

Multiple Primary Malignant Tumors of the Female Reproductive System as the Risk Indicators for Oncopathologies Development

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Abstract The aim of the research was to study the frequency of development of synchronous and metachronous tumors, as well as the combination of various types of cancer among patients with primary multiple malignant tumors of the female reproductive system, which is important for improving the diagnosis of this category of patients. **Material and methods.** 80 patients with multiple primary malignant tumors with lesions of the female reproductive system (II-III clinical stages of the disease) were included in the study. **Results.** In our studies, synchronous tumors were found in 22 (27.5%), and metachronous tumors – in 58 (72.5%) patients. 9 (23.7%) from 38 patients with breast cancer were diagnosed with synchronous cancer of the second breast, and 3 (7.9%) were diagnosed with ovarian cancer. At the same time, synchronous breast cancer was detected in 5 (22.7%) of 22 patients with primary ovarian cancer, in 3 (25.0%) of 12 patients with uterine body cancer and in 2 (25.0%) of 8 patients with cervical cancer. Metachronous tumors were diagnosed in 26 (68.4%) patients with breast cancer, in 17 (77.3%) with ovarian cancer, in 9 (75.0%) with uterine body cancer and in 6 (75.0%) patients with cervical cancer. The most often metachronous tumors were detected in the period from 6 months to 1 year and from 1 year to 2 years in 26 (44.8%) patients. **Conclusion.** Thus, each of the female reproductive system tumors should be considered as an indicator of other oncopathologies risk. And effective dispensary monitoring will allow to monitor the development of multiple primary malignant tumors in this type of patients in advance.

Keywords Metachronous tumors, Primary multiple malignant tumors, Tumors of the female reproductive system, Synchronous tumors

1. Introduction

There is an increasing interest in studying issues related to the problem of multiple primary malignant tumors (MPMT) among oncologists due to the wide spread increase in the number of patients with this type of oncopathology [2,19]. Many researchers agree that polyineoplasias are most often found in women. It is associated with an increase in the incidence of the reproductive system hormone-dependent tumors, which is functionally represented by the mammary glands, uterus and ovaries [14,18]. Malignant tumors of the reproductive system are the most frequent in the structure of cancer morbidity in women and their total share exceeds 35%. According to various authors, the frequency of MPMT of the female reproductive system ranges from 0.8% to 12.6% of all cancer cases of these localities [1,6,11].

The issue of the time boundary between the synchronicity and metachronism of the malignant tumors development has been open for a long time [13]. Currently, most authors

consider the most reliable, although rather conditional interval of occurrence of the second metachronous tumor, a period of more than 6 months from the diagnosis of the first one. In the vast majority of cases (75-80%) metachronous tumors occur in the period from 3 to 15 years, although isolated cases of the second tumors occurrence at a later time are described [7,20].

According to various authors data in patients with breast cancer (BC) MPMT occurs in 1.9-7.1% of cases. Most often, breast cancer is associated with malignant tumors of the female reproductive system (33-42%): ovarian cancer (OC) (15-17%), uterine body cancer (UBC) (12-14%), cervical cancer (CC) (10-12%). Next in the frequency of occurrence is cancer of the colon and rectum (12-13%), then the stomach (14-15%) and thyroid cancer (7.7%). The remaining localizations of malignant tumors are described in single observations [2,3].

Among UBC patients, the most frequent combination is noted with breast tumors, which confirms the hormonal dependence of malignant cervical tumors. In UBC patients, the relative risk of breast cancer (BC) is 13.6% in the first year, 5.3% in the fifth, 3.9% in the tenth and 3.0% in the fifteenth year. In patients with breast cancer, the relative risk

of UBC is 9.0% in the first year, 2.4% in the fifth, 2.2% in the tenth, and 3.6% in the fifteenth year. Consequently, in patients with both BC and UBC, the risk of a second tumor developing is realized mainly in the first year due to synchronous polyineoplasias. The synchronicity of UBC and OC development and the relatively short interval between the development of UBC and BC, indirectly indicate the common pathogenetic mechanisms of these malignant tumors development [16,17].

The **aim** of the research was to study the frequency of development of synchronous and metachronous tumors, as well as the combination of various types of cancer among patients with primary multiple malignant tumors of the female reproductive system, which is important for improving the diagnosis of this category of patients.

