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GENITOURINARY SYNDROME OF MENOPAUSE IN WOMEN AFTER SURGICAL AND CHEMICAL (HORMONAL AND CHEMOTHERAPY) CASTRATION

ABSTRACT
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ABBREVIATIONS LIST

AV – atrophic vaginitis
BV – bacterial vaginosis
VA – vaginal atrophy
VC - vaginal Candidiasis
VHI – vaginal health index
GSM – genitourinary syndrome of menopause
ER – estrogen receptors
CNS - coagulase-negative staphylococci
BFVC – blood flow velocity curve
NV – nonspecific vaginitis
CPM – conditionally pathogenic microorganisms
HST – hormonal substitution treatment
CFD – colour flow Doppler imaging
Pi – pulse index
Ri – resistive index
S/D – systolic/diastolic ratio

I. INTRODUCTION

The Genitourinary symptom in menopause is a group of symptoms, which develop after and around menopause as a result of low estrogen levels and hypo and trophic changes in the genitourinary tract in women. Apart from vaginal dryness and dyspareunia, there are a number of urinary complaints, differing in frequency, such as dysuria, pollakiuria, nycturia, imperative incontinence, hyperactive bladder, frequent urinary infections. These lead to low self-esteem and lower quality of life.

II. PURPOSE AND GOALS

1. Dissertation purpose

To find the frequency and different iterations of the syndrome of genitourinary atrophy after surgical and chemical (hormonal and chemotherapy) castration.

2. Goals

1. To determine the frequency distribution of all patients, included in the study, according to: vaginal pH; vaginal cleanliness; number of lactobacilli; subjective vulva-vaginal and urinary symptoms.
2. To determine the vaginal pH, the vaginal cleanliness and number of lactobacilli after the two types of castration (surgical and chemical).
3. To determine the frequency of the subjective symptoms, related to the vaginal component of the genitourinary syndrome in menopause (GSM) – dyspareunia, vaginal dryness, and pruritus vuvle (dryness of the vulva) after both types of castration (surgical and chemical).
4. To determine the frequency of subjective symptoms, related to the urinary component of the genitourinary syndrome in menopause (GSM) – nocturia, dysuria, pollakiuria, imperative incontinence, stress incontinence, mixed incontinence after both types of castration (surgical and chemical).
5. To determine the prognostic significance of the following factors: age, type of castration, oncological disease leading to dyspareunia, vaginal dryness, pruritus vulve, vaginal pH, vaginal cleanliness, and number of lactobacilli.
6. To determine the prognostic significance of the following factors: age, type of castration, oncological disease leading to nocturia, dysuria, pollakiuria, imperative incontinence, stress incontinence, mixed incontinence.
7. To perform comparative analysis between the two types of castration: surgical and chemical, with regards to the symptoms, comprising the vaginal component of the genitourinary syndrome in menopause (GSM) – dyspareunia, vaginal dryness, vaginal pH, vaginal cleanliness, number of lactobacilli.
8. To perform comparative analysis between the two types of castration: surgical and chemical, with regards to the symptoms, comprising the urinary component of the genitourinary syndrome in menopause (GSM) – nocturia, dysuria, pollakiuria, imperative incontinence, stress incontinence, mixed incontinence.

III. MATERIALS AND METHODS (CLINICAL SAMPLE AND METHODOLOGY)

1. Materials

A prospective clinic-epidemiological study was performed, encompassing 67 patients in University Multiprofile Hospital for Active Treatment (UMHAT) "XXX" with a diagnosis xxx for the period between xxxx and 2021. The studied clinical sampleis of middle age 40.27±3.90 years in the 30-45 years range. Of the participants included in the reference, 35 (52.2%) have surgical castrations and 32 (47.8%) – with chemical therapy (chemotherapy and/or hormonal therapy).
(Fig. 1)

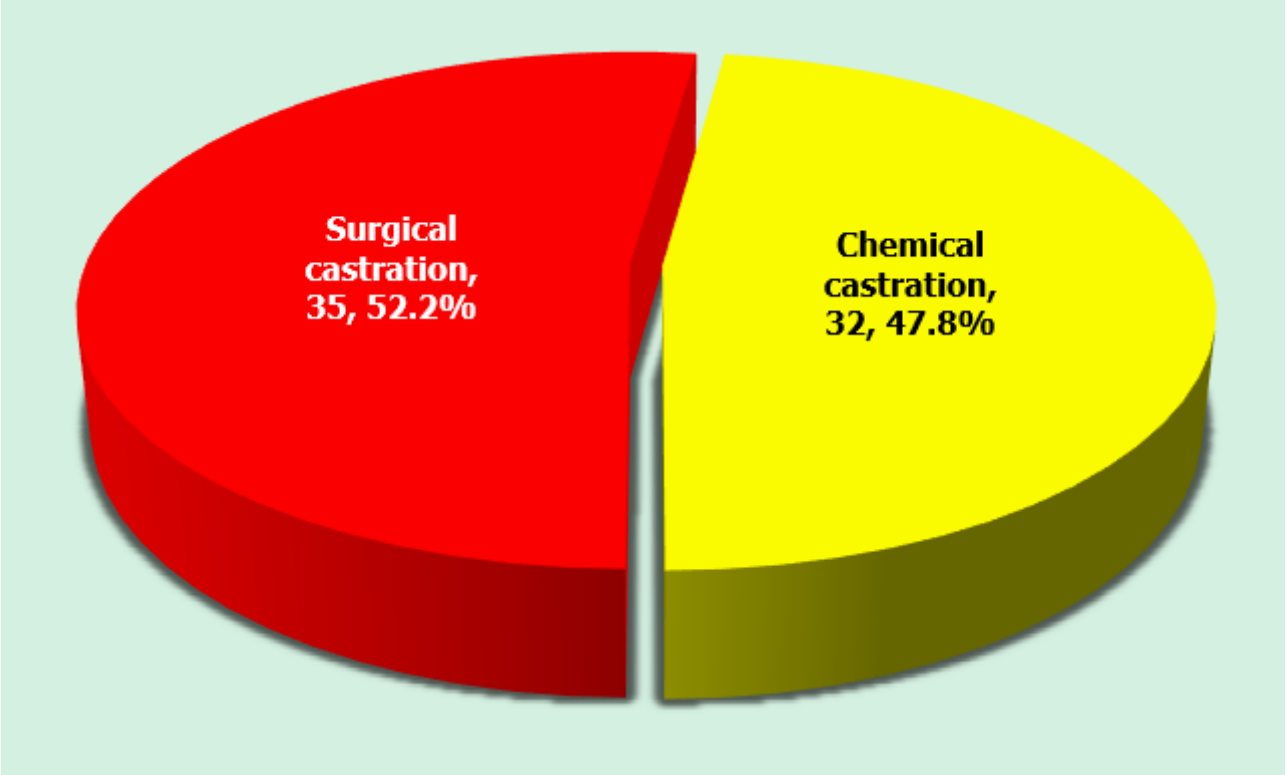

Fig. 1. Frequency distribution of the studied sample according to type of castration

The highest number age group (20) in the patients with surgical castration is 41-45 years, followed by 36-40 with 10 and the lowest one (5) – 30-35 years. Among the women with chemical castration, the highest number age group is 41-45 years (17), followed by 36-40 years with 10 and the lowest one (5) – 30-35 years. (Fig. 2).

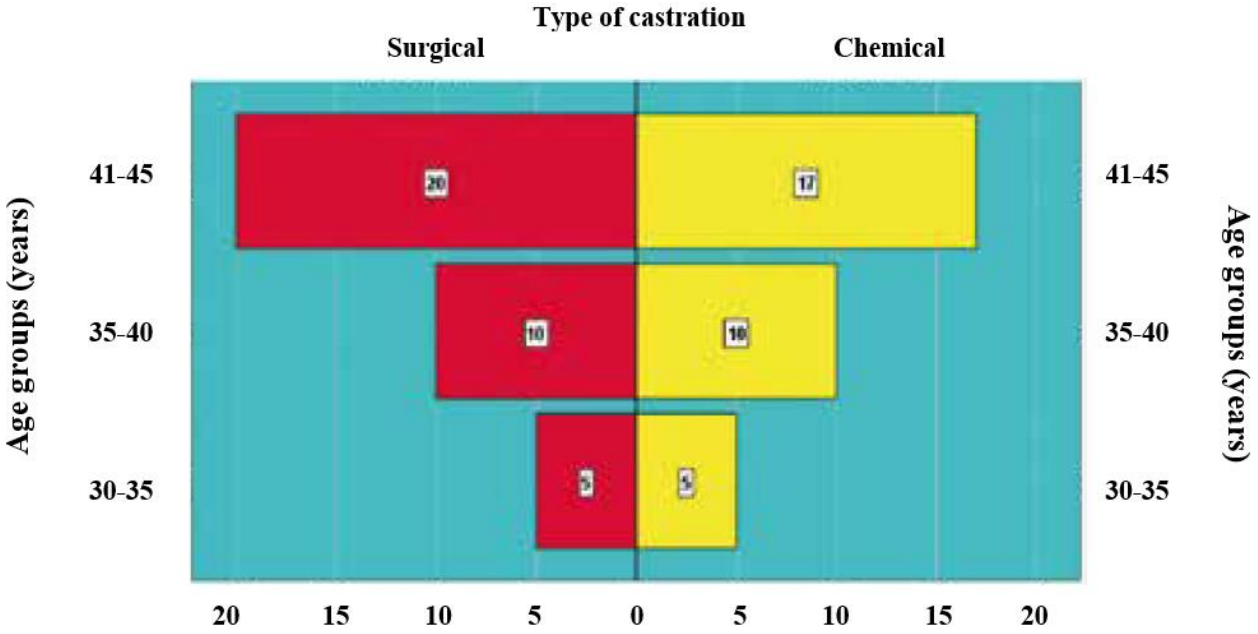

Fig. 2. Distribution of the study participants according to type of castration and age group

Figure 3 shows:

- The largest relative share (47.8%) are patients who have as a main disease breast cancer, followed by those with cervical cancer (25 or 37.3%);
- The fewest number are ones with ovarian cancer – 14.9%.

Almost half (47.8%) of the study participants have had surgery (of the mammary) + chemical therapy (chemotherapy and/or hormonal therapy). Significantly less (29.9%) are the patients with surgery + CT and the last group (with 10.4%) –only surgical intervention (Fig. 4).

