis of this disease (6,7). For endometrial carcinoma, radiation therapy is now the mainstay of treatment (6,7). Based on a classification system performed by Bokhman, endometrial carcinoma is divided into two groups 1 and 2 based on etiology and clinical features (8,9). PI3KCA mutations have been observed in 36% of type I endometrial carcinoma (10). In the second type, endometrial carcinoma typically occurs as aneuploidy and P53 mutations (11,12). These genetic changes are important due to being the basis of efficient and growing cancer detection techniques using the consequence proteins that require microscopic quantities of the patient's sample, and it is now possible to identify low molecular weight proteins in the patient's serum sample. Then they are examined by powerful and new bioinformatics tools to classify cancer and non-cancer patients into the relevant groups. Advances in molecular biology in recent decades have helped enhance researchers' understanding of the complex response to genetic modification, transcription, and translation in human cancers. These molecular changes are the basis of efficient and growing cancer detection techniques that require microscopic quantities of the patient's sample, and it is now possible to identify low molecular weight proteins in the patient's serum sample. Then they are studied with powerful and new bioinformatics tools to classify cancer and non-cancer patients into the relevant groups. In this study, we examined current molecular approaches in endometrial carcinoma diagnosis.

Methods

This was a systematic review of the literature based on the PRISMA guidelines (13). The first stage was the selection of articles based on the search of the online databases of PubMed and Scopus with keywords of the “endometrial cancer; endometrial carcinoma; molecular biomarker “. All articles related to the topic were selected. There was no time limit on the search. The articles found were published in the period 2008 to 2022. Then, the search results were reviewed based on the relationship between the title of the article and then the abstract and text of the article with the aim of the research.

Results

Finally, 12 articles (15-26) were selected for descriptive review as shown in table 1. Of course, due to the weaknesses and methodological shortcomings of the articles and the large dispersion of variables, there was a limited possibility to perform more accurate calculations for pooled analyses; Finally, in the

third stage, studies were analyzed and summarized based on the conclusions. Individual variables such as CA-125, HE4, Serum-Amyloid-A, Sperm-associated antigen 9, YKL-40, and Visfatin were evaluated as diagnostic or prognostic factors, as well as some studies investigating a panel of proteins for endometrial cancer prediction. The majority of studies found that the proteins and panels studied were more diagnostic than prognostic.

Discussion

Over the past three decades, researchers have reported a great deal of information about genes and proteins and their role in the production of normal and cancer cells (27). One of their most important discoveries has been the role of mutated genes in the production of cancer cells. Environmental factors that cause genetic mutations are being identified. Also, with the help of various molecular methods, the expression power of defective genes and proteins can be determined. Even finding new biomarkers that are indicative of a type of cancer can be of great help in the early detection and timely treatment of cancer.

In this review, current molecular biomarkers of endometrial cancer were evaluated. We found some interesting evidence about the application of CA-125, HE4, Serum-Amyloid-A, Sperm-associated antigen 9, YKL-40, and Visfatin in endometrial carcinoma diagnosis.

In Moore et al.'s study, the HE4 level was evaluated to assess tumor involvement and it was found that levels of HE4 were significantly lower in people with IA stage than in IB stage. There was also no association between HE4 levels with lymph node involvement and ectopic involvement. However, there is a significant relationship between the amount of HE4 and the depth of myometrial involvement, and the degree of the lesion (28). So, HE4 has both diagnostic and prognostic values; but some prognostic biomarkers could address more pathological characteristics of the tumor. This is of great importance to perform the treatment for the patient in the best ways and to plan properly. However, this requires proving the effectiveness of these methods in much more studies.

Conclusion

Several research exploring a panel of proteins or individual proteins for endometrial cancer prediction, are being assessed as diagnostic or prognostic markers. The proteins and panels investigated in the majority of studies were found to be more diagnostic than prognostic. Of course, it cannot be said that these methods are a complete replacement for the traditional methods of diagnosing endometrial carcinoma today.