2. Material and Methods

80 patients with multiple primary malignant tumors with lesions of the female reproductive system (II-III clinical stages of the disease) were included in the study, which were examined and treated in the departments of oncomammology, oncogynecology and chemotherapy-2 of Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology from 2015 to 2021. In accordance with the objectives of the study, the patients were divided into the following groups: group 1- 38 (34.5%) patients with breast cancer (BC); group 2-22 (20.0%) patients with ovarian cancer (OC); group 3-12 (10.9%) patients with uterine body cancer (UBC); group 4-8 (7.3%) patients with cervical cancer (CC).

The age of the examined BC patients varied from 23 to 79 years, the mean age was 46.8 ± 7.3 years; in OC patients the age ranged from 24 to 68 years, the mean age was 45.7 ± 6.4 years; in UBC patients the age varied from 32 to 76 years, the mean age was 48.6 ± 6.8 years; in CC patients the age ranged from 25 to 69 years and the mean age was 43.5 ± 7.0 years.

Disease-specific staging was performed according to the International Clinical Classification TNM (7th ed. and 8th ed.) and FIGO (2009 and 2016) [4,8,9,10]. As it follows from the data presented in the main groups, in BC patients IIB and IIA stages of the disease were more common; in patients with OC - IIB, IIA and IIIC stages; in UBC patients - I IB and IIC stages and in CC patients - IIB and IIIB stages of the tumor process.

3. Results and Discussion

The results of the study showed that infiltrating ductal cancer prevailed in patients with breast cancer – 22 (57.9%) cases. A mixed form of ductal and lobular types of cancer was revealed in 9 (23.7%) cases, infiltrating cancer occurred in 3 (7.9%) patients. The study of the OC morphological structure showed that 10 (45.5%) patients had serous

cystadenocarcinoma, 6 (27.3%) – undifferentiated cancer, 4 (18.2%) – endometrioid cancer and 2 (9.1%) patients – mucinous cystadenocarcinoma, respectively.

Histological analysis of UBC biopsy samples showed that in 8 (66.7%) patients endometrioid carcinoma was detected, in 2 (16.7%) cases – serous-papillary adenocarcinoma, in 1 (8.3%) patient – mixed carcinoma and 1 (8.3%) patient – light cell carcinoma. The morphological structure of the CC was also studied. Histologically, 4 (50.0%) patients had squamous cell carcinoma with keratinization, 3 (37.5%) – without keratinization. Adenocarcinoma was detected in 1 (12.5%) patient.

When analyzing the family oncological history of the examined patients, breast cancer (BC) was noted in 22 (57.9%) blood relatives on the maternal line, 2 (5.3%) of them had ovarian cancer (OC) and 4 (10.6%) had a combination of OC and BC.

The study of the anamnesis data showed that in most of the patients – 35 (43.8%) - the symptoms of the disease appeared in the period from 3 to 6 months.

In our studies, synchronous tumors were found in 22 (27.5%), and metachronous tumors – in 58 (72.5%) of the examined patients. Synchronous tumors, occurred in the period from 3 to 6 months, were found in 12 (31.6%) patients with breast cancer, synchronous second breast cancer was found in 9 (23.7%) of them, and ovarian cancer – in 3 (7.9%) cases. In patients with primary detected OC, UBC, and CC, synchronous breast cancer was simultaneously detected in 5 (22.7%), 3 (25.0%) and in 2 (25.0%) patients, respectively (Tab. 1).

Table 1. Distribution of examined patients with synchronous tumors, n=80

| Primary detected tumor | Synchronous tumor | Patients quantity | |
|---------------------------------|-------------------|-------------------|------|
| | | absolute | % |
| Breast cancer (BC), n=38 | BC | 9 | 23.7 |
| | OC | 3 | 7.9 |
| Ovarian cancer (OC), n=22 | BC | 5 | 22.7 |
| Uterine body cancer (UBC), n=12 | BC | 3 | 25.0 |
| Cervical cancer (CC), n=8 | BC | 2 | 25.0 |

Table 2. Distribution of examined patients with metachronous tumors, n=80

| Primary detected tumor | Metachronous tumor | Patients quantity | |
|---------------------------------|--------------------|-------------------|------|
| | | absolute | % |
| Breast cancer (BC), n=38 | BC | 14 | 36.8 |
| | UBC | 7 | 18.4 |
| | OC | 5 | 13.2 |
| Ovarian cancer (OC), n=22 | BC | 17 | 77.3 |
| Uterine body cancer (UBC), n=12 | BC | 7 | 58.3 |
| | OC | 2 | 16.7 |
| Cervical cancer (CC), n=8 | BC | 6 | 75.0 |