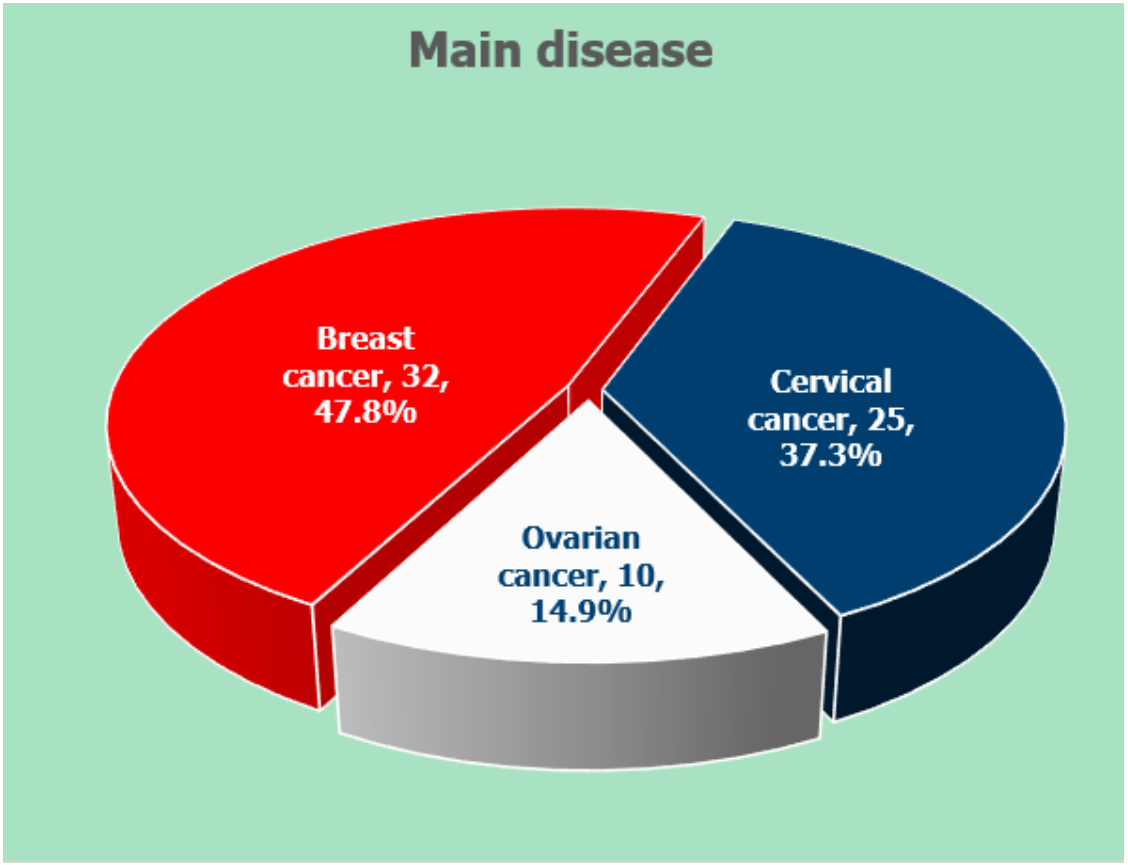

Fig 3. The frequency distribution of patients according to main disease

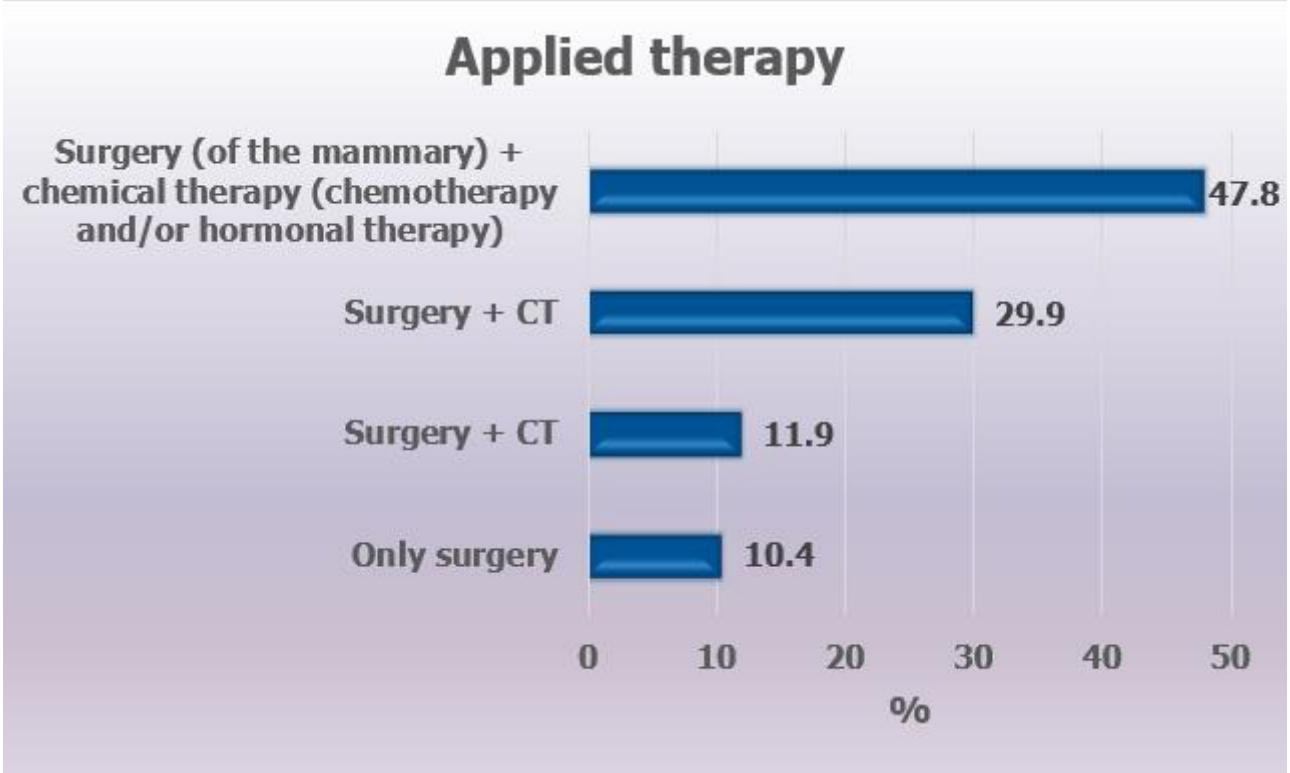

Fig. 4. Frequency distribution of the studied sampleaccording to the applied therapy

2. Methods

A. Statistical methods

The data were entered and processed in the following statistical software: IBM SPSS Statistics 25.0 and MedCalc Version 19.6.3.The level of significance at which the null hypothesis is rejected was set as $p<0.05$.

The following methods were applied:

1. Descriptive analysis–the frequency distribution of the studied symptoms is presented in tables.

2. Graphicalanalysis – to visualise the results.

3. Comparison of relative shares.

4. Fisher Freeman Halton exact test and $\chi 2$ test–used to check hypotheses for the presence of a relationship between the category variables.

5. Shapiro-Wilk Normality test – to check the distribution for normality.

6. Single factor dispersion analysis ANOVA – parametric test to check hypotheses for a difference between the arithmetic medians of a few independent samples.

7. Kruskal-Wallis non-parametric test – to check the hypotheses for difference between a few independent samples.

8. Student's T-test – to check hypotheses for difference between the arithmetic medians of two independent samples.

9. Mann-Whitney U-test–to check hypotheses for difference between two independent samples.

B. Chemical castration when applying chemotherapy and/or hormonal therapy

The clinical sample, subjected to chemical castration, includes patients with BREAST CARCINOMA.

The systemic chemical therapy includes chemotherapy and/or endocrine therapy for patients with hormone-receptor-positive tumours (ER+ and/or PgR+) and target treatment for hospitalised patientswith specified biomarkers. The chemical treatment is applied as adjuvant for patients who have had radical surgeries with early carcinoma. Adjuvant therapy is carried out according to the criteria of the latest St. Gallen consensus. Neoadjuvant chemotherapy is applied:

- before surgical treatment of tumours in order to reduce their size and create conditions for an organ-saving surgery;
- in cases of locally advanced tumours (stage IIIA) for immediate treatment of micro metastases and creating technical conditions for easier surgical treatment;
- in cases of inoperable locally advanced tumours (stages IIIB, C), including in cases of inflammatory carcinomas, in order to reduce the size and create conditions for radical surgery or definitive radiation therapy. The systemic chemical treatment is the main therapeutic method for metastatic diseases, it leads to clinical remission in 60-75% of cases, significantly reduces the disease symptoms and improves quality of life;
- in cases of tumours with medium and high risk;
- in cases of "triple negative" breast cancer the application of carboplatin with taxanecould be discussed.

2.1 Neoadjuvant systemic therapy

It always starts after a morphological verification of the tumour, study of the receptor status (ER, PgR and HER2) and full clinical stage evaluation.The programmes used are the same as with adjuvant chemotherapy.

CEF

Fluorouracil – 500 mg/m2 I.V., day 1

Epirubicin – 90 mg/m2 I.V., day 1

Cyclophosphamide – 500 mg/m2 I.V., day 1

Repeat every 21 days, a total of 4-6 cycles.

In case there is an adverse effect or resistance to anthracyclines – monotherapy withtaxane (4-6 cycles).

EC–T

Epirubicin – 75 mg/m2 I.V., day 1

Cyclophosphamide – 600 mg/m2 I.V., day 1

Repeat every 21 days; 4 cycles, followed by Docetaxel – 75 mg/m2 I.V., day 1, every 21 days, 4 cycles, or Paclitaxel – 80 mg/m2 I.V., weekly, 12 weeks.

T-EC (applied in cases of hormone-receptor-positive, HER2-negative carcinoma).

Paclitaxel – 175 mg/m2 I.V., day 1,Every 21 days, 4 cycles;

Epirubicine – 90 mg/m2 I.V., day 1 Ciclophosphamide – 600 mg/m2 I.V.,

day 1,Every 21 days, 4 cycles.

Paclitaxel + Carboplatin (in cases of triple negative carcinoma)

Paclitaxel – 80 mg/m2 I.V. weekly, 12 weeks Carboplatin AUC

4–6 I.V., day 1

Repeat every 21 days.

In cases of hormone-receptor-positive tumours with adverse effects to chemotherapy, Tamixofen therapy or aromatase inhibitors are applied – 4-6 months.

In cases of HER2-positive tumours:

Trastuzumab (added to the chemotherapy) – 8 mg/kg I.V. loading dose, followed by 6mg/kg I.V. every 21 days or a fixed dose of 600 mg S.C. every 21 days; the combination is not applied with anthracyclines, except for in clinical studies; Combination:

Pertuzumab + Trastuzumab + Docetaxel

Pertuzumab – 840 mg I.V., followed by 420 mg I.V., day 1

Trastuzumab – 8 mg/kg loading dose, followed by 6 mg/kg,

Day 1 or a fixed dose of 600 mg S.C. every 21 days

Docetaxel – 75 mg/m2 (up to 100 mg/m2) I.V., day 1

Repeat every 21 days.

** Fixed combination of Pertuzumab+Trastuzumab for subcutaneous application with Docetaxel.

For patients, receiving a treatment programme based on anthracyclines, the fixed combination of Pertuzumab+Trastuzumab must be applied after finishing the full anthracyclines treatment programme.

Surgery is followed by adjuvant therapy.

*Pertuzumab 1200 mg/Trastuzumab** 600 mg S.C. as a loading dose, followed by a maintaining dose Pertuzumab 600 mg/Trastuzumab 600 mg S.C., every 21 days.*

Docetaxel – 75 mg/m^2, later increased to 100 mg/m^2.

If a carboplatin treatment programme is applied, Docetaxel is applied with a dose of 75 mg/m^2 throughout the full cycle without increasing it.

The therapeutical response is evaluated after four cycles. If the originally operable tumour has progressed (in the course of the neoadjuvant chemotherapy), a surgical treatment is undertaken; if the original tumour is static, the surgical treatment is undertaken after neoadjuvant chemotherapy of 4-6 cycles.

In stage IIIC, surgical treatment is only undertaken if there is full remission of supraclavicular lymph nodes. Otherwise, definitive radiation treatment is applied.

2.2 Adjuvant systemic therapy

The treatment is recommended in cases when there is a relative reduction expected of the definite risk of relapse and death with an acceptable level of unwanted medicine reactions. The choice of method for systemic chemical treatment (chemotherapy and/or endocrine therapy and/or targeted treatment) is based on the presence of a number of prognostic factors: size of the original tumour, engagement of axillary lymph nodes, histological type, degree of differentiation (G), estrogen status (ER), progesterone (PgR) and HER2-receptors, proliferative Ki-67 index (under or above 15-20%), age, general condition (PS) and accompanying diseases (Table 1). Tumours, which do not express ER/PgR are considered endocrine non-sensitive; in those cases, chemotherapy is the only choice. As an addition to the chemotherapy and endocrine therapy in cases of hyperexpression of HER2, Trastusumab adjuvant treatment is added.

According to the progression risk of the disease, patients with operable carcinomas are divided in three categories (Table 1).

According to the biological subtypes of the carcinoma (luminal A, luminal B, non-luminal, basal-like, etc.), the systemic adjuvant therapy is defined in six categories (Table 1A).

Table 1. Risk assessment in cases of breast carcinoma

Low risk	Negative lymph nodes and all of the below: Tumour ≤ 2 cm G1 Lack of spread peritumour vessel invasion (tumour emboli) Lack of hyperexpression of HER2. Presence of ER and/or PgR expression Age ≥ 35 years
Medium risk	Negative lymph nodes and at least one of the following: Tumour > 2 cm G2-3 Presence of spread peritumour vessel invasion (tumour emboli) Presence of hyperexpression of HER2. Lack of ER and/or PgR expression. Age < 35 years
High risk	1-3 positive lymph nodes with lack of ER and/or PgR expression or presence of hyperexpression of HER2 ≥ 4 positive lymph nodes

Table 1A. Biological subtypes: definition and therapy

Subtype	**Clinical-pathological definition**	**Therapy**	**Therapy notes**
Luminal A	ER+ and/or PgR+, HER2-negative, low Ki67 (<15-20%)	Only endocrine therapy	Some require cytostatic (high nodal status and other risk criteria)
Luminal B (HER2-negative)	ER+ and/or PgR+, HER2-negative, high Ki67	Endocrine ± cytostatic therapy	Inclusion and type of cytostatic according to the hormonal expression and risk levels
Luminal B (HER2-positive)	ER+ and/or PgR+, any Ki-67, HER2-positive	Cytostatic + anti-HER2 + endocrine therapy	There is a lack of data, supporting the rejection of cytostatic
HER2 positive (non-luminal)	HER2-positive, lack of ER and PgR	Cytostatic + anti-HER2 therapy	In cases of very low risk (pT1a and negative nodal status) it can be traced without systemic therapy
Basal-type, triple negative (ductal)	Lack of ER and PgR, HER2-negative	Cytostatic therapy	
Special and histological subtypes			
A. Hormone-sensitive		Endocrine therapy	The medullar and

(cribriform, tubular and mucinous) B. Hormonenon-sensitive (apocrine, medullar, adenoid-cystic, and metaplastic)		Cytostatic therapy	adenoid-cystic carcinomas can be treated without cytostatic if they have negative nodal status

2.2.1. Endocrine adjuvant therapy

Tumours with ≥ 1% ER or PgR expression and those with indefinite hormonal status are considered to be endocrine sensitive and are subject to endocrine therapy within the volume of complex treatment.

In cases of premenopausal patients, a standard five-year treatment includes:

Tamoxifen – 20 mg daily P.O. (independently or in combination with LHRH agonist). In cases of high relapse risk Tamoxifen is taken for ten years.

Anastrozole – 1 mg P.O. daily is preferred in cases of DCIS in postmenopausal women.

Ovary ablation is achieved through LHRH agonist or surgically. The LHRH agonist should be applied for 2 to 5 years, even though its optimal duration is not categorically defined. In cases of premenopausal patients the combination of LHRH agonist and aromatase inhibitor is not used, nor is the aromatase inhibitor used individually. Tamoxifen should not be taken simultaneously with chemotherapy, until the best combination of LHRH agonist (together with or following chemotherapy) is determined.

In cases of postmenopausal patients, the aromatase inhibitor for five years is the preferred choice. For patients, who have been treated with Tamoxifen 20 mg/daily P.O., it is recommended that they switch to Exemestane 25 mg/daily – up to 5 years. Especially in cases of positive nodal status. The optimal duration of up to 10 years with Tamoxifen and following that AI therapy – Tamoxifen or Tamoxifen – AI.

2.2.2. Bisphosphonatetherapy

Patients who are treated with aromatase inhibitors should also take supplements with Exemestane 25 mg/daily, in combination with LHRH agonist (in cases with high relapse risk).