References

1. Amant F, Moerman P, Neven P, Timmerman D, Van Limbergen E, Vergote I. Endometrial cancer. The Lancet. 2005 Aug 6;366(9484):491-505.
2. Sorosky JI. Endometrial cancer. Obstetrics & Gynecology. 2008 Feb 1;111(2):436-47.
3. Burke WM, Orr J, Leitao M, Salom E, Gehrig P, Olawaiye AB, Brewer M, Boruta D, Herzog TJ, Shahin FA, SGO Clinical Practice Endometrial Cancer Working Group. Endometrial cancer: a review and current management strategies: part II. Gynecologic oncology. 2014 Aug 1;134(2):393-402.
4. Saso S, Chatterjee J, Georgiou E, Ditri AM, Smith JR, Ghaem-Maghami S. Endometrial cancer. Bmj. 2011 Jul 6;343.
5. Purdie DM, Green AC. Epidemiology of endometrial cancer. Best practice & research Clinical obstetrics & gynaecology. 2001 Jun 1;15(3):341-54.
6. Braun MM, Overbeek-Wager E, Grumbo RJ. Diagnosis and management of endometrial cancer. American family physician. 2016 Mar 15;93(6):468-74.
7. Wright JD, Medel NI, Sehouli J, Fujiwara K, Herzog TJ. Contemporary management

of endometrial cancer. The Lancet. 2012 Apr 7;379(9823):1352-60.
8. Suarez AA, Felix AS, Cohn DE. Bokhman Redux: Endometrial cancer “types” in the 21st century. Gynecologic oncology. 2017 Feb 1;144(2):243-9.
9. Wilczyński M, Danielska J, Wilczyński J. An update of the classical Bokhman's dualistic model of endometrial cancer. Przegląd Menopauzalny= Menopause Review. 2016 Jun;15(2):63.
10. Oda K, Stokoe D, Taketani Y, McCormick F. High frequency of coexistent mutations of PIK3CA and PTEN genes in endometrial carcinoma. Cancer research. 2005 Dec 1;65(23):10669-73.
11. Bansal N, Yendluri V, Wenham RM. The molecular biology of endometrial cancers and the implications for pathogenesis, classification, and targeted therapies. Cancer control. 2009 Jan;16(1):8-13.
12. Sherman ME. Theories of endometrial carcinogenesis: a multidisciplinary approach. Modern Pathology. 2000 Mar;13(3):295-308.
13. Moher D, Altman DG, Liberati A, Tetzlaff J. PRISMA statement. Epidemiology. 2011 Jan 1;22(1):128.
14. Kommoss S, McConechy MK, Kommoss F, Leung S, Bunz A, Magrill J, Britton H, Grevenkamp F, Karnezis A, Yang W, Lum A. Final validation of the ProMisE molecular classifier for endometrial carcinoma in a large population-based case series. Annals of Oncology. 2018 May 1;29(5):1180-8.
15. Yuan J, Mao Z, Lu Q, Xu P, Wang C, Xu X, Zhou Z, Zhang T, Yu W, Dong S, Wang Y. Hypermethylated PCDHGB7 as a Biomarker for Early Detection of Endometrial Cancer in Endometrial Brush Samples and Cervical Scrapings. Frontiers in Molecular Biosciences. 2021;8.
16. Perez-Sanchez C, Colas E, Cabrera S, Falcon O, Sanchez-del-Río A, García E, Fernández-de-Castillo L, Muruzabal JC, Alvarez E, Fiol G, González C. Molecular diagnosis of endometrial cancer from uterine aspirates. International journal of cancer. 2013 Nov 15;133(10):2383-91.
17. Kumar NU, Sridhar MG, Srilatha K, Habebullah S. CA 125 is a better marker to differentiate endometrial cancer and abnormal uterine bleeding. African health sciences. 2018 Nov 29;18(4):972-8.
18. Nicklin J, Janda M, Gebski V, Jobling T, Land R, Manolitsas T, McCartney A, Nascimento M, Perrin L, Baker JF, Obermair A. The utility of serum CA-125 in predicting extra-uterine disease in apparent early-stage endometrial cancer. International journal of cancer. 2012 Aug 15;131(4):885-90.
19. Liu J, Han L, Jiao Z. The diagnostic value of human epididymis protein 4 for endometrial cancer is moderate. Scientific Reports. 2021 Jan 12;11(1):1-7.
20. Dong C, Liu P, Li C. Value of HE4 combined with cancer antigen 125 in the diagnosis of endometrial cancer. Pakistan Journal of Medical Sciences. 2017 Jul;33(4):1013.
21. Cocco E, Bellone S, El-Sahwi K, Cargnelutti M, Buza N, Tavassoli FA, Schwartz PE, Rutherford TJ, Pecorelli S, Santin AD. Serum amyloid A: a novel biomarker for endometrial cancer. Cancer: Interdisciplinary International Journal of the American Cancer Society. 2010 Feb 15;116(4):843-51.
22. Baser E, Togrul C, Ozgu E, Ayhan S, Caglar M, Erkaya S, Gungor T. Sperm-associated antigen 9 is a promising marker for early diagnosis of endometrial cancer. Asian Pacific Journal of Cancer Prevention. 2013;14(12):7635-8.
23. Qin R, Liao M, Qin W, Wang J, Zheng F, Ma N, Zhao Y, Qin A. The Diagnostic value of Serum YKL-40 in Endometrial Cancer: a meta-analysis. Biomarkers. 2022 Jan 3(just-accepted):1-4.

