 doi:10.20944/preprints202207.0124.v1

DIAGNOSTICS OF OVARIAN TUMORS IN POSTMENOPAUSAL PATIENTS

Chingis Mustafin[1], Sergey Vesnin[2], Aran Turnbull[3], Michael Dixon[3], Igor Goryanin[3,4]

1 People' Friendship University of Russia, Moscow, Russia

2 Medical Microwave Radiometry (MMWR) LTD, Edinburgh, UK

2 University of Edinburgh, Edinburgh, UK

3 Okinawa Institute Science and Technology, Okinawa, Japan

Abstract: *Ovarian cancer is the third most common female genital cancer. Therefore, the timely diagnosis and comprehensive treatment of postmenopausal patients with benign ovarian tumors remains crucial in the field of gynecology. The significance of ovarian tumors depends on their frequency and their effects on the quality of life of a woman, as well as the possible development of ovarian cancer. Most ovarian cancers are diagnosed late and as a result are difficult to treat and often carry a poor prognosis. Currently there is no clear algorithm available for examining and accurately diagnosing patients with postmenopausal ovarian tumors; moreover, reliable criteria allowing dynamic observation and determining surgical access and optimal surgical intervention measures in postmenopausal patients is lacking.*

Key words: *post menopause, tumour marker, ovarian tumors, ovarian lesions.*

The diagnosis and treatment of ovarian neoplasms remains crucial in gynecology [1]. This issue is relevant due to the widespread prevalence of tumors and tumor-like formations in the ovaries as well as the continuing upwards trend of ovarian cancer incidence along with only a marginal decrease in mortality and an increase in the five-year survival [2]. In several countries, including Russia, ovarian cancer ranks eighth (4.3% frequency) among all malignant neoplasms in women of all age groups [3,4].

Ovarian neoplasms account for up to 25% of all tumors of the female genital organs and world-wide incidence peaks in the early post-menopausal period around the ages of 55-64 with a median age at diagnosis of 63.

Indeed, in Russia, according to recent statistics, there are currently more than 21 million women at the menopausal stage. The average age of menopausal women ranges from 49 to 51 years, and women live almost one-third of their lives in conditions of estrogen deficiency [6]. Moreover, benign ovarian tumors are prevalent in 2.5%–18% of postmenopausal women [7].

 doi:10.20944/preprints202207.0124.v1

Screening, which allows diagnosing a malignant ovarian tumor at an early asymptomatic stage of its development, is the most important and optimal way to reduce mortality. However, the screening revealed a number of problems that required significant diagnostic effort to identify risk groups, make the correct diagnosis and appropriate treatment, for which the health systems in the screening countries were not ready.

Screening for ovarian cancer is not recommended in the general population of women, nor in women without risk factors (low-risk group).To date, no clear algorithm is available for examining ovarian tumors in women; furthermore, no reliable criteria are available to select the optimal management strategy for each individual patient, including dynamic observation or surgical intervention [8]. Therefore, obstetricians and gynecologists need to urgently explore a research method that would allow reliable differential diagnosis of tumours and tumour-like formations in the ovary at the prehospital stage. Numerous studies have reported that a systematic gynecological examination does not significantly affect the identification of ovarian formations [9,10]. Difficulties in the differential diagnosis of ovarian tumors are associated with the absence of early signs of the disease and limited clinical symptoms at early stages of the disease [11,12]. Moreover, at present no gold standard method is available worldwide for early diagnosis, which may help in identifying the malignant neoplasms at borderline tumor stage and early stages of malignancy [13], since echography of the pelvic organs and determination of serum CA-125 in combination are recognized as ineffective for screening at the early stages of ovarian cancer [14].

Until 1981, only one biomarker was used to diagnose ovarian cancer, that is, cancer embryonic antigen (CEA). CEA was first described in 1965 as a serum biomarker in mucinous colon cancer, and in 1976, as a marker in women with ovarian cancer [15,16]; however, in 1981, the CA-125 antigen, be found in ovarian, cervical, endometrial cancer, GIT carcinoma and breast cancer, was identified [17]. Carbohydrate antigen 125 (CA125) is presently the most common serum marker for ovarian tumor. It is widely used for preoperative diagnostics, treatment evaluation, and monitoring patients with ovarian cancer. Benjapibal et al. found that the detection of serum CA-125 alone has a certain degree of accuracy in differentiating malignant and benign ovarian tumors [18]; however, the specificity of the CA 125 test in benign ovarian tumors is 73.2%, whereas in malignant tumors, it is approximately 99.3% [19,20].

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 7 July 2022 doi:10.20944/preprints202207.0124.v1

At present, CA-125 is widely used to assess the effectiveness of treatment and prognosis of the disease; however, the use of several markers, particularly during initial examination of patients with ovarian formations, will increase the likelihood of detecting a tumour [20]. Bian et al. investigated the predictive value of several tumor markers, including cancer antigen 72-4, cancer antigen 15-3, and CA-125; the sensitivity of detecting ovarian cancer using these three tumor markers in combination was apparently higher than that using individual markers [21]. Several studies have demonstrated that the addition of vascular endothelial growth factor (VEGF) improves the specificity of CA-125 for detecting early stage ovarian tumors [22].