In cases with ductal carcinoma in situ (DCIS), a mandatory Tamoxifen is prescribed and is combined with radiation therapy – 42.5-50.4 Gy. vitamin D and calcium. Bone density test is recommended – DEXA (dual X-ray absorptiometry) and in cases of osteoporosis, a prompt treatment is recommended. Bisphosphonates protect the skeleton from bone loss in patients with iatrogenic premature menopause and in postmenopausal patients, who are being treated with aromatase inhibitors.

2.2.3. Biological therapy in cases of bone loss

Patients with early breast carcinoma, going through adjuvant endocrine therapy are considered postmenopausal and with higher risk of bone fractures, especially those being treated with aromatase inhibitors. After selection and evaluation by the treating medical oncologist, these cases

are subject to treatment for bone loss with Denosumab – 60 mg S.C. for 6 months, same as women with post-menopausal osteoporosis without breast carcinoma. When Denosumab is selected for treatment, both the bone mineral density (T-score values)and the patient's risk factors are considered.After the medical oncologist has determined the indications for the biological therapy, the treatment of the underlying osteoporosis is applied either by an endocrinologist or rheumatologist.

2.2.4. Adjuvant chemotherapy

In cases of medium risk and negative nodal status
EC
Epirubicin – 90 mg/m2 I.V., day 1 Cyclophosphamide – 600 mg/m2 I.V., day 1, every 21 days (6 cycles).
FEC90
Fluorouracil – 500 mg/m2 I.V., day 1 Epirubicin – 90 mg/m2 I.V., day 1 Cyclophosphamide – 500 mg/m2 I.V., day 1. Every 21 days (6 cycles).
Docetaxel + Cyclophosphamide
Docetaxel – 75 mg/m2 I.V., day 1 Cyclophosphamide – 600 mg/m2 I.V., day 1. Every 21 days (6 cycles).
CMF
Cyclophosphamide – 600 mg/m2 I.V., day 1
Metothrexate – 40 mg/m2 I.V., day 1 Fluorouracil – 600 mg/m2 I.V., day 1. every 21 days (6 cycles).
Epirubicin, followed by CMF:
Epirubicin 100 mg/m2 i.v. D.1
Repeated every 3 weeks – 4 cycles, followed by:
Cyclophosphamid 750 mg/m2 i.v. D.1 Methotrexate 50 mg/m2 i.v. D.1
5-FU 600 mg/m2 i.v. D.1
Repeated every 3 weeks – 4 cycles
AC
Doxorubicin 60 mg/m2 i.v. D.1
Cyclophosphamide 600 mg/m2 i.v. D.1
Repeated every 3 weeks – 4 cycles.
In cases of high risk and hyperexpression of HER2, regardless of the nodal status:
EC–T
Epirubicin – 90 mg/m2 I.V., day 1
Cyclophosphamide – 600 mg/m2 I.V., day 1. Every 21 days (3-4 cycles), followed by:
Paclitaxel – 175 mg/m2 I.V. every 3 weeks (3 or 4 cycles) oили 80mg/ m2 weekly (12 consecutive weeks), or
Docetaxel –100 mg/m2 every 21 days (3 or 4 cycles).
TEC
Docetaxel – 75 mg/m2 I.V., day1 Epirubicin – 60 mg/m2 I.V., day 1
Cyclophosphamide – 600 mg/m2 I.V., day 1. Every 21 days (6 cycles) .
AC/EC, followed by Paclitaxel – dose-dense therapy (treatment where the doses are given more often);
Paclitaxel монотерапия – 12 infusions
Doxorubicin 60 mg/m2/ Farmorubicin 90 mg/m2 i.v. D.1

Cyclophosphamide 600 mg/m2 i.v. D.1

Repeat every 2 weeks with G-CSF – 4 cycles; in case of adverse effects – every 3 weeks, after that:

Paclitaxel 80 – 100 mg/m2 i.v. weekly (one hour infusion) with a solution of Dexamethasone: 12+12+8 mg i.m. / i.v.+ H1 blocker + allergosan/antialerzin .

In case there are adverse effects to the anthracyclines, 6 cycles of monotherapy with Docetaxel – 100 mg/m^2 every 21 days is carried out.

In case of patients with hyperexpression of HER2 Trastuzumab treatment is carried out.

It is not used with tumours less than 0.5 cm and negative nodal status, with high positive hormonal receptors (high response), with left ventricle ejection fraction (LVEF) under 50% and with considerable cardio-vascular comorbidity. Application of Trastuzumab, together with endocrine adjuvant therapy without chemotherapy is not supported by evidence from clinical studies.

Anti HER2 treatment begins together with chemotherapy with taxanes:

Monotherapy with Trastuzumab with a loading dose of 8 mg/kg, followed by 6mg/kg or Trastuzumab – fixed dose of 600 mg S.C., every 21 days, applied for 12 months from the beginning;

Combination Docetaxel + Pertuzumab + Trastuzumab in patients with high relapse risk (see Table 1).

Pertuzumab – 840 mg I.V. loading dose, followed by 420 mg I.V., day 1 Trastuzumab – 8 mg/kg loading dose, followed by 6 mg/kg, day 1 or Trastuzumab – fixed dose of 60 mg S.C., every 21 days; Repeat every 21 for one year

or

** fixed combination of Pertuzumab+Trastuzumab subcutaneous – Pertuzumab 1200 mg/Trastuzumab** 600 mg S.C. as a loading dose, followed by maintaining dose Pertuzumab 600 mg/Trastuzumab 600 mg S.C., every 21 days for a total of one year)up to 18 cycles).

In HER2-positive patients with a residual invasive disease in the breast and/or lymph nodes after neoadjuvant therapy of the basis of taxanes and HER2 – target therapy: Trastuzumab emtansine (T-DM1) – 3.6 mg/kg every 21 days for a total of 14 cycles.

Maintaining adjuvant treatment

Neratinib** is recommended for continuous adjuvant treatment of older patients with an early stage of hormone-receptor-positive breast cancer with hyperexpression/amplification of HER2, which have finished adjuvant therapy with medical products on the basis of trastuzumab less than a year ago.

Carboplatin + Docetaxel + Trastuzumab

Carboplatin AUC 4–6 I.V., day 1 Docetaxel – 75 mg/m2 I.V., day 1

Trastuzumab – 8 mg/kg loading dose, followed by 6 mg/kg, day 1

Repeat every 21 days, with the protection of G-CSF.

The recommended dose of neratinib is 240 mg (six tablets of 40 mg), taken orally once daily, continuously for 1 year.

In cases of patients who have had no effect from the neoadjuvant chemotherapy with anthracyclines: Docetaxel – 100 mg/m^2 every 21 days (6 cycles).

In cases of patients with triple non-negative carcinoma, there is no standard programme for adjuvant treatment, as there are no convincing data for the addition of platinum coordinative compounds.

2.3 Systemic therapy with relapsed or metastatic diseases

In cases with hormone-receptor positive tumours, lack of visceral life-threatening metastases, (visceral crisis), postmenopausal patients, premenopausal patients with only bone metastases and life expectancy of over two years without progression after surgery, treatment starts with endocrine therapy, independent or combined with a target agent, unless there is or it is suspected that there might be or it is proven that there is endocrine resistance.

The preferred first line of ET for postmenopausal women depends on the type and duration of the adjuvant ET, as well as on the time elapsed since the end of the adjuvant ET.

In case there is no effect after at least two lines of endocrine therapy or if the disease is quick developing, treatment continues with cytostatic therapy.

The choice is based on the evaluation of a group of factors.

Factors for evaluating metastatic breast carcinoma
Factors, related to the disease
Life expectancy without progression (LEWP)
Previous treatment and responses to it
Biological factors (ER, PgR, HER2)
Number and location of metastases
Necessity for quick control of the disease/symptoms

Factors, related to the patient
Patient preferences
Biological age
Menopausal status
Comorbidity and PS
Socioeconomical and psychological factors
Access to treatment in the country

2.3.1. First line of endocrine therapy

Tamoxifen – 20 mg P.O. daily –for pre- and postmenopausal patients, who have not undergone adjuvant chemotherapy with Tamoxifen; for those who have taken Tamoxifen, if the relapse is after survival without disease for over 12 months, the treatment can continue with Tamoxifen.

Aromatase inhibitor (nonsteroid or steroid) – for postmenopausal patients with relapse after adjuvant endocrine therapy or adverse effects from Tamoxifen.

Fulvestrant – 500 mg I.M. every 28 days – for postmenopausal patients without previous endocrine therapy or with relapse after adjuvant endocrine therapy with antiestrogen (selective estrogen-receptor modulator or aromatase inhibitor).

Ribociclib (600 mg P.O. daily, 21 days, 7 days break) + Fulvestrant (500 mg I.M. every 28 days) as a starting hormone-based therapy. For women in pre- or perimenopause, hormonal therapy should be combined with LHRH agonist.

Palbociclib (125 mg P.O. daily, 21 days, 7 days break) + Fulvestrant (500 mg I.M. every 28days0 – for pre- (having LHRH agonist simultaneously) and postmenopausal patients without previous systemic therapy for advanced disease.

Abemaciclib (300 mg P.O. daily, every 28 days) + Fulvestrant (500 mg I.M. every 28 days) as a starting hormone-based therapy. For women in pre- or perimenopause, hormonal therapy should be combined with LHRH agonist.

Ovarian ablation (LHRH agonist or surgical) plus endocrine therapy, same as for postmenopausal women:

- for premenopausal patients;
- for premenopausal patients, who have not received adjuvant Tamoxifen,
- when Tamoxifen therapy has been suspended for more than 12 months, monotherapy with Tamoxifen is preferred.

Everolimus (10 mg P.O. daily) + Exemestane (25 mg P.O. daily) – for postmenopausal patients after adjuvant treatment with nonsteroid aromatase inhibitors or Tamoxifen.

Palbociclib (125 mg P.O. daily, 21 days, 7 days break) + aromatase inhibitor – for pre/peri- (having LHRH agonist simultaneously) and postmenopausal patients without previous systemic therapy for advance disease.

Ribociclib (600 mg P.O. daily, 21 days, 7 break) + aromatase inhibitor – for pre/peri- (having LHRH agonist simultaneously) and postmenopausal patients as a starting hormone-based therapy.

Abemaciclib (300 mg P.O. daily, every 28 days) + as a starting hormone-based therapy. For women in pre- or perimenopause, hormonal therapy should be combined with LHRH agonist.

Alpelisib ** (300 mg P.O. daily, every 28 days) + Fulvestrant – 500 mg I.M. every 28 days –in case of relapse after adjuvant endocrine therapy (only in the presence of PIK3CA mutation in tumour or plasma samples through validated test).

2.3.2. Second line of endocrine therapy

After the first line of Tamoxifen, the treatment is changed to aromatase inhibitor or Fulvestrant. After the first line with nonsteroid aromatase inhibitors, the treatment is changed to Exemestane or Tamoxifen.

After progression with the first line of endocrine therapy with AI, the options are:

Palbociclib (125 mg P.O. daily, 21 days, 7 days break) + Fulvestrant (500 mg I.M. every 28 days) – for pre- (having LHRH agonist simultaneously)and postmenopausal patients without previous systemic therapy for advanced disease.

Ribociclib (600 mg P.O. daily, 21 days, 7 days break) + Fulvestrant (500 mg I.M. every 28 days) as a starting hormone-based therapy. For women in pre- or perimenopause, hormonal therapy should be combined with LHRH agonist.

Abemaciclib (150 mg P.O. twice daily, 28 days, without a break) + Fulvestrant (500 mg I.M. every 28 days), as a starting hormone-based therapy or for women, who have previously received endocrine therapy. For women in pre- or perimenopause, hormonal therapy should be combined with LHRH agonist.

After progression of the first line of endocrine therapy with Fulvestrant, the options are:

Palbociclib (125 mg P.O. daily, 21 days, 7 days break) + aromatase inhibitor – for pre/peri (having LHRH agonist simultaneously) and postmenopausal patients without previous systemic therapy for advance diseases.

Ribociclib (600 mg P.O. daily, 21 days, 7 days break) + aromatase inhibitor – for pre/peri (having LHRH agonist simultaneously) and postmenopausal patients as a starting hormone-based therapy.

Abemaciclib (150 mg P.O. twice daily, 28 days, without a break) + AI as a starting hormone-based therapy or for women, who have previously received endocrine therapy. For women in pre or perimenopause, hormonal therapy should be combined with LHRH agonist.

Alpelisib ** (300 mg P.O. daily, every 28 days) + Fulvestrant – 500 mg I.M. every 28 days – for patients with previous endocrine monotherapy (only in the presence of PIK3CA mutation in 33 tumour or plasma samples through validated test).

For postmenopausal patients after the first line with nonsteroid aromatase inhibitors or after the first line of chemotherapy with following aromatase inhibitor and progression, the treatment is changed to Everolimus (10mg P.O. daily) + Exemestane (25 mg P.O. daily).

After the first line of aromatase inhibitors, gestagens (Medroxyprogesterone Acetate, Megestrol acetate) may be used.

In case of disease progression after the second line of endocrine therapy, androgens or others of the already used medical products are applied, without standard from clinical studies. In case of hormonal resistance, chemotherapy or clinical study options are discussed. It is not recommended to apply simultaneously chemo- and endocrine therapy. For copositive patients (hormone-receptor positive and HER2 hyperexpression), anti-HER2 treatment can be added to the endocrine therapy (which does not contain CDK4/6 inhibitor):

- Trastuzumab (2 mg/kg I.V. weekly, after single loading dose of 4 mg/kg) + Anastrozole (1mg P.O. daily) – for postmenopausal patients;
- Lapatinib (1500 mg P.O. daily) + Letrozol (2.5 mg P.O.daily) – for postmenopausal patients.

