The Role of Molecular Markers in Endometrial Cancer: An Overview of the Important Markers

Nokhostin F[1], Nurzadeh M[2] and Yousefi Sharami SR[3]*

[1]Department of Obstetrics and Gynecology, Faculty of Medicine, Shahid Sadughi University of Medical Sciences, Yazd, Iran
[2]Department of Fetomaternal, Faculty of Medicine, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran
[3]Department of Obstetrics and Gynaecology, Faculty of Medicine, Kurdistan University of Medical Sciences, Sanandaj, Iran

Abstract

Cancer markers could be described as expressed molecular products by Neoplasia tissues or metabolized and secreted by tumors. Tumor markers can be identified biochemically in the body's fluids like blood or urine. Cancer markers could be used as a means to supervise the patient's response to treatment or the prediction of relapse, progress, or metastases, or even the survival of the patient. In recent years, due to an increase in obesity life expectancy in cancer cases, specifically endometrial cancer has risen dramatically. By researching and investigating cancer markers, a day could be envisioned when all types of cancers could be detected through a simple blood test, treated and millions of lives could be saved annually. Through biological methods to identify new markers of diagnosing cancer, over the past decades, many studies have been done on cancer markers. By using this data and its clinical applications, accurate diagnosis could be reached, patients could be alerted of the possibility of the disease and help them get cured. In this study, we have looked at cancer markers to diagnose, Prognosis, and monitor endometrial cancer.

Keywords: Cancer; Endometrial Cancer; Cancer Markers; Prognosis

Introduction

Cancer is one of the most complex human problems in the realm of health which human society is facing and every year a huge emotional and financial price is imposed on human society [1]. It is the third deadly disease after cardio-vascular and infectious diseases in developing countries and the second reason of death after cardio-vascular disease in developed countries. With its timely diagnosis, we could prevent a lot of pain and ultimately death of patients. Studies show that more than one third of the population of the world is afflicted with a form of cancer and more than 20% of death is due to this disease. Also, 10% of all the medical care expenses in developed countries is spent on this disease [2].

Cancer is a type of disease which includes changes in the condition and expression of various genes which alters the survival advantage of proliferation potential of somatic or fetal cells. These changes usually occur in three different classes of genes including oncogenes, genes that suppress tumors and healing genes of DNA and changes the genotype and phenotype of cells and their resistance against dying mechanism built in the cells (apoptosis), along with disturbing the order of cell proliferation [3]. This disease is very complex and is not caused by one factor and many factors such as lifestyle, family background and genetics, epigenetic are responsible for that. In other words, cancer is caused by different factors and known types of cancer share various proliferation points. Cancer has many tissue, tumor and cell aspects [4].

One of the most common types of cancer in women and in industrial countries is endometrial cancer. In 2017, endometrial cancer affected 61380 women in the U.S and because of that 10920 people died. This amount of spreading and death also exists in other countries [5]. Endometrial cancer is showing a considerable increase in the world and it seems that obesity and changes in lifestyle are its main causes in developed counties. Reports exist about the connection between obesity and an increase in BMI as dangerous factors in uterus cancer [6,7]. The progress of endometrial cancer is multi-faceted and is a multi-level process. After the first bleeding of vagina after menopause, 70 percent of patients can be diagnosed in early stages. Nonetheless, 30 percent of patients are facing a high danger of advancement in of endometrial cancer [8].

Material and Methods

This study will look at endometrial cancer and its different markers from 1980 to 2018 in simple terms and the connection between the role of markers and diagnosis, Prognosis and monitoring the treatment. This study was done in April of 2020 and in order to find the related studies resources such as Nature, WHO, NCBI, PsycINFO, ISC PubMed, Medline were used. The study began with research about

the different types of makers of endometrial cancer, with a look at different aspects and topics related to endometrial cancer, its severity and treatment, different types of markers, and the role of prognosis or diagnosing markers. To gather data in related resources keywords were looked up such as endometrial cancer, endometrial, biological markers, cancer makers, immune system, endometrium and cancer, the outbreaks of endometriosis, danger factors in cancer. After looking at studies with repetitive topics and the ones with irrelevant subjects they were omitted and out of 386 studies, 62 which covered the subject and content were used in this study.

Endometrial Cancer

Endometrial cancer is a type of cancer that begins from the cell layer of the uterus. Endometrium is the covering layer of uterus which is the muscular and hollow organ in women's pelvis. Endometrial cancer is also called uterus cancer. Endometrial cancer can often be diagnosed due to the unmoral bleeding of vagina. This type of cancer is the most common type of cancer in female's genital and half of female cancer patients are afflicted with this disease. Furthermore, second to breast cancer, lung cancer and colorectal cancer, it is the fourth most common type of cancer among women [9]. The third most common cause of death of women due to cancer after ovarian cancer and cervical cancer is endometrial cancer. In Iran, many studies have been done on this type of cancer and many factors have been pointed in the survival of the patients such as the role of timely diagnosis, prevention and treatment [10,11].