Currently, the HE4 tumor marker is also commonly used worldwide. Human epididymis protein 4 (HE4), a member of the protease inhibitor family, is formed in the epithelium of numerous tissues of the female genital tract (fallopian tubes, endometrium, and endocervix). The expression of the HE4 gene is markedly increased in ovarian cancer cells, and owing to protein low molecular weight (25 kDa), it is abundantly found in the bloodstream. Many researchers have reported that a statistically significant increase in the level of HE4 is observed in patients at stages I–II of the disease, even earlier than the appearance of CA125 [23, 24, 25]. According to a systematic review and meta-analysis by Lin, the sensitivity and specificity of HE4 in detecting epithelial malignant ovarian tumors was 74% and 87%, respectively, and for borderline tumors, it was 80% and 75%, respectively [26]. Moreover, numerous studies have reported that in almost 50% of ovarian cancer cases with CA-125 values not exceeding the discrimination level, a significant increase was detected in HE4 [27]. Brown et al. emphasized that HE4 was increased in approximately 10% of cases of ovarian cancer with negative CA-125 indicators [28].

Wu et al. suggested that serum CA-125 in combination with carcinoembryonic antigen, alpha-fetoprotein, carbohydrate antigen 19-9, and human chorionic gonadotropin (b-hCG) can positively enhance cancer detection [29]; however, these tumor markers lack specificity. One tumor marker is often associated with several tumors in various organs or in the same organ. Furthermore, the tumor marker may often be detected in the blood as a result of a reaction to inflammatory diseases, or it can occur in benign tumors. For example, CA-125 is the main antigen associated with ovarian cancer; however, its levels can be reactively increased in the presence of lung cancer, pancreatic cancer, breast cancer, liver cancer, malignant tumors of the gastrointestinal tract, pelvic inflammatory disease in women, endometriosis, ovarian cysts, pancreatitis, and other conditions.

The initial step for creating an algorithm for the differential diagnosis of benign and malignant tumors were taken in 1990 by Jacobs et al. In an attempt to establish the most accurate risk factors (considering age, menopausal status, and level of the CA-125 marker), the authors

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 7 July 2022 doi:10.20944/preprints202207.0124.v1

developed the risk of malignancy index (RMI) scale with a sensitivity of 85% and specificity of 97% [30].

In 2010, Moore et al. proposed a new prognostic model, the ROMA scale, which combines measurements of tumor markers CA-125 and HE4 [31]. The ROMA scale exhibited a sensitivity of 85.3% in patients with stage I and II ovarian cancer, compared with 64.7% in the case of the RMI scale ($p< 0.0001$). Furthermore, in 2011, Montagnana et al. found that the effectiveness of the ROMA scale is remarkably higher in postmenopausal women than in premenopausal women. Moreover, studies on the combination of markers HE4 and CA-125 did not reveal better results than those on HE4 alone [32]. In a meta-analysis by Dayyani et al., it was observed that the ROMA scale exhibited diagnostic advantages when compared to a study reporting the levels of tumor markers CA-125 and HE4 only in patients with early ovarian cancer and in postmenopausal women; however, in this group of patients, the effectiveness of the ROMA scale was higher than that in the levels of individual markers [33]. The RMI and ROMA methods exhibit high sensitivity (83.3% and 75%, respectively) and specificity (95.3% and 100%, respectively) [34].

In 2016, a meta-analysis was carried out to identify the optimal predictive model for ovarian cancer, which compared the most common RMI assessment model, 2 IOTA scales (simple rules and LR2), and the ROMA scale. It was revealed that the combination of IOTA simple rules and the subjective assessment by a doctor using ultrasound diagnostics has the highest sensitivity and specificity (91% and 91%, respectively) in comparison with the RMI scale (sensitivity 75%, specificity 92%) [34].

With the development of fine-needle biopsy, cytology can be applied in research related to the qualitative diagnosis of gynecological tumors. Mehdi et al. conducted a study with 42 patients, and reported that the cytological diagnosis was appropriate in 34 cases and accuracy was 80.9% [35]. Ultrasound mini surgery can remarkably increase the diagnosis of nosological type of volumetric pathological formations of the small pelvis and reduce the number of abdominal (unjustified) operations, simple ovarian cysts, as well as peritoneal cysts [36]. Moreover, the anatomical localization of the ovaries limits the widespread clinical use of cytology in ovarian tumors. Thus, accurate diagnosis in the case of borderline tumors and early stages of ovarian involvement is difficult. Furthermore, it is an invasive operation that can cause the spread of tumor cells. Hence, presently the use of fine-needle biopsy of the ovaries in formations up to 50 mm in size holds critical significance.

Ultrasound is the preferred method for examining the female reproductive system; it exhibits a relatively high level of safety compared to other types of preoperative examination.