2.3.3. First line of chemotherapy for HER2 negative patients, who have not received adjuvant anthracyclines

EC

Epirubicin – 90 mg/m2 I.V., day 1 Cyclophosphamide – 600 mg/m2 I.V.,day 1. Repeat every 21 days.

CEF90

Fluorouracil – 500 mg/m2 I.V., day 1

Epirubicin – 90 mg/m2 I.V., day 1 Cyclophosphamide – 500 mg/m2 I.V.,day 1. Repeat every 21 days, with the protection of G-CSF.

CEF120

Fluorouracil – 500 mg/m2 I.V., day 1

Epirubicin – 120 mg/m2 I.V., day 1 Cyclophosphamide – 500 mg/m2 I.V.,day 1. Repeat every 21 days, with the protection of G-CSF.

Liposomal Doxorubicin + Cyclophosphamide

Liposomal Doxorubicin – 60–75 mg/m2 I.V., day 1 Cyclophosphamide– 600 mg/m2 I.V., day 1. Repeat every 21 days.

ED

Epirubicin – 50 mg/m2 I.V., day 1 Docetaxel – 75 mg/m2 I.V., day 1.Repeat every 21 days

Epirubicin + Paclitaxel

Epirubicin – 50 mg/m2 I.V., day 1 Paclitaxel – 175 mg/m2 I.V., ay 1.Repeat every 21 days.

Docetaxel + Cyclophosphamide

Docetaxel – 75mg/m2 I.V., day 1

Cyclophosphamide – 600 mg/m2 I.V., day 1. Repeat every 21 days, with the protection of G-CSF.

NAV + FU + FA

Vinorelbine – 25 mg/m2 I.V., дни 1 and 8 Fluorouracil – 450 mg/m2 I.V.,days 1–5 Leucovorin – 50 mg/m2 I.V., days 1–5. Repeat every 21 days.

CMF

Cyclophosphamide – 100 mg/m2 P.O. daily, days 1–14 Metothrexate– 40 mg/m2 I.V., day 1

Fluorouracil – 500 mg/m2 I.V., day 1

Repeat every 28 days (6 cycles).

CMF

Cyclophosphamide – 600 mg/m2 I.V., day 1 Metothrexatee – 40 mg/m2I.V., day 1 Fluorouracil – 600 mg/m2 I.V., day 1

Repeat every 21 days (6 cycles).

2.3.4. First line of chemotherapy for patients, who have received adjuvant anthracyclines

Cisplatin + Docetaxel

Cisplatin – 60 mg/m2 I.V., day 1 Docetaxel – 75 mg/m2 I.V., day 1. Repeat every 21 days.

Cisplatin + Fluorouracil

Cisplatin – 20 mg/m m2 2 I.V., days 1–3 Fluorouracil – 450 mg/m2 I.V.,days 1–3 Repeat every 28 days.

Paclitaxel + Carboplatin

Paclitaxel – 175 mg/m2 I.V., day 1 Carboplatin AUC4–6 I.V., day 1.

Repeat every 21 days.

Paclitaxel + Cisplatin

Paclitaxel – 175 mg/m2 I.V., day 1 Cisplatin – 60 mg/m2 I.V., day 1.Repeat every 21 days.

Docetaxel + Cyclophosphamide

Docetaxel – 75 mg/m2 I.V., day 1 Cyclophosphamide – 600 mg/m2 I.V.,day 1. Repeat every 21 days, with the protection of G-CSF.

Paclitaxel + Gemcitabine

Paclitaxel – 175 mg/m2 I.V., day 1 Gemcitabine – 1250 mg/m2 I.V., days1 and 8 Repeat every 21 days.

Docetaxel + Capecitabine

Docetaxel – 75 mg/m2 I.V., day 1

Capecitabine – 2000–2500 mg/m2 P.O. daily, days 1–14 Repeat every 21 days.

NAV + FU + FA + CDDP

Vinorelbine – 25 mg/m2 I.V., days 1 and 8 Fluorouracil – 450 mg/m2 I.V.,days 1–3 (5) Leucovorin – 50 mg/m2 I.V., days 1–3 (5) Cisplatin – 20 mg/m2

I.V., days 1–3 (5). Repeat every 28 days.

Vinorelbine + Capecitabine

Vinorelbine – 20 mg/m2 I.V., days 1 and 8 Capecitabine – 1600 mg/m2 P.O.daily, days 1–14. Repeat every 21 days.

Paclitaxel + Bevacizumab

Paclitaxel – 90 mg/m2 I.V., days 1, 8 and 15

Bevacizumab – 10 mg/kg I.V. every 2 weeks (15 mg/kg I.V. every 21 days). Repeat every 28 days.

Vinblastin + Mitomycin C

Vinblastin – 10 mg TOT I.V., day 1 and 8 Mitomycin C – 8 mg/m2, day 1

Repeat every 21 days.

Vincristine + Fluorouracil + FA

Vincristine – 2 mg TOT I.V., day 1

Fluorouracil – 450 mg/m2 I.V. continuous infusion, days 1–3

Leucovorin – 50 mg/m2 I.V., days 1–3

Repeat every 28 days.

Monotherapy

Docetaxel – 100 mg/m2 I.V., day 1 Repeat every 21 days.

Paclitaxel – 80 mg/m2 I.V. weekly.

For patients with germinative BRCA1/2 mutations, who have HER2 negative, HR positive locally advanced or metastatic breast cancer, previously treated with anthracycline and taxanes, unless it is not suitable, which have progressed during or after the previous endocrine therapy or are unsuitable for endocrine therapy.

*Olaparib** tabl. – 2 x 300 mg P.O. daily until progression or unacceptable toxicity.*

2.3.5. Chemotherapy in cases of anthracycline and taxanes resistance

Eribulin mesylate – 1.23 mg/m2 I.V., days 1 and 8 Repeat every 21 days.

Capecitabine ± Bevacizumab

Capecitabine – 2000 mg/m2 P.O. daily, days 1–14

± Bevacizumab – 15 mg/kg I.V., day 1

Repeat every 21 days.(The programme is applied to patients who have already had anthracyclines and taxanes in the last 12 months).

Vinorelbine – 30 mg/m2 I.V., days 1, 8, 15 (repeat every 4 weeks)

Or days 1 and 8 (Repeat every 21 days).

Vinorelbine + Gemcitabine

Vinorelbine – 25 mg/m2 I.V., days 1 and 15 Gemcitabine – 1000 mg/m2 I.V.,days 1 and 15 Repeat every 21 days.

Vinblastin + Mitomycin C

Vinblastin – 10 mg TOT I.V., days 1 and 8 Mitomycin C – 6–8 mg/m2, day1 Repeat every 21 days.

Vincristine + Ifosfamide/Mesna + Cisplatin

Vincristine – 2 mg TOT I.V., day 1 Ifosfamide – 1000 mg/m2 I.V., days1–3

Mesna – 400 mg/m2 I.V. at hours 0, 4 and 8 after the beginning of ifosfamide.

Cisplatin – 25 mg/m2 I.V., days 1–3

Repeat every 21 days.

Capecitabine + Ixabepilone

Capecitabine – 2000 mg/m2 P.O. daily, days 1–14 Ixabepilone – 40 mg/kg I.V., day 1

Repeat every 21 days.

Nab-paclitaxel

The treatment shown as monotherapy is treatment of metastatic breast carcinoma in adult patients, who were unsuccessful with the first line of treatment of the metastatic disease and for which no standard treatment is given, including anthracycline 260 mg/m^2, applied intravenously for 30 minutes every 3 weeks until progression or unacceptable toxicity.

2.3.6. Metronomic chemotherapy

Cyclophosphamide – 50 mg general dose P.O. daily – independently or for specific chosen patients in combination with

Metothrexate – 5 mg P.O., days 1 and 2 of each week, until unacceptable toxicity or progression. All other programmes can be applied, which have not been applied to a specific patient.

Cyclophosphamide + Metothrexate

Cyclophosphamide – 50 mg P.O. daily Metothrexate – 2.5 mg P.O.

daily, days 1 and 4 Repeat every 21 days.

Cyclophosphamide – 2 x 50 mg P.O. daily, days 1–14, repeat every 21 days. Capecitabine – 2 x 828 mg/m2 P.O. daily, days 1–14, repeat every 21 days.

2.3.7. Chemotherapy in cases with hyperexpression of HER2

First line is applied for HER2 positive, metastatic or locally relapsed patients, who have not received previous anti-HER2 therapy for metastatic disease.

Docetaxel + Trastuzumab + Pertuzumab

Docetaxel – 75 mg/m2 I.V., day 1 (6 cycles)

Trastuzumab – 8 mg/kg, 6 mg/kg I.V., day 1 (until progression)

Pertuzumab – 840 mg (loading dose), 420 mg (maintaining dose until progression) I.V., day 1

Repeat every 21 days

or

fixed combination of Pertuzumab+Trastuzumab for subcutaneous application – Pertuzumab 1200 mg/Trastuzumab** 600 mg S.C. as a loading dose, followed by a maintaining dose. Pertuzumab 600 mg/

Trastuzumab 600 mg S.C., every 21 days until progression.

Paclitaxel + Trastuzumab

Paclitaxel – 175 mg/m2 I.V., day 1

Trastuzumab – 2 mg/kg I.V. weekly, after a single loading dose of 4 mg/kg. Repeat every 21 days (6-8 cycles).

Docetaxel + Trastuzumab

Docetaxel – 75 mg/kg I.V., day 1

Trastuzumab – 2 mg/kg I.V. weekly, after a single loading dose of 4 mg/kg. Repeat every 21 days (6-8 cycles).

Vinorelbine + Trastuzumab

Vinorelbine – 30 mg/m2 I.V. days 1, 8 and 15 or days 1 and 8

Trastuzumab – 2 mg/kg I.V. weekly, after a single loading dose of mg/kg. Repeat every 21-28 days.

Capecitabine + Trastuzumab

Capecitabine – 2500 mg/m2 P.O. daily, days 1–14

Trastuzumab – 2 mg/kg I.V. weekly, after a single loading dose of 4 mg/kg. Repeat every 21 days.

For patients with HER2+, HR+ status:

Second line – in case of progression during treatment with trastuzumab – containing programmes:

Trastuzumab emtansine (T-DM1) – 3.6 mg/kg I.V. Repeat every 21 days.

Lapatinib (1500 mg P.O. daily) plus aromatase inhibitor, orTrastuzumab plus aromatase inhibitor, or

Trastuzumab + pertuzumab + aromatase inhibitor

Lapatinib + Capecitabine

Lapatinib – 1250 mg P.O. daily, days 1–21 Capecitabine – 2000 mg/m2 P.O. daily, days 1–14

Repeat every 21 days.

Lapatinib + Letrozole (for postmenopausal patients)

Lapatinib – 1500 mg P.O. daily Letrozole – 2.5 mg P.O. daily. Continue until progression.

Trastuzumab + Lapatinib (± aromatase inhibitor)

Lapatinib – 1000 mg P.O. daily

Trastuzumab – loading dose 4 mg/kg I.V., followed by 2 mg/kg weekly. Continues until progression.

When Trastuzumab is not used, all programmes for metastatic disease can be used, except for CMF.

In cases of metastatic HER2 positive disease Trastuzumab can also be used in a three-week cycle. In case of progression while Trastuzumab is used, only the accompanying chemotherapy is amended. In all therapeutic programmes, containing Trastuzumab, it can be applied both as an I.V. (every 21 days or weekly) and as S.C. in a fixed dose of 600 mg every 21 days.

In all therapeutic programmes, containing Pertuzumab + Trastuzumab for venous application, the following combination can also be used: Pertuzumab + Trastuzumab for subcutaneous application in a fixed dose Pertuzumab 1200 mg/Trastuzumab** 600 mg S.C. as a loading dose, followed by a maintaining dose of Pertuzumab 600 mg/Trastuzumab** 600 mg S.C.

For patients with unresectable or metastatic HER2 positive breast cancer, who have received two or more previous treatments of the main anti-HER2 therapy:

Trastuzumab deruxtecan** 5.4 mg/kg intravenous infusion once every 3 weeks (21-day cycle), until progression of the disease or unacceptable toxicity.

2.4 Triple negative carcinoma

Chemotherapy

In cases of relapse after adjuvant anthracycline-based chemotherapy as standard treatment, taxane-based first line chemotherapy is applied. In cases of progression after anthracycline and/or taxanes, the following is recommended:

Eribulin mesylate – 1.23 mg/m2 I.V., day 1 and 8, every 21 days; Cisplatin

+ Gemcitabine;

Carboplatin – AUC6 I.V., with the protection of G-CSF.

After adjuvant therapy without anthracyclines, all programmes can be applied, including platinum-based, since there are no standard recommendations.

Immunotherapy

Atezolizumab* in combination with nab-paclitaxel as first line (1L) is recommended for treating adult patients with inoperable locally advanced or metastatic triple negative breast cancer (TNBC) with a tumour expression of PD-L1 ≥ 1%, who have not received previous chemotherapy for metastatic disease. The recommended dose of Atezolizumab* is 840 mg, applied through intravenous infusion, followed by nab-paclitaxel 100 mg/m^2. at every 28 day cycle, Atezolizumab* is applied in days 1 and 15, and the nab-paclitaxel in days 1, 8 and 15. It is recommended that patients are treated with Atezolizumab until progression of the disease or uncontrollable toxicity.