The mean age of women struggling with this disease is reported to be 61 [12]. The frequency of the occurrence of endometrial cancer in societies is increasing in a way that in the U.S, the death rate caused by endometrial cancer is rising at a rate of 1.4% per year and approximately 40 percent of the cases are preventable

It is possible to diagnose whether we are dealing with a malignant case of endometrial or not if done in time. It is imperative to analyze the extracted tissue by hysteroscopy. The risk factors in raising the probability of causing endometrial malignancy are: estrogen-based hormonal treatment, diabetes and having a background in cancer, high BMI and etiology of infertility. In most cases, surgery is needed and if needed it is followed by radiotherapy, while chemotherapy is used only in rare cases. Approximately, 25 percent of patients come out with metastases [13-16]. (Figure 1)

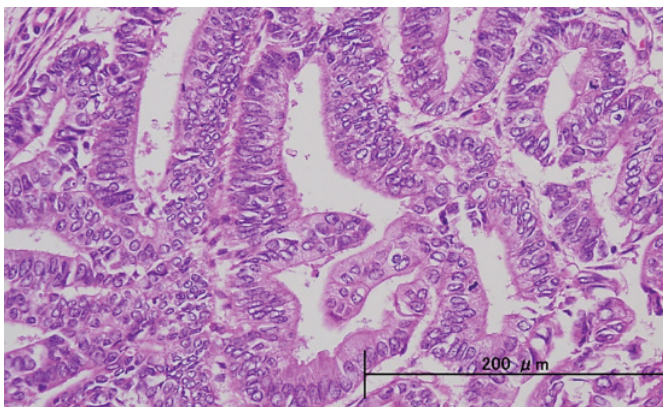It is possible that in different types of cancers, particular changes

Figure 1: Adenocarcinoma of the Endometrium, Grade 1, and the spherical structure of cell node in the proliferation phase, with classification and mutual lumen border with neoplastic cells [17].

occur in the expression of genes during the expansion of cancer. These changes have to be considered before receiving medication, since treatment methods may bring changes in the results. In the study carried out by Elsazar et al. The sensitivity and features of sonography of vaginal trance and Transrectal to identify risky cases, cervical involvement and anal involvement were 78 and 89.1 percent respectively [18]. Also, in other studies done through MRI tomography and histology, a low sensitivity and high risk were demonstrated. Due to the side effects of Lymphadenectomy and shooting techniques, tumor markers are considered as suitable substitutes for the above mentioned methods and could be used to battle this disease [19].

Since cancer is spreading in the world ever faster, using methods which are non-aggressive and possess more power and precision in the timely diagnosis and monitoring of process of treatment can play an important role in the treatment of cancer. The philosophy behind the numerous researches that are done on markers is identification and setting ways which are less aggressive in the treatment of this disease.

Cancer Markers

In order to make a precise evaluation and identifying cancer cells to choose the best treatment, we can use cytology findings, radiology, blood cells and cancer markers [20]. By using cancer markers, diagnosis will be faster and less need will be for using aggressive means. Numerous cancer markers have been found in cells which are mostly of protein, Glycoprotein and RNA and DNA base [21].

Cancer markers are molecules which are found in all parts of the body including blood and body tissues, and we can use the increase or decrease in these cells to screen through, diagnose, monitor or treat the patients. In many occasions, molecular markers predict the existence of a cancer part in the body and with a proper and timely surgery we can prevent from the growth and proliferation of the cancer node in the body. Also, by looking at the cancer markers, we can gain some valuable information about the way cancer cells respond to treatment, resurgence of disease or its relapse [22]. Using cancer markers is not the main way to diagnose cancer but a laboratory tool to support the diagnosis.

Cancer markers are categorized into a tissue-specific type and cancer type. The first category includes markers which indicate the existence of tumors in the cancer tissue and they could be used to monitor the process of treatment, the extent of the development of cancer, the way and the extent to which the disease has responded to treatment and so on. Of the most important markers related to this group are CA125 and CEA and CA19-9. The second group includes cancer-specific markers which indicate the existence of cancer tissue in specific tissues in which cancer has spread. Of the most important markers of this type are Beta-globulin, AFP and PSA [23].

Endometrial Cancer Makers

Cancer markers indicate the biochemistry of the existence of tumor. In other words, tumor makers are those molecules which are identifiable in the body fluids and plasma. Tumor markers are biochemical molecules which are measurable and identifiable in malignancies. These markers are produced either by tumor cells or by the body in response to tumor and are normally transferred into blood and are measurable in the blood accordingly [3].