 doi:10.20944/preprints202207.0124.v1

Ultrasound has become the standard diagnostic method for evaluating epididymal tumors and is used as a first-line method in patients with suspicious isolated ovarian lesions [37]. This method mainly confirms the presence of a tumor, differentiates ovarian lesions from lesions of the uterus or fallopian tubes, and determines the internal structure of the tumor. Recently, ultrasound is widely used in preoperative diagnosis, postoperative examination, and long-term follow-up of patients with ovarian tumors. Using a combination of several modes of ultrasound imaging, the accuracy of differentiation between benign and malignant ovarian tumors is continuously improved. Two-dimensional (2D) ultrasound is the most commonly used method to assess the size, shape, location, internal structure, and physical properties of tumors in clinical practice; however, certain limitations and difficulties arise while differentiating malignant and benign ovarian tumors due to the complexity of the tumor tissues and their surrounding structures. Colour Doppler sonography can be used to monitor the spread of tumor blood flow, vascular morphology, and hemodynamics, such as blood flow velocity, resistance index (RI), pulsatile index (PI), and other indicators. It can provide more diagnostic information and can be more useful than 2D ultrasound in differentiating benign and malignant ovarian tumors. In real time, three-dimensional (3D) ultrasound can obtain 3D reconstruction of any tissue and organ based on 2D ultrasound. Therefore, more information regarding the internal structure, position, and size of the lesions can be obtained using 3D ultrasound than 2D, such as the characteristics of the cyst walls and septa. Ultrasound in combination with dopplerometry helps in assessing the characteristics of blood flow in the ovarian formations and in conducting more accurate differential diagnosis of tumors and tumor-like formations [38]. Several studies have reported that gray-scale ultrasound and color Doppler imaging (CDM) cannot accurately determine the topical location and structure of the tumor at the preoperative stage [39].

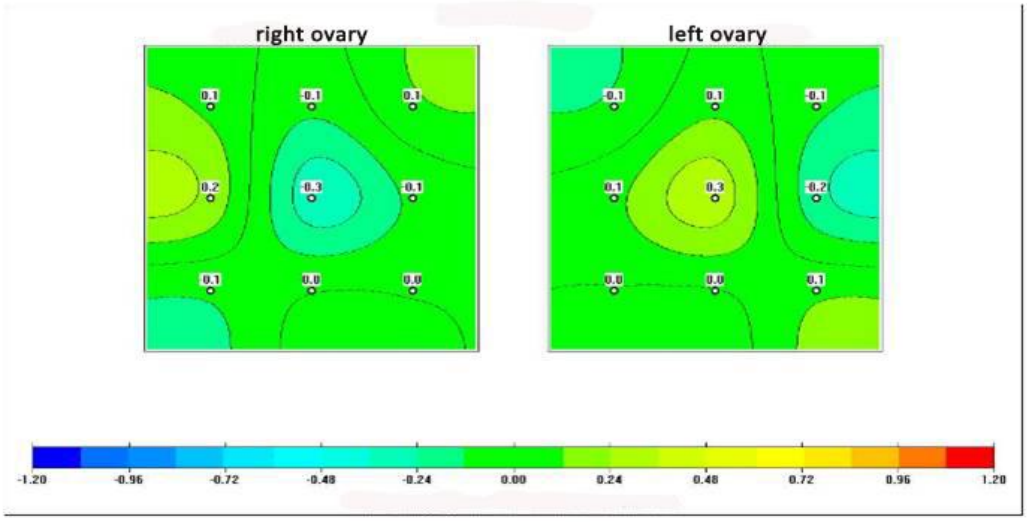
In 1999, the International Ovarian Tumor Analysis (IOTA) group for the ultrasound analysis of ovarian tumors was formed. The core objective of this group is to create mathematical models (LR2, Simple Rules, ADNEX), using the simplest logistic analysis to calculate the risk of malignancy of ovarian tumors. The IOTA group, based on randomized studies, has developed ultrasound criteria, “B-rule” for benign and “M-rule” for malignant tumors [13]. In 2010, a Phase II IOTA study proved the effectiveness of a model for detecting ovarian malignancies (sensitivity and specificity of 95% and 91%, respectively), based on specific changes in the ovarian tissues recorded using an ultrasound [40]. The model exhibited a sensitivity of 92% and a specificity of 96% [41]. The use of high-resolution transvaginal echography in combination with various qualitative and quantitative Doppler techniques often makes it possible to visualize the tumor growth and neovascularization at initial stages of their development; however, the technique depends on the class of equipment and the experience of the researcher.

 doi:10.20944/preprints202207.0124.v1

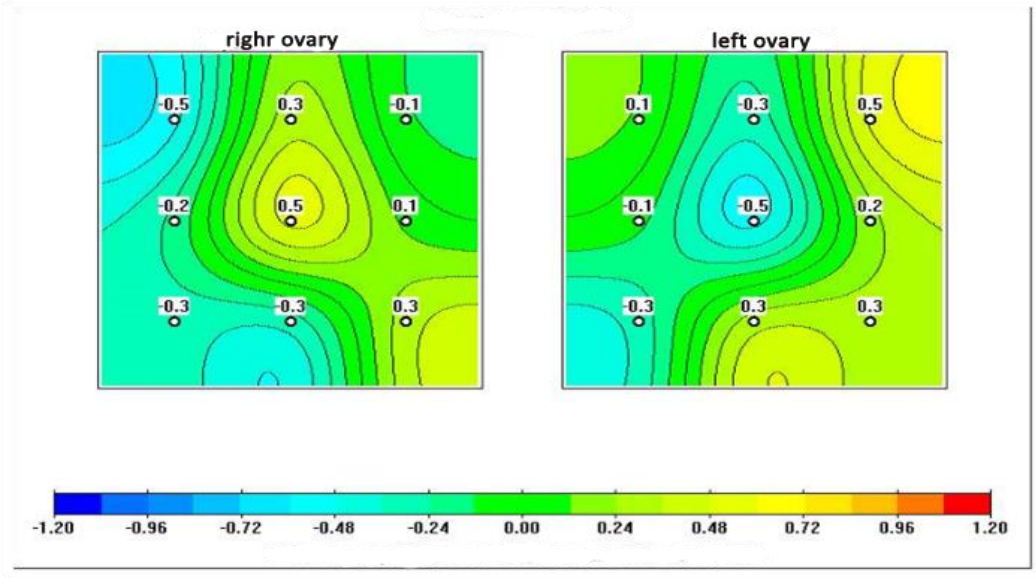
As additional diagnostic methods, several authors used computed tomography (CT) and magnetic resonance imaging. These examinations alone are most often recommended for analyzing the prevalence of a malignant process, as well as during observation in the postoperative period and in the process of anticancer treatment; however, CT is ineffective in primary detection and determination of the tumor type in uterine appendages and assessment of local spread in the small pelvis. Magnetic resonance imaging determines the position, size, boundaries, components, and angiogenesis of tumors of the appendages; however, MRI, similar to CT, is not recommended for the primary assessment of postmenopausal ovarian cysts due to low specificity and radiation exposure [13]. MRI should be used as an imaging technique if the ultrasound characteristics of an ovarian cyst are uncertain and inconclusive [42]. Therefore, MRI has an important clinical role in detecting ovarian tumors and determines whether the tumor is benign or malignant.