Target therapy

For patients with germinative BRCA1/2 mutations, who have HR negative / HER2 negative locally advanced or metastatic breast cancer, previously treated with anthracyclines and taxane, unless they are not suitable for such treatment.

Monotherapy with Olaparib tabl. – 2 x 300 mg P.O. daily, until progression or unacceptable toxicity.

Carboplatin – AUC5 I.V. + Docetaxel – 100 mg/m^2 I.V., every 21 days, with the protection of G-CSF. Application of the following can also be discussed: vinca alkaloids, Irinotecane, Mitomycin C, Ixabepilone**.

Talazoparib** 1 x 1 mg P.O. daily, until progression.

2.5 Inflammatory carcinoma (Mastitis carcinomatosis)

The treatment starts with chemotherapy according to the programmes, included in point III. In cases of full clinical remission, a definitive radiotherapy is carried out and in some cases – operative treatment, following the radiotherapy. In cases of hormone-receptor positive tumours, endocrine therapy can be applied. For premenopausal women with hormone-receptor positive status, ovarian suppression is applied (chemical or surgical).

C. Surgical castration

It is performed on all patients, for whom the first treatment was a double adnexectomy (with or without total/radical hysterectomy). Those are the patients with a diagnosis of cervical carcinoma or ovarian carcinoma.

D. Microbiology of the vaginal secretion (evaluation of the vaginal cleanliness and the number of lactobacilli). Evaluation of the pH measurements of the vaginal secretion using factory manufactured litmus paper sticks

The materials were acquired by a cotton tampon from the back arch of the vagina, after menstruation. All rules for indexing, acquiring, packaging and transportation of the samples to the clinical laboratory were observed according to the Rules for good medical practice in clinical microbiology. The following was sent to the laboratory: one tampon in transport environment and two smears in slides, acquired by rotating the tampon. In the laboratory, these smears are died, respectively according to Gram and with methyl blue according to Loeffler. They are looked at with

a microscope through an immersive lens. The result from the microscope examination includes the number of leucocytes, the number and morphology of the epithelium cells, the presence and morphology of Lactobacillus spp., the Gram affiliation and morphology of the microorganisms and their relationship. Also noted is the presence of blastospores and pseudomycel and the presence of trichomonas. Special attention is given to check whether "clue cells" are seen under the microscope, which are indicative of anaerobic infections with Gardnerella vaginalis, etc.

The culture eamination included a culture of blood agar, a culture of red bacteria (MacConkey agar), a culture of yeast and yeast-like fungi (Sabouraud agarwith chloramphenicol) and a culture in liquid environment for trichomonas. From the liquid environment for trichomonas, after 48 hours of cultivation at 37 degrees Celsius, native preparations are made, which are studied under a microscope to look for trichomonas with their specific morphology (shape and presence of flagella) and rotary movements. The final reading of the cultures for yeast and yeast-like fungi was done after a 48-hour cultivation at 37 degrees Celsius. In cases of a positive result, a preparation of the isolated yeast fungus was made, and an identification of candidachromogram and anti-microgram. The cultures on blood agar and MacConkey agar were read on the 24^{th} hour and finally on the 48^{th} hour after cultivation at 37 degrees Celsius.

When reading the bacterial growth and the growth of the yeast and yeast-like fungi, their quantity was also accounted in the culture examination report.

The microscope examination and its results have a significant importance for the exact microbiological diagnosis. The presence of leucocytes, the reduction of Lactobacillus spp, the presence of basal epithelium cells in the vaginal secretion, using the microscope to look specifically at certain bacteria draws the attention of the clinical microbiologist towards an inflammatory bacterial process. The presence of pseudochyphes and/or yeast shows the presence of a chronical and/or acute vaginal candidiasis. The presence of cells, suspected of trichomonas points towards Trichomonas vaginalis infection. Since the microscope examination of died smears gives a high percentage of false positive results for Trichomonas vaginalis, the laboratory performs a culture study for Trichomonas vaginalis. The culture is the golden standard in microbiological studies. In a culture examination for Trichomonas vaginalis the errors are brought to a minimum. The specific movements of the parasite are found usingthe microscope. The bacterial vaginosis diagnosis is also done through microscope examination. To reach this diagnosis, its pathognomonic "clue cells" are studied under microscope and the lactobacilli can also be seen. The bacteria, causing aerobic vaginitis usually have mass growth. In order to avoid false positive or negative results, it is extremely important to follow the rules of indexing, acquiring, packaging and transportation of samples to the laboratory. After acquiring the sample material for the culture study, the sooner it is performed, the lesspossibility for errors.

The combination of results from the microscope and culture examinations give the microbiological diagnosis, but the evaluation of the general condition of the patient, the anamnesis data and the gynaecological examination give a more realistic idea of the etiological meaning of the isolated microorganisms. It is in the patient's best interests that the clinical microbiologist and the clinical physician collaborate closely.

Every result from an examination of the vaginal secretion from the clinical microbiology laboratory was accompanied by a conclusion. The conclusion was giving the most likely microbiological diagnosis. In the conclusions, the most frequently used terms were – bacterial vaginosis, aerobic vaginitis, intermediate (transitional) state towards aerobic vaginitis, chronic acute candida mycosis, acute candida mycosis, inflammatory process with etiological cause Trichomonas vaginalis. In case a microbiological diagnosis is not possible, for example there aremicroscope data

for a bacterial process but a lack of etiologically significant aerobic bacteria found in the culture study, recommendation for further diagnostic conduct were given.

E. Questionnaire for evaluating the subjective symptoms of patients

QUESTIONNAIRE

1. Do you have vaginal dryness?
   ☐ NO ☐ YES
2. Do you have discomfort or pain during sexual intercourse (dyspareunia)?
   ☐ NO
   ☐ SLIGHT PAIN
   ☐ MEDIUM TO STRONG PAIN
   ☐ VERY STRONG PAIN
3. Do you have trouble keeping urine in when sneezing or coughing or spontaneous urination (incontinence)?
   ☐ NO ☐ YES
4. do you have cystitis-like complaints (burning, irritation and discomfort at the end of urinating)?
   ☐ NO ☐ YES
5. Do you often urinate during the night, and do you get up more than twice (nycturia)?
   ☐ NO ☐ YES
6. Do you often urinate during the day?
   ☐ NO ☐ YES
7. Do you have uncontrollable urges to urinate?
   ☐ NO ☐ YES

F. Data processing

The data was processed through a STUDY CARD (Attachment 1) and entered in table EE and statistically analysed.

IV. RESULTS AND DISCUSSION

1. Frequency distribution of all patients, included in the study: vaginal pH; vaginal cleanliness; number of lactobacilli; subjective vulva-vaginal and urinary symptoms.

Fig. 5 clearly shows that according to the vaginal pH:

- The highest number (39 or 43.3%) are those with highly alkaline pH, followed by those with alkaline pH (38.8%);
- The lowest number (17.9%) are those with acidic pH (normal);

The results of Fig. 6 show that according to vaginal cleanliness:

- First are those with degree III (41.8%), followed by those with degree II (34.3%);
- Last are patients with degree I (three or 4.5%).

According to the number of lactobacilli (Fig. 7):

- Highest number (30 or 44.8%) are in the category “Reduced”, followed by “None” with 34.3%;
- The lowest number are those with normal quantity – 20.9%.

The lead in the subjective symptoms, related to the urinary component of the genitourinary syndrome (GSM) in menopause, is nocturia with 56.7%, followed by mixed incontinence with

23.9%. Imperative incontinence is last with 4.5% (Fig. 8).***(The sum of the percentages is over 100 because some of the patients have given more than one answer).***

Regarding the vulva-vaginal symptoms (Fig. 9):

- The highest number (65.7%) are study participants with vaginal dryness, followed by those with dyspareunia (50.7%);
- The lowest number are patients with lack of such symptoms 19.4%, and there are none with Pruritus vulvae;

The sum of the percentages is over 100 because some of the patients have given more than one answer.