HCG Markers

Some types of uterus cancer whose reproductive cells get cancer

produce HCG cancer markers. This cancer marker was the first maker which was used to diagnose cancer [24].

The early 1982, HCG was first thought of as a tumor marker, after analyzing 456 different types of cancer by immunoprecise. Of these cases, 18.9 percent of the patients were diagnosed with positive endometrial HCG malignancy and it was determined that distinguished week tumors and/or aggressive ones had a high level of HCG. In later studies, this marker was used to diagnose endometrial cancer and was used as a useful indicator in describing uterus cancer [25,26].

The Human Chronic Gonadotropin is a peptide hormone which includes two subunits of (α,β) which are linked to each other in a non-covalence way and are expressed by two different genes [27]. The HCG tumor marker in a normal state is expressed though binary cells but its high expression in pregnancy and cancer of reproductive cells has also been reported. The amount of HCG in pregnant women usually rises and determining its level is the basis of futility tests.

Studies show that HCG is not a diagnostic maker because its density in serum is very low. That is why it is used in controlling and monitoring the development of disease [28]. Besides, in 85% of patients with cancer of reproductive cells, HCG shows an increase. The amount of this markers shows an increase in only 20 percent of stage1 patients. To be used in the time of diagnosis and evaluating the treatment process, HCG marker and AFP marker are looked at simultaneously and the high amount of this marker is proof for the existence of cancer and a lack of response to treatment [29,30].

If HCG marker is increased in a person who is not pregnant, it can stimulate the growth of tumor. It seems that HCG marker in endometrial malignancy is an important indicator of tumor which is used not only to diagnose cancer cells but also to describe the disease [31].

HE4 Marker

One of the molecular markers of endometrial cancer is the HE4 protein which is of utmost importance in the diagnosis of the severity of the illness. HE4 marker was first found in the distal epithelium of the epididymis [32,33]. The study done by Lou et al. showed that controlling the endometrial cells with pure extra-cell HE4 will lead to a considerable increase in the survival, cell proliferation and DNA synthesis. This could contribute to the development of the malignancy of endometrium and metastases. Recent studies show the importance of this maker in the diagnosis, categorizing and prognosis of endometrial cancer [34,35].

The level of HE4 in stage IA patients is reported meaningfully lower than stage IB patients. Also, there is a meaningful connection between the amount of HE4 and the depth of engagement of myometrium and resultant damages [36,37].

In another study is was noted that tumor markers of patients in the developed stages of IB-III is relatively higher to the patients who are in the initial stages of IA. These results are close to the results of the study done by Minar L, et al. (2015) [38]. In another study done by Bignotti E et al. (2011) it was seen that the amount of HE4 was higher in patients with III-IV level than patients with I-II level [32].

Another study showed that the level of HE4 increases in all levels of endometrial cancer and due to its high sensitivity relative to CA125 in the initial stages of the disease, we can use it as an identifier for the timely diagnosis of the resurgence of cancer and evaluating the treatment responses. Also, in the researches done by Young in 2011,

using the surface of the serum HE4 was suggested to predict the depth of the aggression of the myometrium to evaluate the necessity of a cut in the lymph ties before surgery as factor before surgery [39].

CA125 Marker

The CA125 marker was first identified by Ginath S, et al. (2002) and was used as an anti-gene for ovaries cancer. CA125 marker is one of the most useful tumor markers in endometrial cancer. This anti-gene can be found in mesothelial cells and tissues produced by mullerian epithelium. In healthy people, the density of CA125 is different based on the age, women with menopause in comparison to the younger women ad menstruation cycle is less. But its amount in pregnant women and patients with endometriosis increases. The density of ca125 marker in the serum, urine or body tissues is measured to predict the disease [35,40].

CA125 marker is glycoprotein based and is expressed by the epithelial cells during development. Clinical studies show that this marker has high expression in endometrial cancer in a way that 75% of people afflicted with endometrial cancer in a way that 75% of patients with endometrial cancer have been reported to have a high level of endometrial cancer. In 50% of Stage I patients and 90% of stage II patients this marker is showing a noticeable increase.

Based on the studies done on this marker, this marker is the most important and used marker in diagnosing uterus cancer. This marker is used in the treatment and monitoring of patients [35,41].

In the study that was carried out on 112 patients, there is a noticeable relation between cancer and the level of CA125. An increase was witnessed in the density of CA125 in 15.2 percent of patients with stage I, 33.3 percent of patients with stage II, 5.61% of patients with stage III, and 100 percent of patients with stage IV [42]. In another study done by Sebastineli on 254 patients, the increase was seen in the density of CA125 marker in 16% of patients afflicted with stage I and II of endometrial cancer and in 85% of patients with stage III and IV.