In recent years, thermometric methods have been widely used for examining ovaries, based on the fact that with the development of a tumor, energy consumption and heat release increases. A change in tissue temperature, which can be evaluated using conventional methods, usually precedes structural changes. Using MWR, the internal temperature is measured transabdominally at 9 symmetrical points in the iliac region on both sides. The average value of the internal temperature is obtained on the image of the computer analyzer, which is considered as the standard, and is then compared with the indicators of the internal temperature at each of the 18 points. Moreover, the excess value as compared to that of the standard, the absence of focal hyperthermia, or the degree of its severity is determined. Considering a value of this indicator of 0.5 °C or less, the absence of focal hyperthermia in the projection of ovaries, characteristic of a malignant tumor process, is determined, as no signs of a malignant neoplasm are observed. Furthermore, a value of 0.6–1 °C during projection of one or both ovaries, unexpressed hyperthermia is determined, which is a sign of a borderline tumor process preceding the development of a malignant tumor. Additionally, a value of 1.1 °C or more, in the projection of one or both ovaries, determines pronounced focal hyperthermia, indicating high probability of a malignant process. In 2017, Mustafin and Pak reported the examination of 119 women aged 49–73 years, with the control group comprising 54 apparently healthy women. The accuracy of the proposed forecasting method was 90% [43].

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 7 July 2022 doi:10.20944/preprints202207.0124.v1

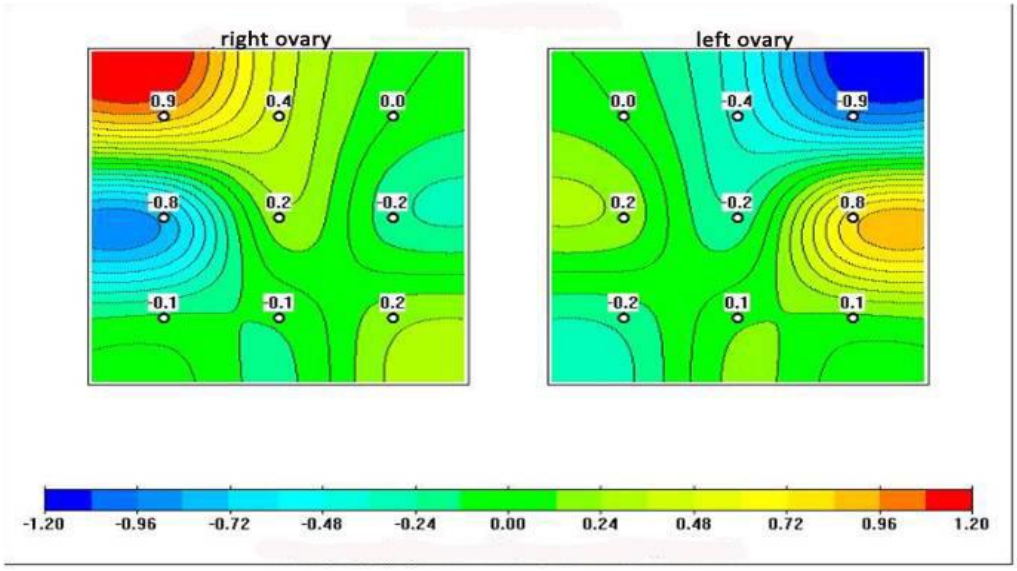


Patient, 62 years old. The ovaries are normal. There are no signs of focal hyperthermia.