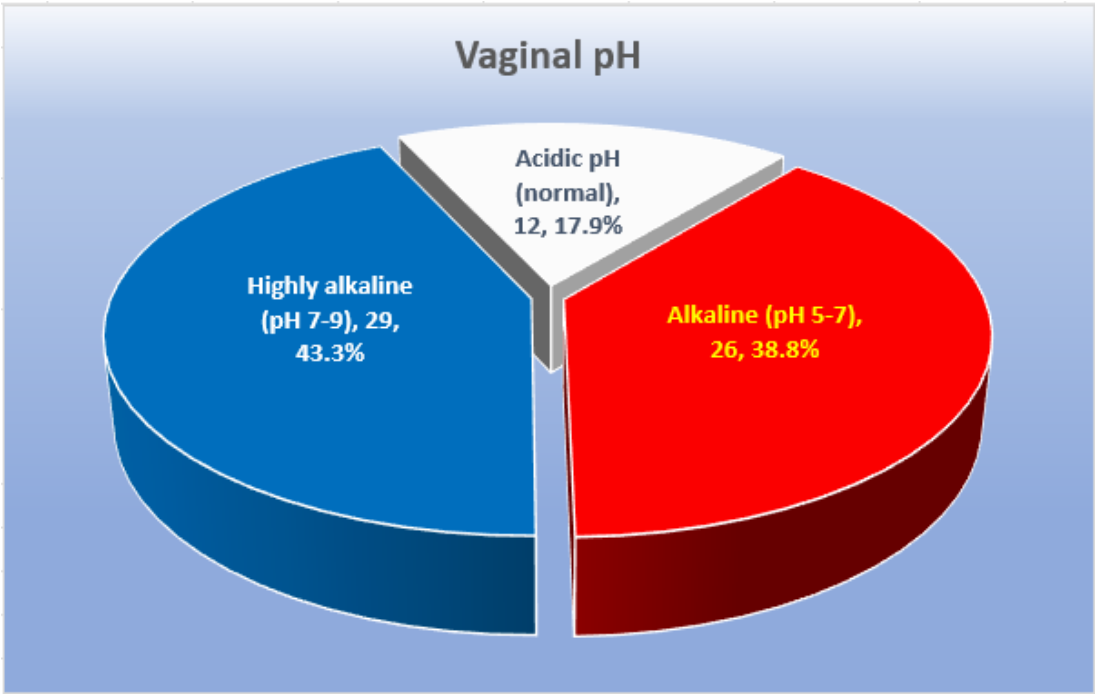

Fig. 5. Frequency distribution of patients according to vaginal pH

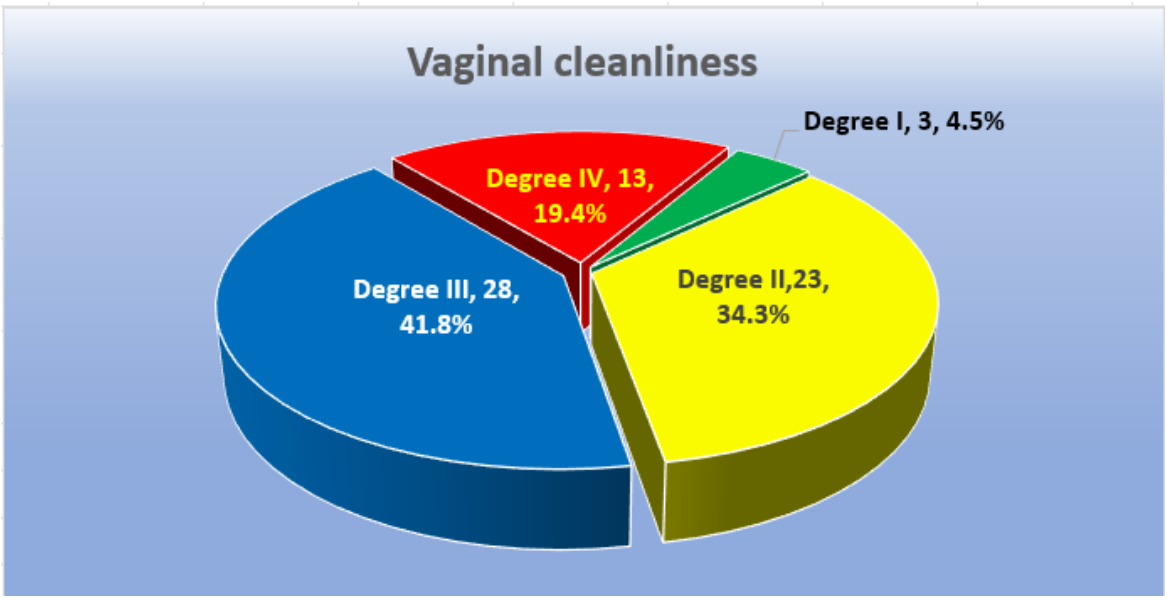

Fig. 6. Frequency distribution of patients according to vaginal cleanliness

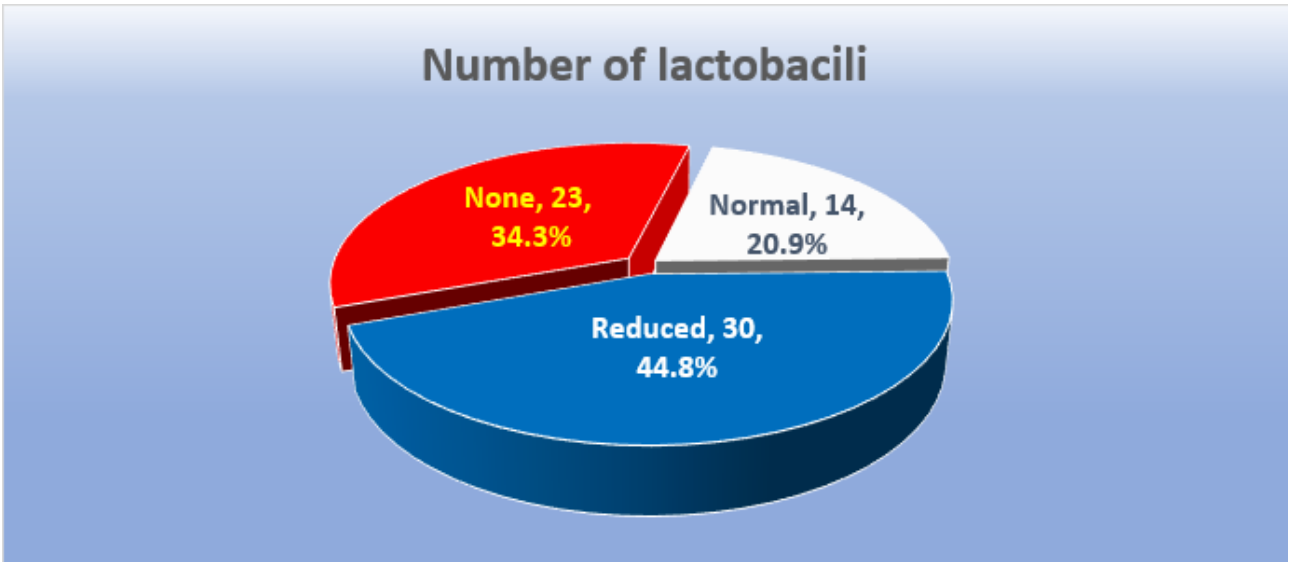

Fig. 7. Frequency distribution of patients according to number of lactobacilli

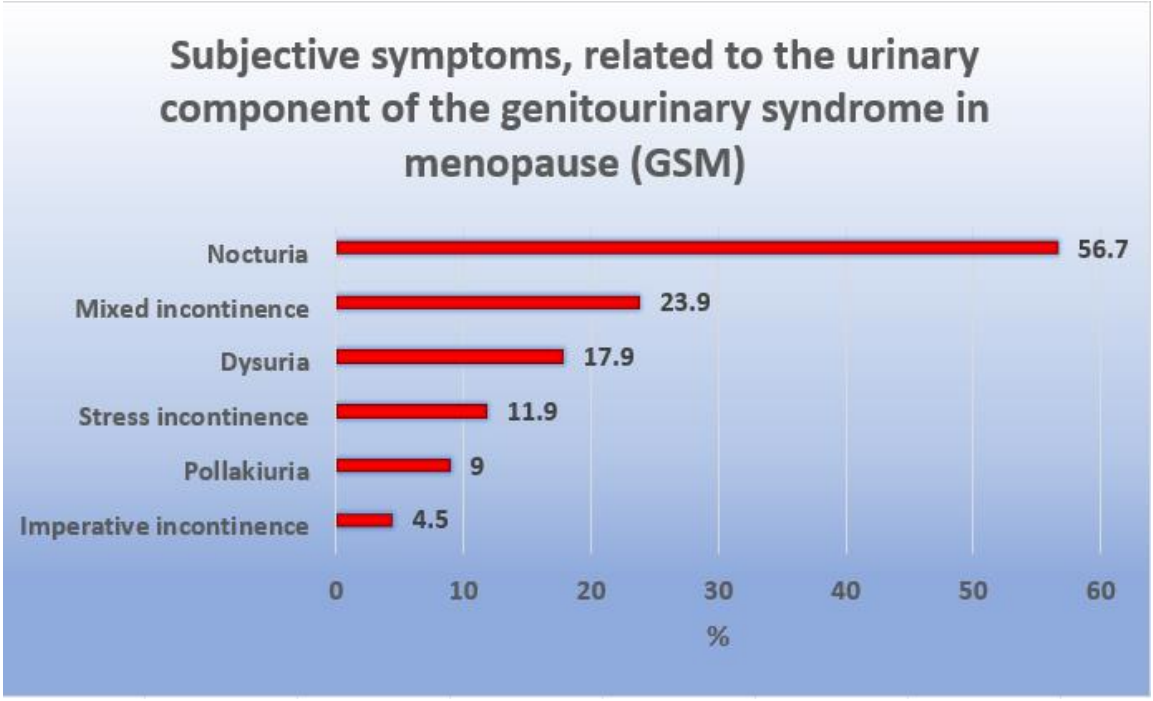

Fig. 8. Frequency distribution of patients according to subjective symptoms, related to the urinary component of the genitourinary syndrome in menopause (GSM) (The sum of the percentages is over 100 because some of the patients have given more than one answer)

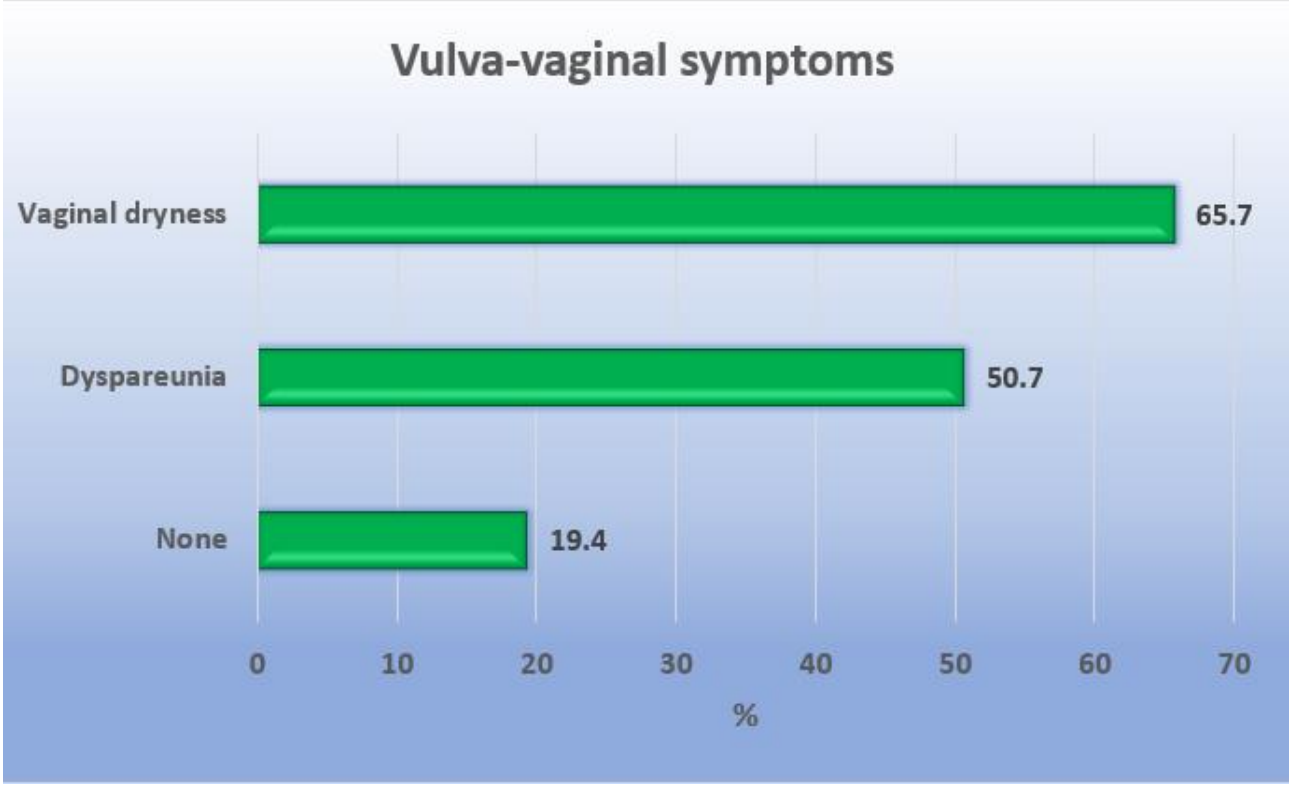

Fig. 9. Frequency distribution of patients according to vulva-vaginal symptoms (The sum of the percentages is over 100 because some of the patients have given more than one answer)

2. Vaginal pH, vaginal cleanliness, and the number of lactobacilli after both types of castration (surgical and chemical).

We can see clearly from Fig. 10 that patients with surgical castration have a higher percentage of alkaline and highly alkaline pH, whereas those with chemical castration – acidic (normal).

Regarding vaginal cleanliness, those undergone surgical castration have a higher percentage only in degree IV, while those with chemical castration – in all other stages (Fig. 11).

Patients with surgical castration have higher percentage when it comes to lack of lactobacilli, while those with chemical castration – normal and reduced numbers (Fig. 12).

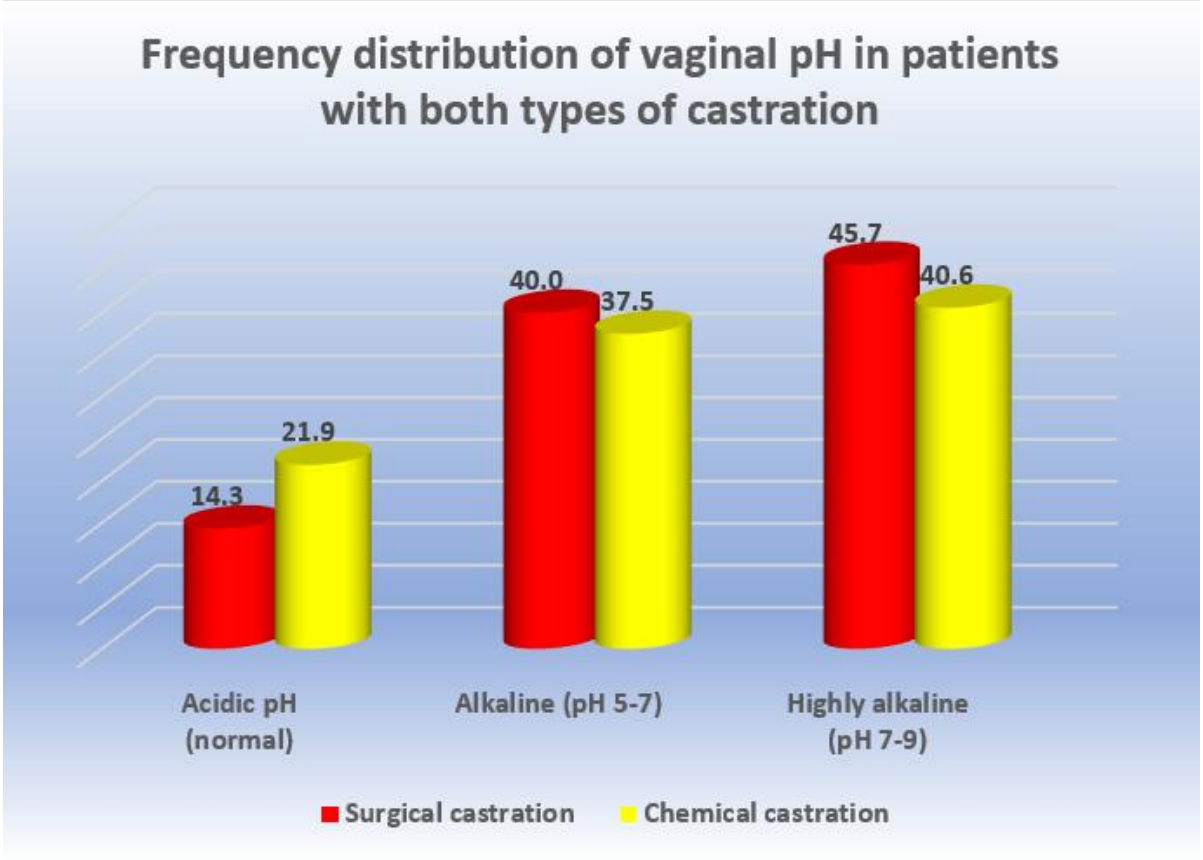

Fig. 10. Frequency distribution of vaginal pH in patients with both types of castration

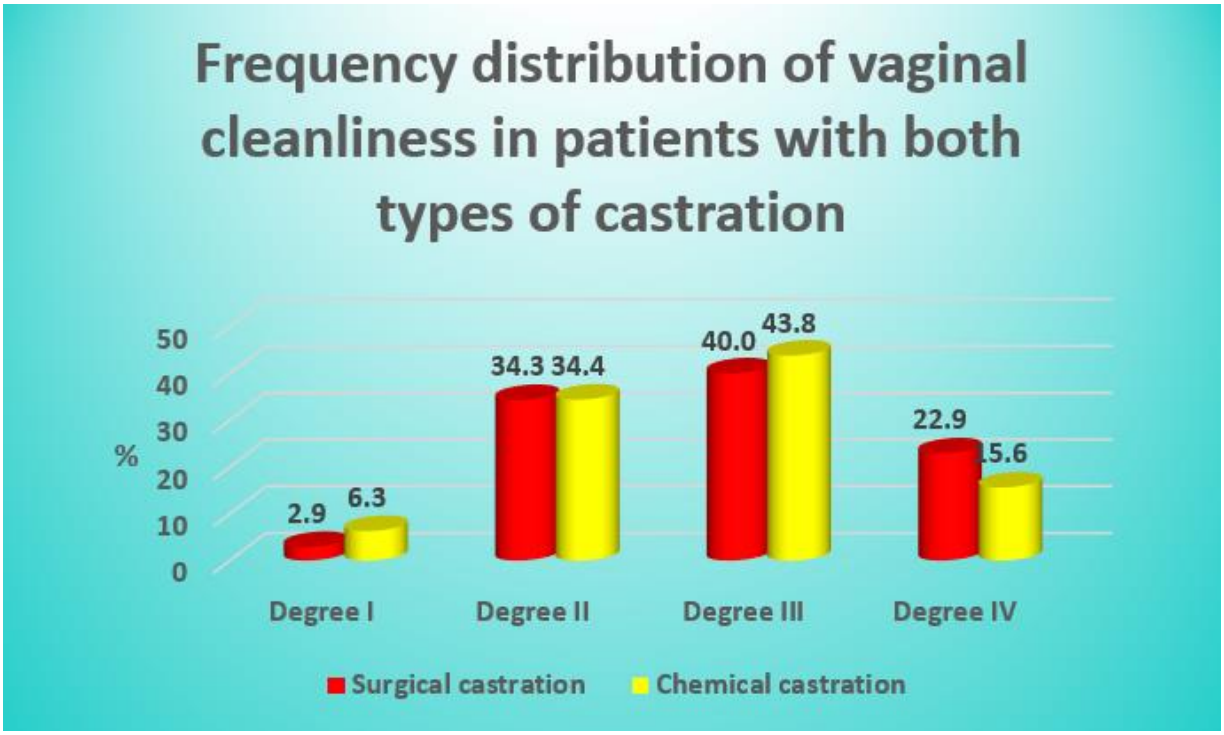

Fig. 11. Frequency distribution of vaginal cleanliness in patients with both types of castration