Also, in this report no connection was found between the type of tissue and surface serum of CA125. Table 1 shows a comparison between CA15-3 cancer markers, CA125, CEA and prolactin in patients with endometrial cancer and patients with unusual uterus bleeding [43].

Studies show that we can use the level of CA125 serum in finding patients with adenocarcinoma in endometrial cancer. Also, the amount of these markers in patients with higher levels is increasing noticeably [36,44].

The prognostic or diagnostic role of CA125 marker was studied by Lundstrøm MS, et al. (2000), and they found a noticeable connection between the level of CA125 before surgery and the level of cancer. The density of less than 35U/ml is evidence for the weak prediction of indexes [45].

Table 1: A comparison between CA15-3, CA125, CEA, prolactin in patients with endometrial cancer and patients with unusual uterus bleeding. The amount of these biomarkers in patients show a meaningful difference. In patients with endometrial cancer, these biomarkers show a noticeable increase [43].

Parameters	Endometrial Cancer (n=38)	Abnormal uterine bleeding (n=40)	p value
CA 15-3 (U/mL)	21.97 (12.53-48.51)	18.75 (9.38-23.89)	0.048*
CA 125 (U/mL)	19.85 (7.2-47.78)	10.95 (6.73-16.97)	0.015*
CEA (μg/L)	2.30 (1.58-5.03)	2.00 (1.45-2.40)	0.033*
Prolactin (ng/mL)	8.36 (6.2-14.3)	7.02 (4.93-10.02)	0.042*

Another study has shown that patients who have had a positive metastasis in lymph node, the level of CA125 serum in them was 10.7 higher than patients without metastasis. However, the amount of HE4 was only 3.8 times more. The density of serum of both tumor markers in patients with metastasis of lymph node was noticeably higher than people without metastases. One of the reasons why cancer markers are noticeably higher when lymph node are metastasis is that when tumor is placed in the uterus, has less access to blood circulation or lymphatic system [46,47].

CA15-3 Marker

In the studies done by Lo S, et al. (1997), CA15-3 was named the most practical in prognosis of endometrial cancer [48]. CA15-3 cancer anti-gene is protein which is built by a range of cells, particular cancer cells of breast and uterus. The CA15-3 produced in the cancer cells move into the blood and can be measured in the blood. In general, the higher the amount of CA15-3 in blood is, a more certain indicator of cancer in body it will be. The data shows that the density of CA15-3 in 24% to 32% of patients with endometrial cancer has increased. As was mentioned, this marker can be used to prognoses and distinguish the patients with intra-uterus disease and extra-uterus disease [49].

Ca72-4 Marker

Ca72-4 anti-gene, was first produced as an anti-gene to react to mice antibodies in 1980, mice with metastasis cancer cells. CA72-4 anti-gene is a glycoprotein which increases in stomach, gut, breast, and ovary and uterus cancer. Also the serum surface of CA72-4 is increased in menopause. CA72-4 may be used alone or in conjunction with CA125 in diagnosing cancer. According to evidence, CA72-4 marker in 22 to 32 percent of patients with endometrial cancer increases. This level is connected with metastasis [42].

In another work, CA72-4 in patients with ovaries cancer was calculated as (71%) and patients with endometriosis (13.8%). they concluded that by determining the amount of CA42-4 maker, we can find out about ovaries cancer and endometrium. A few studies have been done about the role of CA72-4 in diagnosing and prognosing endometrial cancer. Given this fact, Gadochi et al. showed that the amount of CA72-4 serum was increased in patients with endometre by about 22 to 32%. Statistically, there is not meaningful difference in the level of CA42-4 serum in all levels of endometre cancer or in level 1. Also, the amount of CA72-4 has increased by 4% in local patients and 30% in metastasis [50].

Studies have shown that a positive CA72-4 serum is connected to myometre aggression, metastasis, and involvement of Lymphovascular space and metastasis of pelvic lymph node. Measuring the density of CA72-4 serum can be useful in predicting and monitoring the development of the disease.

Findings show that measuring CA72-4 can help distinguishing endometrial cancer from endometrial polyp. Also the pre-surgery level of CA72-4 can be used as a marker in making an initial diagnosis of endometrial cancer [51].