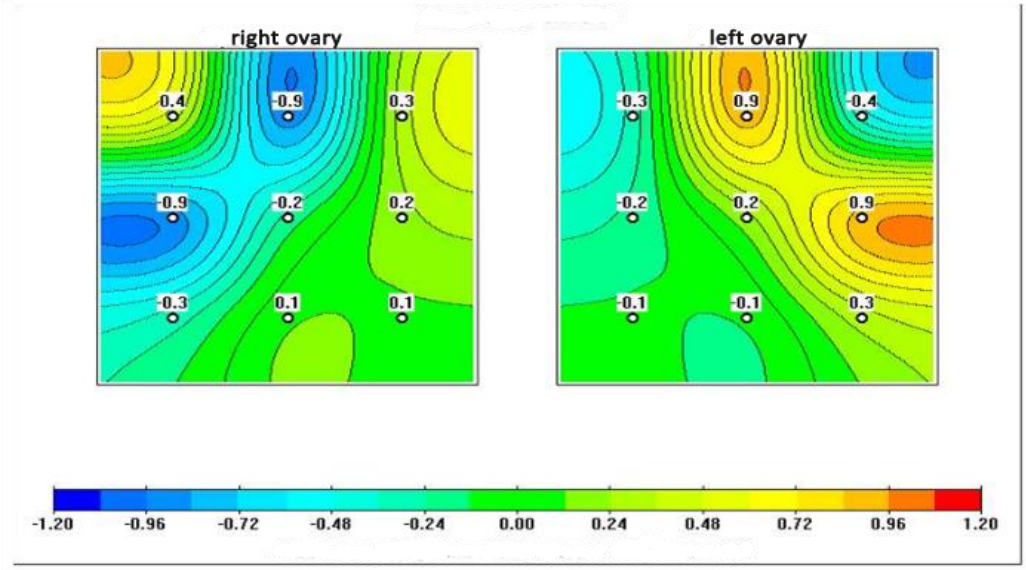


Patient, 65 years old. The ovaries are normal. There are no signs of focal hyperthermia.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 7 July 2022 doi:10.20944/preprints202207.0124.v1

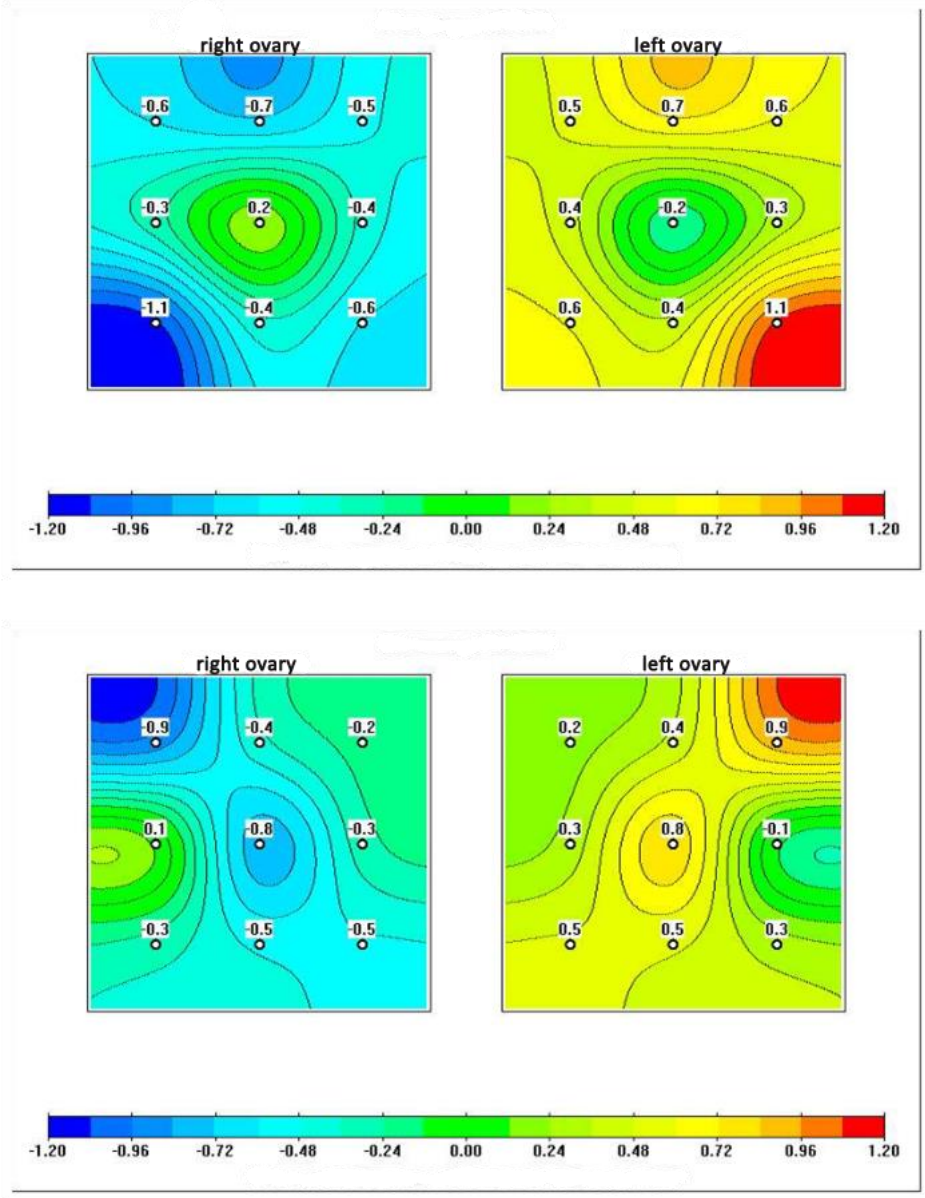


Patient, 72 years old. Risk group. Signs of hyperthermia in the projection of the ovaries.



Patient, 69 years old. Risk group with a high probability. Focal hyperthermia in the projection of the left ovary.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 7 July 2022 doi:10.20944/preprints202207.0124.v1



Patient, 59 years old. Risk group with a high probability. Focal hyperthermia in the projection of the left ovary.