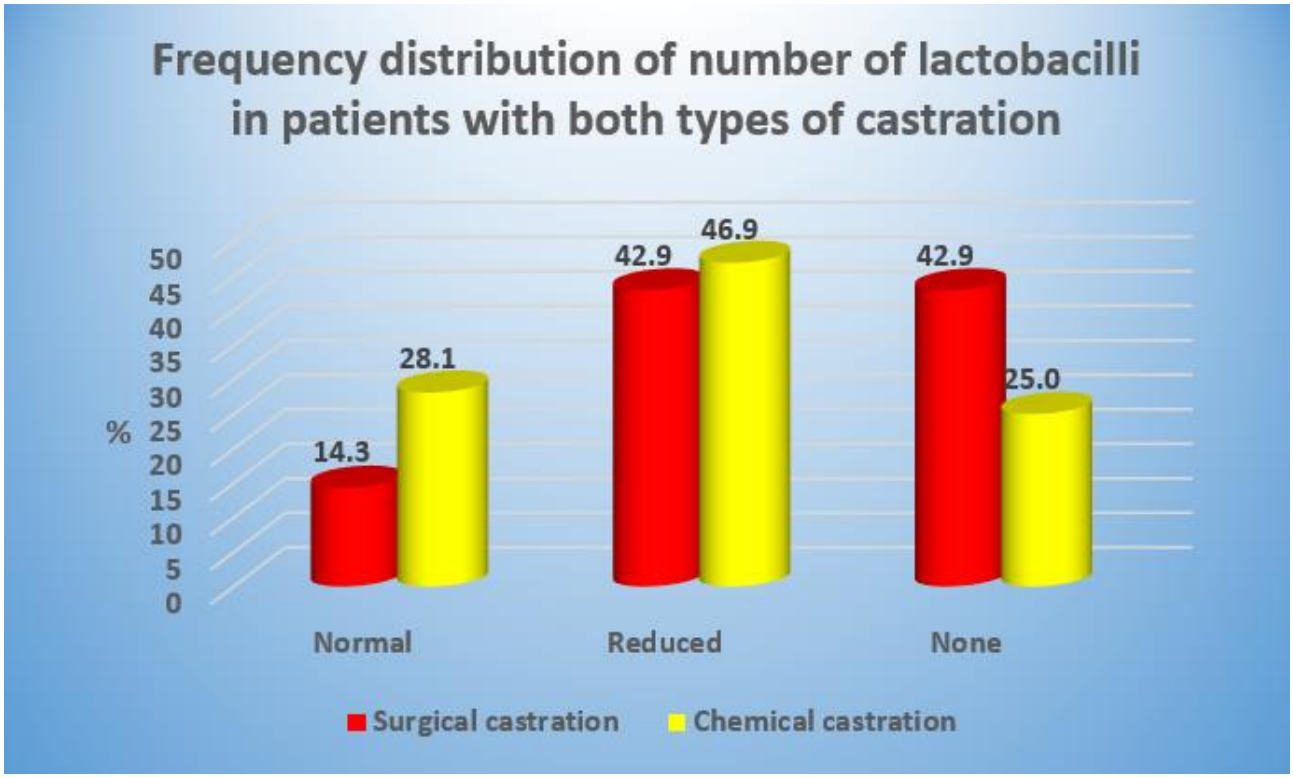

Fig. 12. Frequency distribution of number of lactobacilli in patients with both types of castration

3. The frequency of subjective symptoms, related to the vaginal component of the genitourinary syndrome in menopause (GSM) – dyspareunia, vaginal dryness and pruritus vulve (vulva dryness) after both types of castration (surgical and chemical).

Fig. 13 shows that patients with surgical castration have higher percentage dyspareunia and vaginal dryness, while those with chemical castration – lack of subjective symptoms, related to the vaginal component of the genitourinary syndrome in menopause (GSM). (Pruritus vulve is lacking entirely).

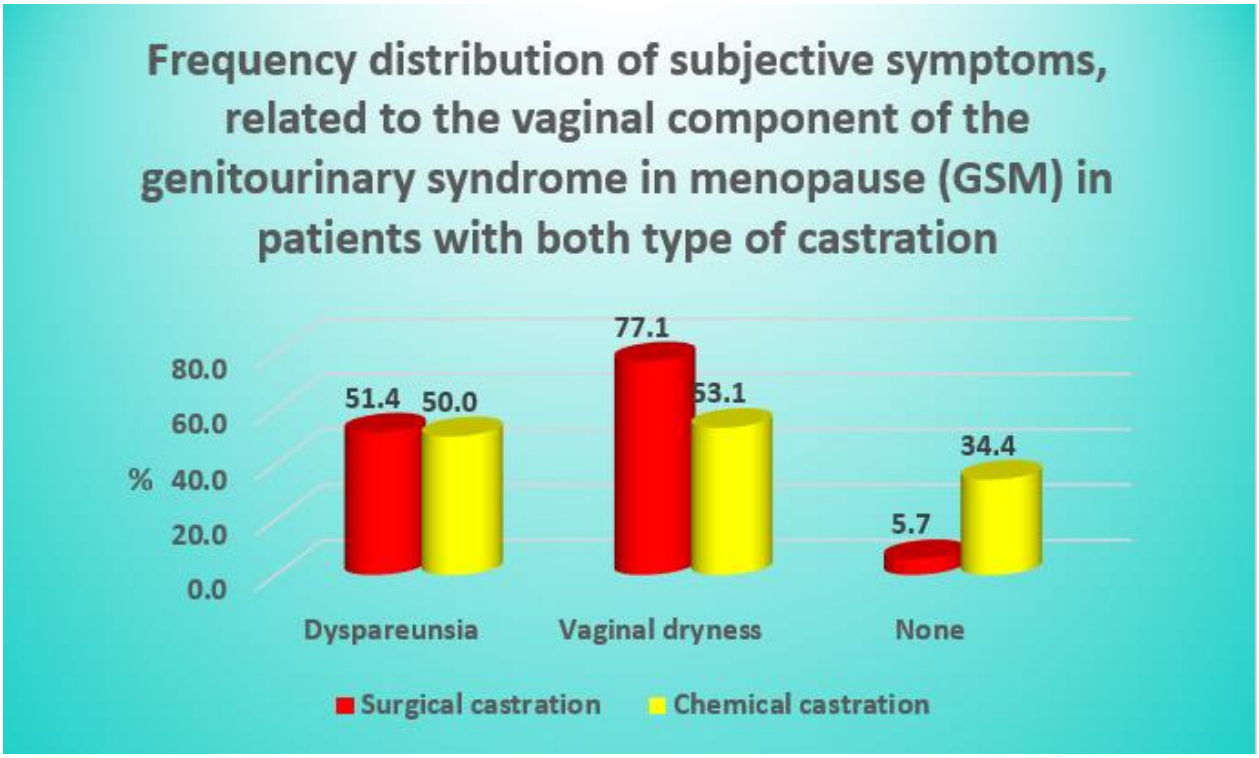

Fig. 13. Frequency distribution of subjective symptoms, related to the vaginal component of the genitourinary syndrome in menopause (GSM) in patients with both type of castration

4. The frequency of the subjective symptoms, related to the urinary component of the genitourinary syndrome in menopause (GSM) – nocturia, dysuria, pollakiuria, imperative incontinence, stress incontinence, mixed incontinence after both types of castration (surgical and chemical).

The results in Fig. 14 show that patients with surgical castration have higher percentage of nocturia, pollakiuria, imperative and stress incontinence than the subjective symptoms, related to the urinary component of the genitourinary syndrome in menopause (GSM) of those with chemical castration – dysuria and mixed incontinence.

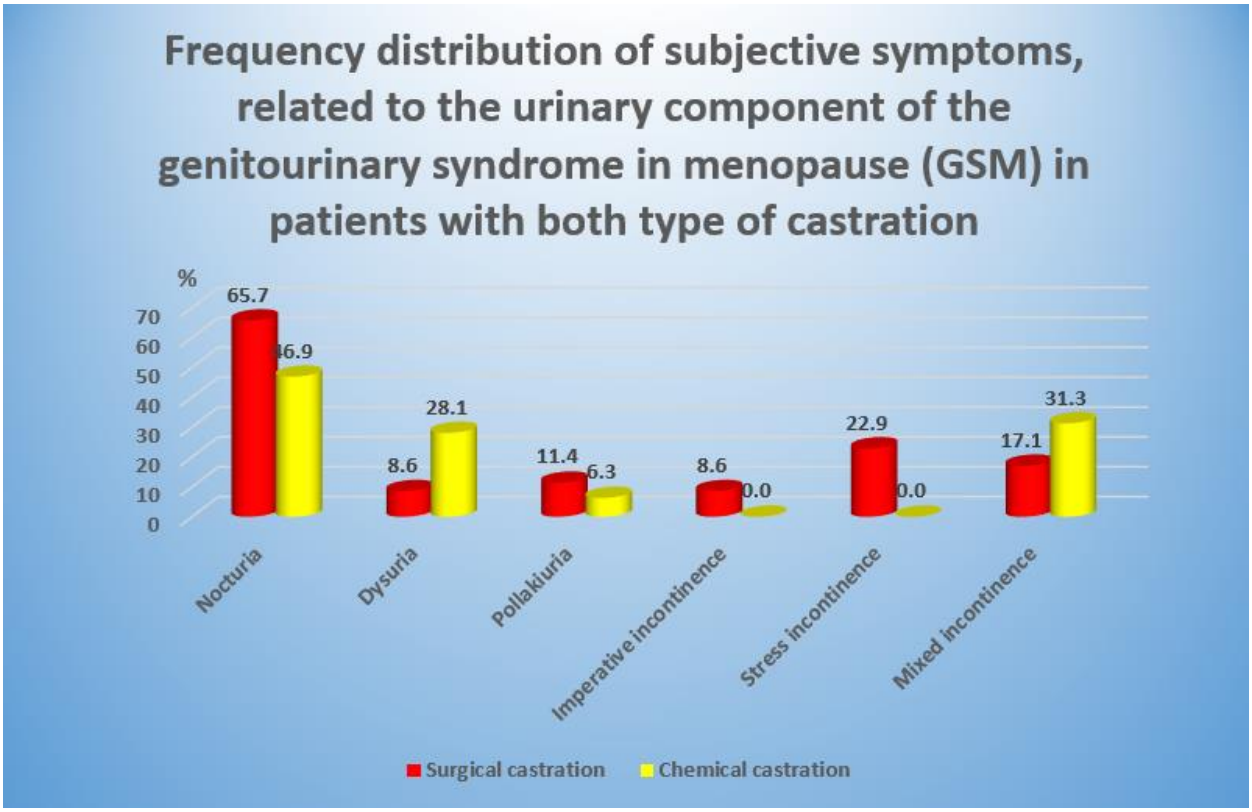

Fig. 14. Frequency distribution of subjective symptoms, related to the urinary component of the genitourinary syndrome in menopause (GSM) in patients with both type of castration

5. Prognostic significance of the factors – age, type of castration, oncological disease, causing: dyspareunia, vaginal dryness, pruritus vulve, vaginal pH, vaginal cleanliness, and number of lactobacilli.

This analysis includes only the patients who have given one answer to the subjective symptoms question, related to the vaginal component of the genitourinary syndrome in menopause (GSM), a total of 43.

Table 2 clearly shows that there is no significant relationship between the age and the vulva-vaginal symptoms, which means that age cannot be its predictor.

The results in Table 3 show that surgical castration is significantly more related to dyspareunia and vaginal dryness (in statistically the same degree), while with chemical castration – there is no vulva-vaginal symptoms.

Table 4 shows that:

Oncological diseases cervical cancer and breast cancer are statistically significantly related to the vaginal component of the genitourinary syndrome in menopause (GSM);

In cervical cancer cases, the relative share of vaginal dryness is significantly higher than those who do not have vulva-vaginal symptoms, but not than those having dyspareunia;

In breast cancer cases, statistically reliably the higher percentage is those without vulva-vaginal symptoms compared to the other two symptoms, whose relative shares are not statistically different among themselves;

In patients with ovarian cancer the difference in percentages in the studied symptoms is statistically irrelevant;

As a conclusion, we can infer that it is statistically reliable to expect dyspareunia and/or vaginal dryness in the study participants with cervical cancer; those with breast cancer as main disease – there is no vulva-vaginal symptoms, while those with ovarian cancer, the prognosis for these kinds of symptoms is irrelevant.