24. Tian W, Zhu Y, Wang Y, Teng F, Zhang H, Liu G, Ma X, Sun D, Rohan T, Xue F. Visfatin, a potential biomarker and prognostic factor for endometrial cancer. Gynecologic oncology. 2013 Jun 1;129(3):505-12.
25. Cymbaluk-Płoska A, Chudecka-Głaz A, Pius-Sadowska E, Sompolska-Rzechuła A, Machaliński B, Menkiszak J. Circulating serum level of visfatin in patients with endometrial cancer. BioMed Research International. 2018 Oct;2018.
26. Urick ME, Bell DW. Clinical actionability of molecular targets in endometrial cancer. Nature Reviews Cancer. 2019 Sep;19(9):510-21.
27. Moore RG, Brown AK, Miller MC, Badgwell D, Lu Z, Allard WJ, et al. Utility of a novel serum tumor biomarker HE4 in patients with endometrioid adenocarcinoma of the uterus. Gynecol Oncol 2008;110(2):196-20

Tables

Table 1. Characteristics of the included studies

study id	year of publication	number of samples	study design	molecular agent	value	sample type
Kommoss et al.	2018	452	retrospective	pragmatic molecular classification tool (ProMisE): including mismatch repair deficient (MMR-D); DNA polymerase epsilon (POLE); p53 abnormal	prognostic marker	
Yuan et al.	2021	143	retrospective	Hypermethylated PCDHGB7	diagnostic	Endometrial Brush Samples
Perez-Sanchez et al.	2013	514	retrospective	algorithm of 5 genes	diagnostic	uterine aspirates
Kumar et al.,	2018	38	retrospective	CA-125	diagnostic	Serum
Nicklin et al.,	2012	760	retrospective	CA-125	prognostic marker	
Liu et al.,	2021	263	retrospective	HE4	diagnostic	Serum
Moore et al.,	2008	327	retrospective	HE4	prognostic	Serum
Dong et al.,	2017	150	retrospective	HE4 + CA 125	diagnostic	Serum
Cocco et al.,	2010	194	retrospective	Serum-Amyloid-A	diagnostic and prognostic	Serum
Baser et al.,	2013	90	cross sectional	Sperm-associated antigen 9	diagnostic	Serum
Qin et al.,	2022	14 studies	meta-analyses	YKL-40	diagnostic	serum
Tian et al.,	2013	234	retrospective	Visfatin	diagnostic	serum
Cymbaluk-Płoska et al.,	2018	128	retrospective	Visfatin	diagnostic	serum