Thus, the examination of patients with ovarian formations includes a detailed study of the history, two-handed vaginal examination, as well as general clinical additional research methods, such as the determination of tumor markers. Each of these methods has its drawbacks: with manual palpation, small ovarian tumors are undetectable, and the echography accuracy is 82.7%. The possibilities of ultrasound diagnostics of ovarian formations depend on various factors such as the class of equipment, the qualifications of the researcher, the visualization conditions of the pelvic organs and the abdominal cavity associated with body mass index and adhesions.

The determination of tumor markers, particularly CA-125, is critical in the diagnosis of ovarian tumors; however, this antigen is not strictly specific for ovarian formations, and its level can be increased in liver cirrhosis, acute pancreatitis, endometriosis, uterine myoma, and in

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 7 July 2022 doi:10.20944/preprints202207.0124.v1

malignant tumors of the gastrointestinal tract and abdominal organs. The specifics of indications for surgery in postmenopausal patients with ovarian formations remains controversial because none of the existing diagnostic research methods in practice provide sensitivity and specificity equal to or at least close to 100%.

Women experience menopause and conditions of estrogen deficiency for almost one-third of their lives at older age. The physiology of postmenopause leads to numerous disorders that contribute to an increase of chronic pathological proliferation. The process could be caused by hormonal regulation (preservation of the receptor status, a high level of expression of aggressive metabolites) or induction of proliferation via involutive–atrophic processes, chronic inflammation, pronounced disorders of microbiocenosis, inducing mutated stem cells.

Estrogen deficiency associated with postmenopause leads to irreversible changes in organs and systems (disturbances in the composition and metabolism with the development of metabolic syndrome in 60% of women, cardiovascular diseases, osteoporosis, and osteopenia), which adversely affect the onset of the disease and hinder the diagnosis process. These features dictate personalized approaches to diagnostics, management, and surgical tactics, considering the high risk of anesthetic and surgical complications, as surgical interventions without clear indications often leads to deterioration of a woman's health and quality of life.

Eventually, whether there is a need to surgically remove the benign ovarian tumors of small sizes (up to 5 cm) in post menopausal patients remains unclear, considering the low percentage of malignancy of these formations.

Discussion

In the UK, during 2001-2004, 202,562 women aged 50-74 were included in the study on the effectiveness of screening for ovarian cancer, who were randomized into three groups. The first group (50625 women) passed the CA-125 test annually, and if it increased, the test was repeated after 6 weeks or transvaginal sonography was performed. The second group (50623) underwent transvaginal sonography annually and, if suspected, the CA-125 test was additionally performed. In the third control group (101314), only observation and examination were carried out in case of symptoms of the disease. All patients with diagnosed ovarian cancer received treatment in large hospitals of the national health system with the presence of gynecological oncologists. The main criterion for effectiveness was mortality from ovarian and fallopian tube cancers.

With a median follow-up of 16 years, ovarian cancer was diagnosed in 2055 women, with a detection rate of 1% in all three groups. In the first group, where the definition of CA-125 was

 doi:10.20944/preprints202207.0124.v1

used as the main test, there was a higher rate of detection of the disease in stage I (by 47%) and a lower frequency in stage IV (by 25%) compared to controls. In the group with transvaginal sonography, the stage distribution of the identified patients did not differ significantly from the control group. However, earlier detection of the disease did not lead to either a decrease in mortality or a longer life expectancy of sick patients compared to controls. A total of 1206 patients died, and the Kaplan-Meier survival curves for all three groups are the same, the number of patients who died was 0.6% in each group.

Thus, proven screening programs with CA-125 determination and transvaginal sonography are unable to reduce mortality from ovarian cancer. A more accurate diagnostic method is required, which has yet to be developed. The authors emphasize that it took more than 30 years from the beginning of the study of CA-125 testing and transavaginal sonography as possible screening methods to obtaining the results of a population-based randomized trial [44-47].

References

1. Urmancheeva A.F., Kutusheva G.F., Ulrikh E.A. Ovarian tumors: clinical picture, diagnosis and treatment. St. Petersburg, Publishing house N-L, 2012.
2. Egunova M.A., Kutsenko I.G. Differential diagnosis of benign and malignant neoplasms of the ovaries (history of the issue). J ObstetWomens Dis 2016; 65 (6): 68–78. DOI: 10.17816/JOWD65668-78.
3. Ionescu C.A., Matei A., Navolan D., et al. Correlation of ultrasound features and the Risk of Ovarian Malignancy Algorithm score for different histopathological subtypes of benign adnexal masses. Med (Baltim) 2018; 97 (31): e11762. doi: 10.1097/MD.0000000000011762.
4. Kaprin A.D., Starinskiy V.V., Petrova G.V. The state of cancer care for the population of Russia in 2017. M: MNIOI im. P.A. Herzen branch of the National Medical Research Center of Radiology of the Ministry of Health of Russia, 2018. -. ill. −236 p. UDC; 616-006: 04-082 (470) "2017" BBK 55.6 C59 ISBN 978-5-85502-237-7.
5. Khairutdinova M.R., Egamberdiev L.D. Management of patients with ovarian formations. Practical medicine. Innov Technol Med 2015; 1 (84): 191–196.
6. Yureneva S.V., Ermakova E.I. Management of women with menopausal disorders (review of clinical guidelines). ReprodProbl 2017; 23 (5): 115–122. doi: 10.17116/repro2017235115-122.
7. Guraslan H., Dogan K. Management of unilocular or multilocular cysts more than 5 centimeters in postmenopausal women. Eur J ObstetGynecolReprod Biol 2016; 203: 40–43. doi: 10.1016/j.ejogrb.2016.05.028. Epub 2016 May 20.