B7-H4 Marker

B7-H4 is a inhibiting immune system protein and plays a probable role in the escape of immune system and tumor generation. B7-H4 is expressed in tumor cells and Macrophage related to tumor in different types of cancer. In many studies the distinctive effects of intra-cells such as a decrease in apoptosis, increase and facilitation of cell proliferation by B7-H4 were pointed out. Also, it has been seen that metastasis in expressive cells of B7-H4 has increased. Apart from the expressed level of B7-H4 in cells, an evaluation of the amount of B7-H4 soluble in serum has indicated that B7-H4 has been used as an important maker to determine the level of disease. B7-H4 has been used to detect and identify uterus cancer in its initial stages. Studies have shown that a simultaneous use of this cancer marker along with CA125 could cause an increase in the precision and accurateness of diagnosis and detecting uterus cancer [52].

KAI1 Marker

KAI1 gene or CD82 is an inhibiting gene of metastasis which suppressed the mobility and aggression of cancer cells. The level of expression of KAI1 can be used as a marker for identifying cancers such as prostate, bladder, breast, colon, stomach, the big intestine, endometrium, skin, lung, liver, Thyroid, and pancreas. KAI1 is a marker of the function of metastasis of cancer cells and it has been seen that there is a reverse correlation between the level of expression of KAI1 and the development and aggression of cancer cells [53,54].

In a study done on women with endometrial cancer with PCR and immunohistochemistry, it was seen that the level of expression of KAI1 gene has a reverse correlation with the development of disease in a way that doesn't show any expression in the metastasis stage [55,56].

MIR-196a Marker

Micro RNAs are a linear sequence of 12 to 25 nucleotide and bear an important part of the adjustment in gene expression which is epigenetic changes [57]. Most of the cancer markers are made of protein and because the number of these proteins are low in clinical samples and post-translation changes, their evaluation faces a lot of difficulties. That is why the use of other biological molecules such as RNAs are really important these days [58,59]. In many studies, RNA markers as potential cancer markers have shown positive results in diagnosis, prognosis and monitoring of the process of treatment [60].

The MiR-196a gene is among the HOX cluster genes and is one of the main regulators of fetus production and oncogenes. Most studies emphasize the key role of MIR-196a in causing cancer and tumor generation [61]. This microRNA, apart from the endometrial cancer, causes other types of cancer such as colorectal, breast cancer and leukemic cancer. Most studies indicate that the expression of MiR-196a in cancer is increasing meaningfully and can be used as a suitable marker in diagnosing cancer [62,63].

Conclusion

Finding new markers as an index for a type of cancer can be a big help in diagnosing and treating it in time [64]. In most cases, cancer can be diagnosed just through biochemistry and to do this cancer markers are normally used. Nonetheless, using cancer makers, one can determine the probability of the occurrence of cancer in some patients. Also, it can be it has helped a lot in determining the origin f cancer in patients with a high level of disease.

Although cancer markers normally function imperfectly as a way of screening testing to diagnose hidden cancers, after finding a special type of cancer by a marker, these markers could provide a way to evaluate the success or failure of treatment. The level of tumor marker could also reflect the stage of illness and be a sign of the speed of the development cancer and help with prognosis [65].

Some of the other applications of cancer markers is monitoring

patients who are under cancer treatment. If the level of the marker is increased at the beginning but decreased during treatment that is an indication that treatment has been effective. On the other hand, if the level indicates an increase, it is probable that treatment has not been effective and other forms of treatment should be applied.

One of the main problems with using biological cancer makers is their low density in tissues with cancer in the initial stages of the disease [66]. Other problems such as the fact that normal cells can cause cancer markers in some cases, or the fact that tumor markers are not always present in the initial stages of cancer are some of the other problems of using cancer markers. At the present, there is a serious controversy over the usefulness of cancer markers in mass screening [67].

Gene changes and molecular markers in endometrial cancer, such as hormonal receptors can help with a better treatment of this type of cancer in the future. Clinical evaluations of the purposeful treatment methods indicate the effectiveness of some of these factors. Nonetheless, purposeful treatment can only lead to some results if done by one factor. Identifying biological markers effectively can determine a response to purposeful treatment and provide appropriate ways to develop different treatment methods.

The outbreak of endometrial cancer in recent years has been on the increase. Although most cases are diagnosed in the initial stages, the chances of survival in the developed stages is very low.

This survey study showed that most of the studies done on the identification and development of cancer markers are on a successful path at the moment and markers such as HCG, HE4, CA125, Mir-196 and CA15-3 play an important role in the diagnosis, prognosis and monitoring the treatment process. It is hoped that in the near future with identifying new markers which have higher sensitivity and specificity to different types of cancer all types of cancer could be identified with a simple blood test and treated to ease the pain of humanity.