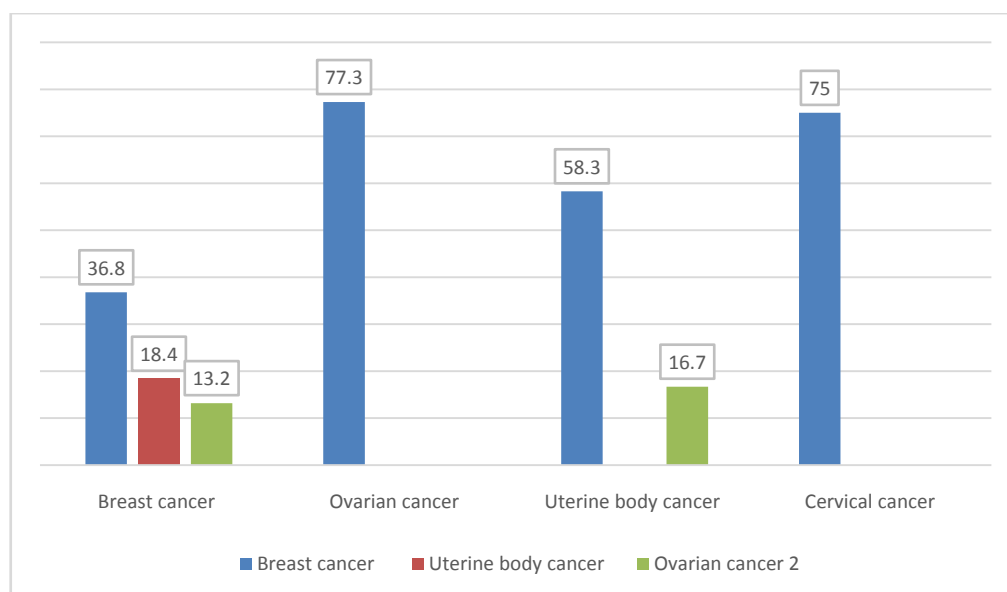


Figure 1. Percentage of metachronous combined tumors in patients with multiple primary malignant tumors, n=80

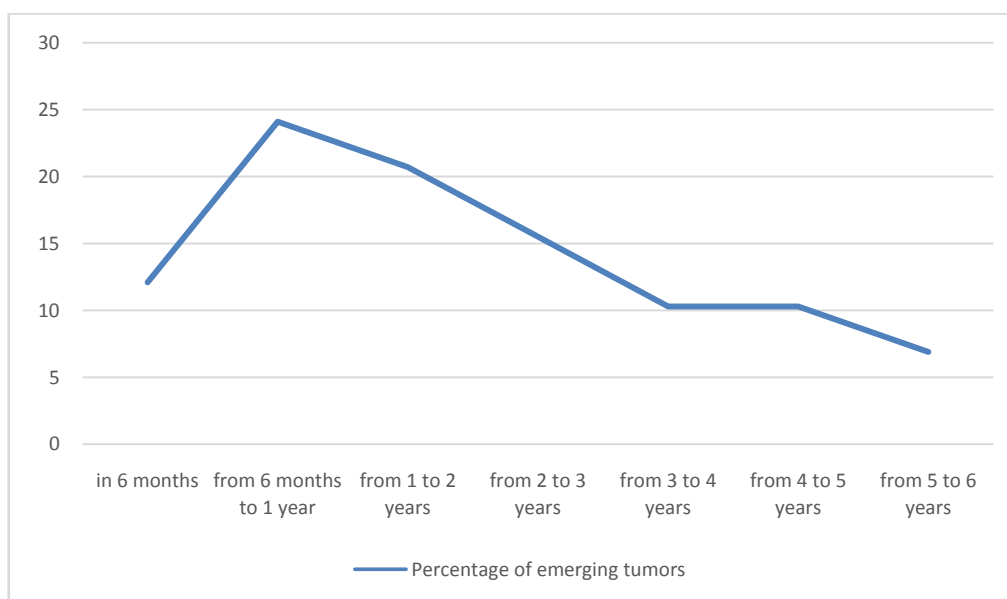


Figure 2. Distribution of metachronous tumors in the examined patients at different follow-up periods, in percentage