8. American College of Obstetricians and Gynecologists. The role of the obstetrician - gynecologist in the early detection of epithelial ovarian cancer in women at average risk. ObstetGynecol 2017; 130 (3): e146–e149. ISSN 1074-861X.

9. Orr B., Edwards R.P. Diagnosis and treatment of ovarian cancer. Hematol Oncol Clin North Am 2018 Dec; 32 (6): 943–964. doi: 10.1016/j.hoc.2018.07.010.

10. Vorobiev A.V., Protasova A.E. General questions of screening. J Pract Oncol 2010. T.11; 2 (S): 53–59.

11. Urmancheeva A.F., Kutusheva G.F., Ulrikh E.A., 2012 Efimova O.A. Complex radiation diagnostics of ovarian tumor formations at the preoperative stage // Povolzhsky oncological bulletin, 2017; 3 (30): Sects 61–64.

12. Zola P., Macchi C., Cibula D., Colombo N., Kimmig R., Maggino T. et al. Follow-up in gynecological malignancies: A state of art. Int J Gynecol Cancer 2015; 25 (7): 1151–1164. doi: 10.1097/IGC.0000000000000498.

13. Clinical recommendations of the Ministry of Health of The Russian Federation "Diagnostics and treatment of benign ovarian neoplasms from the perspective of cancer prevention", 2018.

14. Stewart B.W., Wild C.P. World cancer report, 2014, Lyon: IARC. 916p.

15. Hammarstrom S., Engvall E., Sundblad G., 1976. Carcinoembryonic antigen CEA: purification, structure and antigenic properties, in Health control in detection of cancer, Skandia international Symposia Bostrom H, Larsson T, Ljungstedt N, eds pp. 24–39.

16. Khoo S.K., MacKay E.V. Carcinoembryonic antigen (CEA) in ovarian cancer: factors influencing its incidence and changes which occur in response to cytotoxic drugs. Br J ObstetGynaecol 1976; 83 (10): 753–759. doi: 10.1111/j.1471-0528.1976.tb00739.x.

17. Bast R., Feeney M., Lazarus H., Nadler L., Knapp R. Reactivity of a monoclonal antibody with human ovarian carcinoma. J Clin Investig 1981; 68: 1331–1337. doi: 10.1172/JCI110380.

18. Benjapibal M., Neungton C. Pre-operative prediction of serum CA125 level in women with ovarian masses. J Med Assoc Thai 2007; 90 (10): 1986–1991.

19. Wilbaux M., Hénin E., Oza A., Colomban O., Pujade-Lauraine E., Freyer G., Tod M., You B. "Prediction of tumour response induced by chemotherapy using modelling of CA-125 kinetics in recurrent ovarian cancer patients. Br J Cancer 2014; 110 (6): 1517–1524.

20. Li F., Tie R., Chang K., Wang F., Deng S., Lu W., Yu L., Chen M. Does risk for ovarian malignancy algorithm excel human epididymis protein 4 and CA125 in predicting epithelial ovarian cancer: A meta-analysis. BMC Cancer 2012; 12: 258. doi: 10.1186/1471-2407-12-258.

21. Bian J., Li B., Kou X.J., Liu T.Z., Ming L. Clinical significance of combined detection of serum tumor markers in diagnosis of patients with ovarian cancer. Asian Pac J Cancer Prev 2013; 14 (11): 6241–6243.

22. Robati M., Ghaderi A., Mehraban M., Shafizad A., Nasrolahi H., Mohammadianpanah M. Vascular endothelial growth factor (VEGF) improves the sensitivity of CA125 for differentiation of epithelial ovarian cancers from ovarian cysts. Arch Gynecol Obstet 2013; 288 (4): 859–865.

23. Havrilesky L.J., Whitehead C.M., Rubatt J.M., et al. Evaluation of biomarker panels for early stage ovarian cancer detection and monitoring for disease recurrence. Gynecol Oncol 2008; 110 (3): 374–382. doi: 10.1016/j.ygyno.2008.04.041.

24. Drapkin R., von Horsten H.H., Lin Y. et al. Human epididymis protein 4 (HE4) is a secreted glycoprotein that is overexpressed by serous and endometrioid ovarian carcinomas. Cancer Res 2005; 65 (6): 2162–2169.

25. Gavrilevsky L. et al. Assessment of biomarkers in early stage ovarian cancer. Cancer detection and monitoring of disease recurrence. Gynecol Oncol 2008; 110: 374–382.

26. Lin J., Qin J., Sangvatanakul v. Human. Human epididymis protein 4 for differential diagnosis between benign gynecologic disease and ovarian cancer: a systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol 2013; 167 (1): 81–85. doi: 10.1016/j.ejogrb.2012.10.036.

27. Bast R.C. Jr, Skates S., Lokshin A., Moore R.G. Differential diagnosis of pelvic mass: improved algorithms and novel biomarkers. Int J Gynecol Cancer, IGC.0b013e318251c97d 2012; 22 (Suppl 1): S5–S8.