References

1. Daloii MN, Kashani B (2018) Targeted cancer therapy: review article. J Faculty Med 76: 240-331.

2. Nussbaum RL, McInnes RR, Willard HF (2015) Thompson & Thompson genetics in medicine e-book. Elsevier Health Science.

3. Bhatt AN, Mathur R, Farooque A, Verma A, Dwarakanath B (2010) Cancer biomarkers-current perspectives. Indian J Med Res 132: 129-149.

4. Fitzmaurice C, Allen C, Barber RM, Barregard L, Bhutta ZA, et al. (2017) Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: a systematic analysis for the global burden of disease study. JAMA Oncol 3: 524-548.

5. Siegel R, Miller K, Jemal A (2017) Cancer statistics. CA Cancer J Clin 67: 7-30.

6. Bergström A, Pisani P, Tenet V, Wolk A, Adami HO (2001) Overweight as an avoidable cause of cancer in Europe. Int J Cancer 91: 421-430.

7. Gates EJ, Hirschfield L, Matthews RP, Yap OS (2006) Body mass index as a prognostic factor in endometrioid adenocarcinoma of the endometrium. J Natl Med Assoc 98: 1814.

8. Li J, Dowdy S, Tipton T, Podratz K, Lu W-G, et al. (2009) HE4 as a biomarker for ovarian and endometrial cancer management. Expert Rev Mol Diagn 9: 555-566.

9. Ben-Shachar I, Pavelka J, Cohn DE, Copeland LJ, Ramirez N, et al. (2005) Surgical staging for patients presenting with grade 1 endometrial carcinoma. Obstet Gynecol 105: 487-493.

10. Hasani SS, Gilani MM, Akhavan S, Mousavi A-S, Saffarieh E, et al. (2017) The clinicopathologic characteristics and 3-year survival rates of epithelial ovarian cancer in Iran during 2011-2017. Age 49: 50-53.

11. Saffarieh E, Sharami SRY A Review on the Management of Endometriosis induced Pain Endometriosis.

12. Creasman WT, Odicino F, Maisonneuve P, Beller U, Benedet JL, et al. (2001) Carcinoma of the corpus uteri. J Epidemiol Biostat 6: 47-86.

13. Marsden DE, Hacker NF (2001) Optimal management of endometrial hyperplasia. Best Pract Res Clin Obstet Gynaecol 15: 393-405.

14. Emons G, Heyl W (2000) Hormonal treatment of endometrial cancer. J Cancer Res Clin Oncol 126: 619-623.

15. Hecht JL, Mutter GL (2006) Molecular and pathologic aspects of endometrial carcinogenesis. J Clin Oncol 24: 4783.

16. Amant F, Moerman P, Neven P, Timmerman D, Van Limbergen E, et al. (2007) Treatment modalities in endometrial cancer. Curr Opin Oncol 19: 479-485.

17. Nakayama K, Nakayama N, Ishikawa M, Miyazaki K (2012) Endometrial serous carcinoma: its molecular characteristics and histology-specific treatment strategies. Cancers 4: 799-807.

18. Alcázar J, Pineda L, Caparrós M, Utrilla-Layna J, Juez L, et al. (2016) Transvaginal/transrectal ultrasound for preoperative identification of high-risk cases in well-or moderately differentiated endometrioid carcinoma. Ultrasound Obstet Gynecol 47: 374-379.

19. Meissnitzer M, Meissnitzer T, Forstner R (2015) Gynecological tumors of the true pelvis: Radiological diagnosis for pelvic tumors made simple. Radiologe 55: 1117-1130.

20. Sorosky JI (2008) Endometrial cancer. Obstet Gynecol 111: 436-447.

21. González-Masiá JA, Garcia-Olmo D, García-Olmo DC (2013) Circulating nucleic acids in plasma and serum (CNAPS): applications in oncology. Onco Targets Ther 6: 819-832.

22. Park Y, Lee JH, Hong DJ, Lee EY, Kim HS (2011) Diagnostic performances of HE4 and CA125 for the detection of ovarian cancer from patients with various gynecologic and non-gynecologic diseases. Clin Biochem 44: 884-888.

23. Leboeuf R, Langlois MF, Martin M, Ahnadi CE, Fink GD (2006) "Hook effect" in calcitonin immunoradiometric assay in patients with metastatic medullary thyroid carcinoma: case report and review of the literature. J Clin Endocrinol Metab 91: 361-364.

24. Di Bonito M, Cantile M, De Cecio R, Liguori G, Botti G (2013) Prognostic value of molecular markers and cytogenetic alterations that characterize breast cancer precursor lesions. Oncol Lett 6: 1181-1183.

25. Fenoglio C, Crum C, Ferenczy A (1982) Endometrial hyperplasia and carcinoma: Are ultrastructural, biochemical and immunocytochemical studies useful in distinguishing between them?. Pathol Res Pract 174: 257-284.