Metachronous cancer in terms of 6 months and above was detected in a larger number of patients. Thus, metachronous tumors were subsequently detected in 26 (68.4%) patients with breast cancer, among them metachronous second breast cancer – in 14 (36.8%), UBC – in 7 (18.4%) and OC – in 5 (13.2%) patients. Metachronous breast cancer was detected in 17 (77.3%) and 6 (75.0%) patients with OC and CC, respectively. And in UBC patients, metachronous breast cancer was detected in 7 (58.3%) examined patients and OC – in 2 (16.7%) cases (Tab. 2).

As it follows from Figure 1, a greater variety of combinations of metachronous malignant tumors of the female reproductive system is observed in the case when the primary tumor was breast cancer. In most cases, a

metachronous tumor occurs in the remaining mammary gland. In the case of primary ovarian cancer and cervical cancer, metachronous tumors of the breast alone were observed.

The timing of metachronous tumors occurrence in patients is shown in Figure 2, from which it follows that the most often tumors were detected in the period from 6 months to 1 year and from 1 year to 2 years in 26 (44.8%) patients.

Thus, MPMT represent a significant issue in modern oncology. Most of these polyineoplasias occur in women and are usually manifested at the development of hormone-dependent tumors of the reproductive system and are most often associated with breast cancer. In this regard, each of the tumors of the female reproductive system should

be considered as the risk indicator of other oncopathologies. Effective dispensary monitoring will allow to monitor the development of MPMT in this type of patients in advance.

4. Conclusions

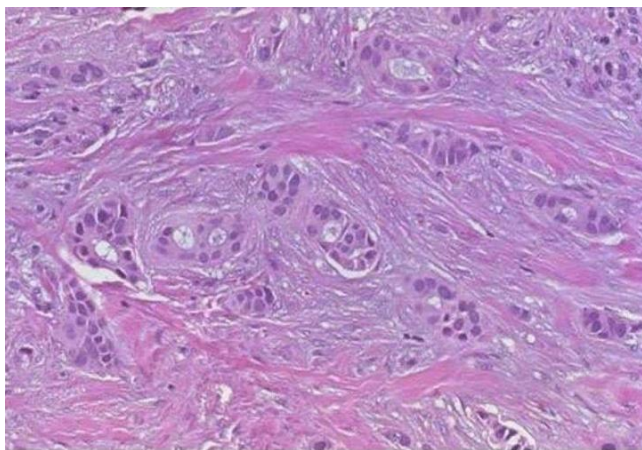
In our studies, synchronous tumors were found in 22 (27.5%) of 80 patients with multiple primary tumors. In our studies synchronous tumors were found in 12 (31.6%) patients with breast cancer, synchronous second breast cancer was found in 9 (23.7%) of them and ovarian cancer – in 3 (7.9%) cases. In patients with primary detection of OC, UBC, and CC, synchronous breast cancer was simultaneously detected in 5 (22,7%), in 3 (25,0%) and in 2 (25.0%) patients, respectively.

Metachronous tumors at the period of 6 months and above were subsequently detected in 26 (68.4%) patients with breast cancer: metachronous second breast cancer – in 14 (36.8%), UBC – in 7 (18.4%) and OC – in 5 (13.2%) patients. Metachronous breast cancer was detected in patients with OC and CC (17 (77.3%) and 6 (75.0%), respectively). In patients with UBC we found metachronous breast cancer and ovarian cancer (7 (58.3%) and 2 (16.7%), respectively).

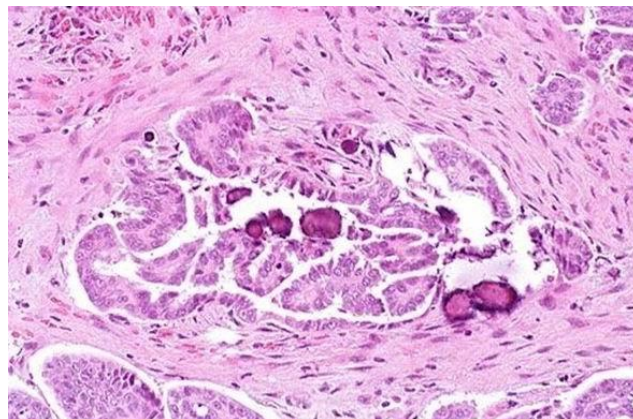
Metachronous tumors were most often detected in the period from 6 months to 1 year and from 1 year to 2 years in 26 (44.8%) patients.