28. Brown et al. Comparative analysis of the expression of CA 125 and a new serum tumor marker HE4 in epithelial ovarian cancer. J Clin Oncol 2008: 26–31 (Suppl): abstract 5533.11.

29. Wu C.M., Li X.L., Li L., Yin L.L., Li Q. Combined detection of tumor makers in the diagnosis of ovarian tumors. Int J Lab Med 2014; 35 (6): 724–725.

30. Jacobs I., Oram D., Fairbanks J. et al. A risk of malignancy index incorporating CA 125, ultrasound and menopausal status for the accurate preoperative diagnosis of ovarian cancer. Br J Obstet Gynaecol 1990; 97 (10): 922–929. PMID: 2223684.

31. Moore R.G., Jabre-Raughley M., Brown A.K. et al. Comparison of a novel multiple marker assay versus the Risk of Malignancy Index for the prediction of epithelial ovarian cancer in patients with a pelvic mass. Am J Obstet Gynecol 2010; 203 (3): 228.03.043; 10 (1016) / j. ajog: e1–6. DOI. PMID: 20471625.

32. Montagnana M., Danese E., Ruzzenente O., et al. The ROMA (Risk of Ovarian Malignancy Algorithm) for estimating the risk of epithelial ovarian cancer in women presenting with pelvic mass: is it really useful? Clin Chem Lab Med 2011; 49 (3): 521–525. DOI: 10.1515/CCLM.2011.075. PMID: 21288178.

33. Dayyani F., Uhlig S., Colson B., et al. Diagnostic performance of risk of ovarian malignancy algorithm against CA-125 and HE4 in connection with ovarian cancer: a meta-analysis. Int J

Gynecol Cancer 2016; 26 (9): 1586–1593. DOI: 10.1097/IGC.0000000000000804. PMID: 27540691.

34. Meys E.M., Kaijser J., Kruitwagen R.F., et al. Subjective assessment versus ultrasound models to diagnose ovarian cancer: A systematic review and meta-analysis. Eur J Cancer 2016; 58: 17–29. doi: 10.1016/j.ejca.2016.01.007. Epub 2016 Feb 27.

35. Mehdi G., Maheshwari V., Afzal S., Ansari H.A., Ansari M. Image-guided fine-needle aspiration cytology of ovarian tumors: an assessment of diagnostic efficacy. J Cytol 2010; 27 (3): 91–95.

36. Dubrovskaya K.S. Diagnostics, treatment and prediction of the outcomes of pelvic neoplasms in gynecological patients Abstract of the dissertation for the degree of candidate of medical sciences, Moscow, 2018.

37. Borisova E.A. 2018 Comprehensive differential diagnosis of tumors of the uterine appendages. Abstract of the dissertation of the candidate of medical sciences, Irkutsk.

38. Suh-Burgmann E., Flanagan T., Osinski T., et al. Prospective validation of a standardized ultrasonography-based ovarian cancer risk assessment system. ObstetGynecol 2018; 132 (5): 1101–1111. doi: 10.1097/AOG.0000000000002939.

39. Valentin L., Ameye L., Savelli L., et al. Adnexal masses difficult to classify as benign or malignant using subjective assessment of gray-scale and Doppler ultrasound findings: logistic regression models do not help. Ultrasound ObstetGynecol 2011; 38 (4): 456–465. doi: 10.1002/uog.9030. Epub 2011 Sep 13.

40. Timmerman D., Ameye L., Fischerova D. et al. Simple ultrasound rules to distinguish between benign and malignant adnexal masses before surgery: prospective validation by IOTA group. BMJ 2010; 341: c6839. doi: 10.1136/bmj.c6839.

41. Froyman W., Landolfo C., De Cock B., et al. Risk of complications in patients with conservatively managed ovarian tumors (IOTA5): a 2-year interim analysis of a multicenter, prospective, cohort study. Lancet Oncol 2019; 20 (3): 448–458. doi: 10.1016/S1470-2045 (18) 30837-4.

42. The management of ovarian cysts in Postmenopausal Women, RCOG Greentop Guisline No. 34. Jul 2016.

43. Mustafin C.K., Pak E.V. Method for screening diagnostics of malignant neoplasms of the ovaries in postmenopausal women 2016. PatentRU 2616989; C1.

44. Final Recommendation Statement: Ovarian Cancer: Screening. U.S. Preventive Services Task Force (USPSTF). December 2016.

45. Screening for Ovarian Cancer: US Preventive Services Task Force Recommendation Statement. US Preventive Services Task Force. Grossman DC, Curry SJ, Owens DK, Barry MJ,

 doi:10.20944/preprints202207.0124.v1

Davidson KW, Doubeni CA, Epling JW Jr, Kemper AR, Krist AH, Kurth AE, Landefeld CS, Mangione CM, Phipps MG, Silverstein M, Simon MA, Tseng CW. JAMA. 2018 Feb 13; 319(6): 588-594.

46. Screening for Ovarian Cancer. Jin J. JAMA. 2018 Feb 13; 319(6): 624. doi: 10.1001/jama.2017.22136.

47. Menon U, Gentry-Maharaj A, Burnell M, et al. Ovarian cancer population screening and mortality after long-term follow-up in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial. Lancet 2021.