26. Ueda G, Yamasaki M, Inoue M, Tanaka Y, Hiramatsu K, et al. (1984) Immunohistological study of isoantigens, carcinoembryonic antigen and human chorionic gonadotropin in adenocarcinomas of the uterus. Nihon Sanka Fujinka Gakkai Zasshi 36: 437-442.

27. Cole LA, Wang Y, Elliott M, Latif M, Chambers JT, et al. (1988) Urinary human chorionic gonadotropin free β-subunit and β-core fragment: A new marker of gynecological cancers. Cancer Res 48: 1356-1360.

28. Sjöström J, Alfthan H, Joensuu H, Stenman UH, Lundin J, et al. (2001) Serum tumour markers CA 15-3, TPA, TPS, hCG β and TATI in the monitoring of chemotherapy response in metastatic breast cancer. Scand J Clin Lab Invest 61: 431-441.

29. Fowler Jr JE, Platoff GE, Kubrock CA, Stutzman RE (1982) Commercial radioimmunoassay for beta subunit of human chorionic gonadotropin: falsely positive determinations due to elevated serum luteinizing hormone. Cancer 49: 136-139.

30. Wilkinson PM, Read G (1997) International Germ Cell Consensus Classification: a prognostic factor-based staging system for metastatic germ cell cancers. J Clin Oncol 15: 594-603.

31. Koelbl AC, Schlenk K, Behrendt N, Andergassen U (2018) The importance of hCG in human endometrial adenocarcinoma and breast cancer. Int J Biol Markers 33: 33-39.

32. Bignotti E, Ragnoli M, Zanotti L, Calza S, Falchetti M, et al. (2011) Diagnostic and prognostic impact of serum HE4 detection in endometrial carcinoma patients. Br J Cancer 104: 1418-1425.

33. Mutz-Dehbalaie I, Egle D, Fessler S, Hubalek M, Fiegl H, et al. (2012) HE4 is an independent prognostic marker in endometrial cancer patients. Gynecol Oncol 126: 186-191.

34. Lu Q, Chen H, Senkowski C, Wang J, Wang X, et al. (2016) Recombinant HE4 protein promotes proliferation of pancreatic and endometrial cancer cell lines. Oncol Rep 35: 163-170.

35. Zamani N, Gilani MM, Mirmohammadkhani M, Sheikhhasani S, Mousavi A, et al. (2020) The utility of CA125 and HE4 in patients suffering from endometrial cancer. IJWHR 8: 95-100.

36. Zamani N, Zamani MZ, Modaresgilani MM (2015) Utility of tumor marker HE4 and CA125 to predict staging in endometrioid adenocarcinoma of the uterus. Tehran Univ Med J TUMS Publications 73: 577-583.

37. Moore RG, Brown AK, Miller MC, Badgwell D, Lu Z, et al. (2008) Utility of a novel serum tumor biomarker HE4 in patients with endometrioid adenocarcinoma of the uterus. Gynecol Oncol 110: 196-201.

38. Minar L, Klabenesova I, Jandakova E, Zlamal F, Bienertova-Vasku J (2015) Prognostic value of human epididymis protein 4 in endometrial cancer and its utility for surgical staging. J Obstet Gynaecol Res 41: 1644-1652.

39. Yang CH, Xu YH, Zhang XY (2011) Expression and significance of human epididymis gene product 4 in tissue and serum of patients with endometrial cancer. Chin J Clin Oncol 38: 516-519.

40. Ginath S, Menczer J, Fintsi Y, Ben-Shem E, Glezerman M, et al. (2002) Tissue and serum CA125 expression in endometrial cancer. Int J Gynecol Cancer 12: 372-375.

41. National Academy of Clinical Biochemistry Laboratory Medicine (2008) Practice guidelines for use of tumor markers in testicular, prostate, colorectal, breast, and ovarian cancers. Clin Chem 54: e11-e79.

42. Yasa C, Takmaz O, Dural O, Akhan SE (2013) The value of tumor markers in endometrial carcinoma: review of literature. J Cancer Ther 4.

43. Kumar NU, Sridhar M, Srilatha K, Habebullah S (2018) CA 125 is a better marker to differentiate endometrial cancer and abnormal uterine bleeding. Afr Health Sci 18: 972-978.

44. Sebastianelli A, Renaud MC, Grégoire J, Roy M, Plante M (2010) Preoperative CA 125 tumour marker in endometrial cancer: correlation with advanced stage disease. J Obstet Gynaecol Can 32: 856-860.s

45. Lundstrøm MS, Høgdall CK, Nielsen AL, Nyholm H (2000) Serum tetranectin and CA125 in endometrial adenocarcinoma. Anticancer Res 20: 3903-3906.