The conducted studies allow us to conclude that multiple primary malignant tumors in female oncopathology are primarily associated with breast cancer, while uterine body cancer is also associated with ovarian cancer, which is observed both in synchronous and metachronous forms of their development. In the case of primary ovarian cancer and cervical cancer, metachronous tumors of the breast alone were observed.

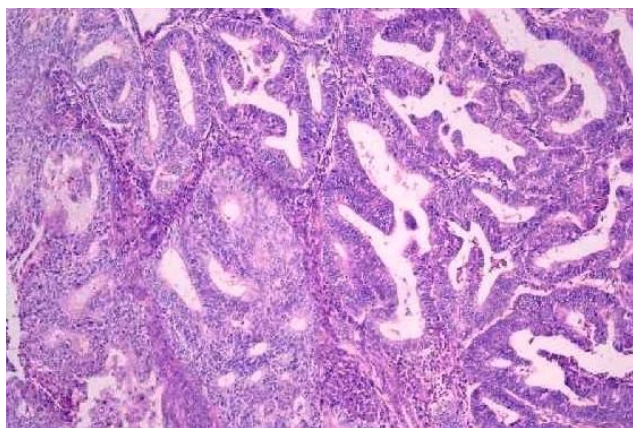
Дополнения



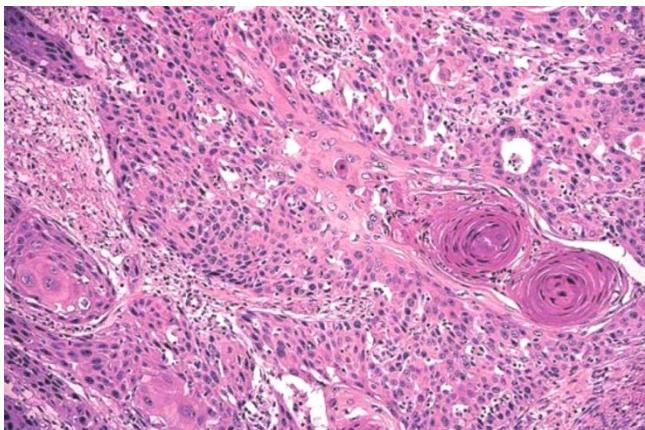
Больная Х. И/б №54628. 15.07.2018 г. Инфильтративный протоковый рак молочной железы. У больной через 1,5 года развился метакронный рак яичников.



Больная Ф. И/б №22431. 21.03.2016 г. Серозная цистаденокарцинома яичника. У больной в течение 4-х месяцев развился рак левой молочной железы.



Больная У. И/б №32561. 12.01.2017 г. Серозная цистаденокарцинома яичника. У больной в течение 3-х месяцев развился рак правой молочной железы.



Больная Ч. И/б №36298. 26.04.2017 г. Плоскоклеточный рак шейки матки с ороговеением. У больной в течение 2-х лет развился рак правой молочной железы.

REFERENCES

- [1] Akulenko L.V. O nasledstvennom rake molochnoj zhelezy, jaichnikov ijendometrija (klinicheskaja lekcija) [On

- hereditary cancer of the breast, ovary and endometrium (Clinical lecture)] // Problemy reprodukcii [Problems of reproduction], 2004. N6. P.20-27. [in Russian].
- [2] Bray F., Ferlay J., Soerjomataram I. et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries // *CA: A Cancer J Clin.* 2018. V.68. N6. P.394-424.
 - [3] Brewer H.R., Jones M.E., Schoemaker M.J. et al. Family history and risk of breast cancer: an analysis accounting for family structure // *Breast Cancer Res Treat.* 2017. V.165. N1. P.193-200. doi: 10.1007/s10549-017-4325-2.
 - [4] Brierley J., Gospodarowicz M.K., Wittekind Ch. TNM classification of malignant tumours. Oxford, UK; Hoboken, NJ: John Wiley & Sons, Inc., 2017.
 - [5] DE Luca A., Frusone F., Vergine M. et al. Breast cancer and multiple primary malignant tumors: Case report and review of the literature. In vivo // 2019. V.33. P.1313-1324. doi: 10.21873/in vivo.11605.
 - [6] De Luca A., Frusone F., Vergine M. et al. Breast Cancer and Multiple Primary Malignant Tumors: Case Report and Review of the Literature // *In Vivo.* 2019. V. 33. N4. P.1313-1324. doi: 10.21873/in vivo.11605.
 - [7] Fedorov V.E., Barsukov V.Yu., Popova T.N. et al. Osobennostitechenijaitrudnostidiagnostikimnozhestvennyhzhlokachestvennyhnoovoobrazovanij [Features of the course and difficulties in the diagnosis of multiple malignant neoplasms] // *Medicinskijal'manah* [Medical almanac], 2011. N2. P.157-160. [in Russian].
 - [8] FIGO Committee on Gynecologic Oncology. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium // *Int. J. Gynecol. Obstet.* 2009. V.105. N2. P.103-104.
 - [9] FIGO Committee on Gynecologic Oncology. Revised FIGO staging for carcinoma of the cervix uteri // *Int. J. Gynecol. Obstet.* 2019. V.145. N1. P.129-135.
 - [10] International Union Against Cancer (UICC). TNM Classification of Malignant Tumours, 7th ed. Sobin L.H., Gospodarowicz M.K., Wittekind Ch., eds. New York: Wiley-Blackwell; 2009.
 - [11] Kaprin A.D., Starinskiy V.V., Petrova G.V. (Ed.) SostojanieonkologicheskijpomoshinaselenijuRossii v 2016 godu [The state of cancer care for the population of Russia in 2016]. M.: MNIOI im. P.A. Gercena FGBU «NMIRC» MinzdravaRossii [M.: MNIOI them. P.A. Herzen FSBI "NMIRC" of the Ministry of Health of Russia], 2017. [in Russian].
 - [12] Maksimov S.Ya. Pervichnomnozhestvennyeopuholiorganovreproduktivnojsistemy [Primarily multiple tumors of the organs of the reproductive system] // *Prakticheskajaonkologija* [Practical Oncology]. 2009. V.10. N2. P.117-123. [in Russian].
 - [13] Motuzyuk I., Sydoruk O., Kovtun N. et al. Analysis of trends and factors in breast multiple primary malignant neoplasms // *Breast Cancer (Auckl)* 2018. V.12: 117822341875995. doi: 10.1177/1178223418759959.
 - [14] Nyqvist J., Parris T., Z. Helou K. et al. Previously diagnosed multiple primary malignancies in patients with breast carcinoma in Western Sweden between 2007 and 2018. *Breast. Cancer. Res. Treat.* // 2020. V.184. N1. P.221-228. doi: 10.1007/s10549-020-05822-z.
 - [15] Ozan H., Ozerkan K., Aker S. et al. A case with three primary tumors of the ovary, endometrium and gallbladder // *Eur. J. Gynaecol. Oncol.*, 2008. V.29. N5. P.551-553.
 - [16] SidorenkoYu.S., Shelyakina T.V., Titova E.V. et al. Problemy pervichno-mnozhestvennyhprocessov u bol'nyhrakommochnozhelezy [Problems of multiple primary processes in patients with breast cancer] // *Sibirskijonkologicheskijzhurnal* [Siberian Journal of Oncology], 2010. V.37. N1. P.18-22. [in Russian].
 - [17] Takatori E., Shoji T., Miura Y. et al. Triple simultaneous primary invasive gynecological malignancies: a case report // *J. Obstet. Gynaecol. Res.*, 2014. V.40. N2. P.627-631. doi: 10.1111/jog.12199.
 - [18] Vogt A., Schmid S., Heinemann K. et al. Multiple primary tumors: challenges and approaches, a review // *ESMO Open.* 2017. V.2. N2. P.e000172-e000172. doi: 10.1136/esmoopen-2017-000172.
 - [19] Zhang L., Feng L., Cong H. et al. Multiple primary malignant neoplasms: A case report and literature review // *Oncol. Lett.* 2019. V.18. N4. P.4210-4220. doi: 10.3892/ol.2019.10779.
 - [20] Zhao J., Tan Y., Wu Y. et al. A rare case of eight multiple primary malignant neoplasms in a female patient: A case report and review of the literature // *Oncol Lett.* 2015. V.9. P.587-590. doi: 10.3892/ol.2014.2789.