46. Hsieh CH, ChangChien CC, Lin H, Huang EY, Huang CC, et al. (2002) Can a preoperative CA 125 level be a criterion for full pelvic lymphadenectomy in surgical staging of endometrial cancer?. Gynecol Oncol 86: 28-33.

47. Abdalla N, Piórkowski R, Stanirowski P, Słomka A, Cendrowski K, et al. (2016) Assessment of levels of the tumor markers HE4 and CA125 considering staging, grading and histological types of endometrial cancer. Prz Menopauzalny 15: 133-137.

48. Lo S, Cheng D, Ng T, Wong L, Ngan H (1997) Prognostic significance of tumour markers in endometrial cancer. Tumour Biol 18: 241-249.

49. Cherchi P, Dessole S, Ruiu G, Ambrosini G, Farina M, et al. (1999) The value of serum CA 125 and association CA 125/CA 19-9 in endometrial carcinoma. Eur J Gynaec Oncol 20: 315-317.

50. Liu P, Zhu Y, Liu L (2015) Elevated serum CA72-4 levels predict poor prognosis in pancreatic adenocarcinoma after intensity-modulated radiation therapy. Oncotarget 6: 9592-9599.

51. Hareyama H, Sakuragi N, Makinoda S, Fujimoto S (1996) Serum and tissue measurements of CA72-4 in patients with endometrial carcinoma. J Clin Pathol 49: 967-970.

52. Simon I, Liu Y, Krall KL, Urban N, Wolfert RL, et al. Evaluation of the novel serum markers B7-H4, Spondin 2, and DcR3 for diagnosis and early detection of ovarian cancer. Gynecol Oncol 106: 112-118.

53. Miranti C (2009) Controlling cell surface dynamics and signaling: how CD82/KAI1 suppresses metastasis. Cell Signal 21: 196-211.

54. Friess H, Guo XZ, Tempia-Caliera AA, Fukuda A, Martignoni ME, et al. (2001) Differential expression of metastasis-associated genes in papilla of vater and pancreatic cancer correlates with disease stage. J Clin Oncol 19: 2422-2432.

55. Liu FS, Chen JT, Dong JT, Hsieh YT, Lin AJ, et al. (2001) KAI1 metastasis suppressor gene is frequently down-regulated in cervical carcinoma. Am J Pathol 159: 1629-1634.

56. FU-Shing L (2003) KAI1 gene relates to squamous cell carcinoma of the larynx. Chinese Med J 116: 1307.

57. Friedländer MR, Lizano E, Houben AJ, Bezdan D, Báñez-Coronel M, et al. Evidence for the biogenesis of more than 1,000 novel human microRNAs. Genome Biol 15: R57.

58. George S, Chaudhery V, Lu M, Takagi M, Amro N, et al. (2013) Sensitive detection of protein and miRNA cancer biomarkers using silicon-based photonic crystals and a resonance coupling laser scanning platform. Lab Chip 13: 4053-4064.

59. Etheridge A, Lee I, Hood L, Galas D, Wang K (2011) Extracellular microRNA: a new source of biomarkers. Mutat Res 717: 85-90.

60. A Macha M, Seshacharyulu P, Ram Krishn S, Pai P, Rachagani S, et al. (2014) MicroRNAs (miRNAs) as biomarker (s) for prognosis and diagnosis of gastrointestinal (GI) cancers. Curr Pharm Des 20: 5287-5297.

61. Izadi A, Moslemi E, Poorhosseini SM, Yassaee VR, Kheiri HR, et al. (2014) UBD identify in paraffin tissues in patients with colorectal cancer. J Isfahan Med School 32: 291.

62. Alonso CR (2002) Hox proteins: sculpting body parts by activating localized cell death. Curr Biol 12: R776-R778.

63. Schimanski CC, Frerichs K, Rahman F, Berger M, Lang H, et al. (2009) High miR-196a levels promote the oncogenic phenotype of colorectal cancer cells. World J Gastroenterol 15: 2089.

64. Schwab M (1999) Oncogene amplification in solid tumors. Semin Cancer Biol 9: 319-325.

65. Nagpal M, Singh S, Singh P, Chauhan P, Zaidi MA (2016) Tumor markers: A diagnostic tool. Natl J Maxillofac Surg 7: 17.

66. Garg A, Ahmed S, Sinha A, Singh HP (2015) Tumor markers–Its advantages and limitations in diagnosis of oral cancer. Univ J Dent Sci 1: 42-45.

67. Cowper SE, Kilpatrick T, Proper S, Morgan MB (1999) Solitary fibrous tumor of the skin. Am J Dermatopathol 21: 213-219.