Table 2. Analysis of the relationship between age and vulva-vaginal symptoms (ANOVA, F = 0.007, P = 0.993)

Vulva-vaginal symptoms	**Age (years)**		
	n	$\bar{X}$	SD
Dyspareunia	10	39.40	4.27
Vaginal dryness	20	39.35	4.61
None	13	39.54	4.56

Table 3. Analysis of the relationship between the type of castration and the vaginal component of the genitourinary syndrome in menopause (GSM) (Pearson Chi-Square = 11.701, df = 2, P = 0.015)

Type of castration	**Frequency**	**Vaginal component of the genitourinary syndrome in menopause (GSM)**			**P**		
		1. Dyspareunia	2. Vaginal dryness	3. None	1-2	1-3	2-3
Surgical	n	6	15	2	0.431	0.039	0.003
	%	60.0[a]	75.0[a]	15.4[b]			
Chemical	n	4	5	11			
	%	40.0	25.0	84.6			

* – repeating letters along the horizontal denote the lack of significant difference, and the varying ones – the presence of it ($p<0.05$)

** – **P** values calculated for surgical castration are also valid for the chemical one

Table 4. Analysis of the relationship between the oncological disease and the vaginal component of the genitourinary syndrome in menopause (GSM) (Fisher-Freeman-Halton exact test = 11.188, P=0.012)

Oncological disease	**Frequency**	**Vaginal component of the genitourinary syndrome in menopause (GSM)**			**P**		
		1. Dyspareunia	2. Vaginal dryness	3. None	1-2	1-3	2-3
Cervical cancer	N	5	12	2	0.608	0.080	0.013
	%	50.0[ac]	60.0[a]	15.4[bc]			
Ovarian cancer	n	1	3	0	0.709	0.254	0.149
	%	10.0[a]	15.0[a]	0.0[a]			
Breast cancer	n	4	5	11	0.406	0.030	0.001
	%	40.0[a]	25.0[a]	84.6[b]			

* – repeating letters along the horizontal denote the lack of significant difference, and the varying ones – the presence of it ($p<0.05$)

The results in Tables 5-7 show that there is no statistically significant relationship between the vaginal pH and the factors age, type of castration and oncological disease, which means that they cannot be its predictor.

Table 5. Analysis of the relationship between age and vaginal pH (Kruskal-Wallis H=2.259, df=2, P=0.323)

Vaginal pH	**Age (years)**		
	n	$\bar{X}$	SD
Acidic pH (normal)	12	41.50	3.71
Alkaline (pH 5-7)	26	39.85	4.01
Highly alkaline (pH 7-9)	29	40.14	3.91

Table 6. Analysis of the relationship between the type of castration and the vaginal pH (Pearson Chi-Square = 11.665, df=2, P=0.767)

Type of castration	**Frequency**	**Vaginal pH**		
		Acidic pH (normal)	Alkaline (pH 5-7)	Highly alkaline (pH 7-9)
Surgical	n	5	14	16
	%	41.7	53.8	55.2
Chemical	n	7	12	13
	%	58.3	46.2	44.8

Table 7. Analysis of the relationship between oncological disease and vaginal pH (Fisher-Freeman-Halton exact test = 1,488, P = 0,854)

Oncological disease	**Frequency**	**Vaginal pH**		
		Acidic pH (normal)	Alkaline (pH 5-7)	Highly alkaline (pH 7-9)
Cervical cancer	n	3	11	11
	%	25.0	42.3	37.9
Ovarian cancer	n	2	3	5
	%	16.7	11.5	17.2
Breast cancer	n	7	12	13
	%	58.3	46.2	44.8

Tables 8-10 show that there is no statistically reliable relationship between the vaginal cleanliness and the factors age, type of castration and oncological disease, which means that they cannot be its predictor.

Table 8. Analysis of the relationship between age and vaginal cleanliness (Kruskal-Wallis H = 1,170, df = 2, P = 0,557)

Vaginal cleanliness	**Age (years)**		
	n	**X̄**	**SD**
Degree I*	3	44.67	0.58
Degree II	23	39.78	4.34
Degree III	28	40.86	2.90
Degree IV	13	38.85	4.67

* this category is not part of the analysis due to lack of statistical representation

Table 9. Analysis of the relationship between the type of castration and vaginal cleanliness(Fisher-Freeman-Halton exact test = 1,044, P = 0,805)

Type of castration	**Frequency**	**Vaginal cleanliness**			
		Degree I	Degree II	Degree III	Degree IV
Surgical	n	1	12	14	8
	%	33.3	52.2	50.0	61.5
Chemical	n	2	11	14	5
	%	66.7	47.8	50.0	38.5

Table 10. Analysis of the relationship between oncological disease and vaginal cleanliness(Fisher-Freeman-Halton exact test = 5,341, P =0,492)

Oncological disease	**Frequency**	**Vaginal cleanliness**			
		Degree I	Degree II	Degree III	Degree IV
Cervical cancer	N	1	11	8	5
	%	33.3	47.8	28.6	38.5
Ovarian cancer	n	0	1	6	3
	%	0.0	4.3	21.4	23.1
Breast cancer	n	2	11	14	5
	%	66.7	47.8	50.0	38.5

Tables 11-12 show that there is no significant relationship between the number of lactobacilli and the factors age and type of castration, which means they cannot be its predictor.

Table 13 shows that:

- The oncological diseases that are looked at, only ovarian cancer is statistically significantly related to the number of lactobacilli
- In cases of this disease, it is reliable to say that it is more probable that there would be lack of lactobacilli

Table 11. Analysis of the relationship between age and number of lactobacilli (Kruskal-Wallis H = 1,790, df = 2, P = 0,409)

Number of lactobacilli	**Age (years)**		
	n	**X̄**	**SD**
Normal	14	39.29	4.46
Reduced	30	40.97	3.68
None	23	39.96	3.82

Table 12. Analysis of the relationship between the type of castration and number of lactobacilli (Pearson Chi-Square = 3,145, df = 2, P = 0,210)

Type of castration	**Frequency**	**Number of lactobacilli**		
		Normal	Reduced	None
Surgical	n	5	15	15
	%	35.7	50.0	65.2
Chemical	n	9	15	8
	%	64.3	50.0	34.8

Table 13. Analysis of the relationship between oncological disease and number of lactobacilli (Fisher-Freeman-Halton exact test = 10,126,P = 0,031)

Oncological disease	**Frequency**	**Number of lactobacilli**			**P**		
		1. Normal	2. Reduced	3. None	1-2	1-3	2-3
Cervical cancer	n	5	13	7	0.637	0.742	0.341
	%	35.7a	43.3a	30.4a			
Ovarian cancer	n	0	2	8	0.327	0.014	0.010
	%	0.0a	6.7a	34.8b			
Breast cancer	n	9	15	8	0.380	0.085	0.273
	%	64.3a	50.0a	34.8a			

* repeating letters along the horizontal denote the lack of significant difference, and the varying ones – the presence of it ($p<0.05$)

6. The prognostic significance of the factors age, type of castration, oncological disease causing: nocturia, dysuria, pollakiuria, imperative incontinence, stress incontinence, mixed incontinence.

This analysis includes only patients who have given one answer to the subjective symptoms question, related to the urinary component of the genitourinary syndrome in menopause (GSM), a total of 53.

Tables 14 and 16 show that there is no statistically reliable relationship between the studied symptoms and the factors age and oncological disease, which means that they cannot be its predictor.

Regarding the type of castration, the following was found (Table 15):

With surgical castration, dysuria can be expected significantly less often than nocturia and stress incontinence;

With chemical castration, dysuria is significantly more likely than stress incontinence and nocturia.

Note: Since the urinary component of the genitourinary syndrome in menopause (GSM) has 6 categories, 15 comparisons are necessary in order to determine the respective relationships. This makes it inconvenient to place the 15 calculated levels of significance (P-s). For this reason, we use only the letter symbols of the significant differences and non-differences.

Table 14. Analysis of the relationship between age and subjective symptoms, related to the urinary component of the genitourinary syndrome (GSM) (Kruskal-Wallis H = 1,252, df = 2, P = 0,535)

Subjective symptoms, related to the urinary component of the genitourinary syndrome (GSM)	**Age (years)**		
	n	**$\bar{X}$**	**SD**
Nocturia	26	39.65	3.44
Dysuria	9	41.11	3.82
Pollakiuria*	4	42.25	3.10
Imperative incontinence*	1	45.00	.
Stress incontinence*	3	41.33	3.21
Mixed incontinence	10	39.10	5.97

* this category is not part of the analysis due to lack of statistical representation

Table 15. Analysis of the relationship between type of castration and subjective symptoms, related to the urinary component of the genitourinary syndrome (GSM)(Fisher-Freeman-Halton exact test = 10,374, P = 0,035)

Type of castration	**Frequency**	**Subjective symptoms, related to the urinary component of the genitourinary syndrome (GSM)**					
		Nocturia	Dysuria	Pollakiuria	Imperative incontinence ♦	Stress incontinence ♦	Mixed incontinence
Surgical	n	14	1	2	1	3	3
	%	53.8[a]	11.1[bc]	50.0[ac]	100.0[ac]	100.0[a]	30.0[ac]
Chemical	n	12	8	2	0	0	7
	%	46.2	88.9	50.0	0.0	0.0	70.0

* repeating letters along the horizontal denote the lack of significant difference, and the varying ones – the presence of it ($p<0.05$)

** p values calculated for surgical castration are also valid for the chemical one
♦ these two categories cannot be compared statistically

Table 16. Analysis of the relationship between oncological disease and subjective symptoms, related to the urinary component of the genitourinary syndrome (GSM) (Fisher-Freeman-Halton exact test = 14,695, P = 0,065)

Oncological disease	**Frequency**	**Subjective symptoms, related to the urinary component of the genitourinary syndrome (GSM)**					
		Nocturia	Dysuria	Pollakiuria	Imperative incontinence	Stress incontinence	Mixed incontinence
Cervical cancer	N	11	1	1	1	2	1
	%	42.3	11.1	25.0	100.0	66.7	10.0
Ovarian cancer	n	3	0	1	0	1	2
	%	11.5	0.0	25.0	0.0	33.3	20.0
Breast cancer	n	12	8	2	0	0	7
	%	46.2	88.9	50.0	0.0	0.0	70.0

7. Comparative analysis between the two types of castration: surgical and chemical, with regards to the symptoms, comprising the vaginal component of the genitourinary syndrome in menopause (GSM) – dyspareunia, vaginal dryness, vaginal pH, vaginal cleanliness, number of lactobacilli.

Table 17 shows that:

- Both types of castration are significantly different in regards to the vaginal component of the genitourinary syndrome in menopause;
- With the surgical castration, dyspareunia and vaginal dryness dominate statistically reliably, where as with the chemical castration – there is no such component.

Tables 18-20 show that neither typeof castration is statistically different according to vaginal pH, vaginal cleanliness, or number of lactobacilli.

Table 17. Comparative analysis of both types of castration relating to the vaginal component of the genitourinary syndrome (GSM)

Type of castration	**Frequency**	**Vaginal component of the genitourinary syndrome (GSM)**			**P**		
		1. Dyspareunia	2. Vaginal dryness	3. None	1-2	1-3	2-3
Surgical	n	18	27	2	0.454	0.021	0.004
	%	52.9a	61.4[a]	15.4b			
Chemical	n	16	17	11			
	%	47.1	38.6	84.6			

* P values calculated for surgical castration are also valid for the chemical one

Table 18. Comparative analysis of both types of castration relating to the vaginal pH (Pearson Chi-square test = 0,665; df = 2; p = 0,667)

Type of castration	**Frequency**	**Vaginal pH**			
		Acidic pH (normal)	Alkaline (pH 5-7)	Highly alkaline (pH 7-9)	**Total**
Surgical	n	5	14	16	35
	%	41.7	53.8	55.2	52.2
Chemical	n	7	12	13	32
	%	58.3	46.2	44.8	47.8
Total	n	12	26	29	67
	%	100.0	100.0	100.0	100.0

Table 19. Comparative analysis of both types of castration relating to the vaginal cleanliness (Fisher-Freeman-Halton exact test: p = 0,805)

Type of castration	**Frequency**	**Vaginal cleanliness**				**Total**
		Degree I	Degree II	Degree III	Degree IV	
Surgical	n	1	12	14	8	35
	%	33.3	52.2	50.0	61.5	52.2
Chemical	n	2	11	14	5	32
	%	66.7	47.8	50.0	38.5	47.8
Total	n	3	23	28	13	67
	%	100.0	100.0	100.0	100.0	100.0

Table 20. Comparative analysis of both types of castration relating to the number of lactobacilli (Pearson Chi-square test = 3,145; df = 2; p =0,210)

Type of castration	**Frequency**	**Number of lactobacilli**			
		Normal	Reduced	None	**Total**
Surgical	n	5	15	15	35
	%	35.7	50.0	65.2	52.2
Chemical	n	9	15	8	32
	%	64.3	50.0	34.8	47.8
Total	n	14	30	23	67
	%	100.0	100.0	100.0	100.0

8. Comparative analysis of both types of castration: surgical and chemical with regards to the symptoms, comprising the urinary component of the genitourinary syndrome in menopause (GSM) – nocturia, dysuria, pollakiuria, imperative incontinence, stress incontinence, mixed incontinence.

The results in Table 21 show that:

Both types of castration are significantly different in the urinary component of the genitourinary syndrome in menopause;

With the surgical castration, stress and imperative incontinence, pollakiuria and nocturia dominate statistically reliably, whereas with the chemical castration – dysuria and mixed incontinence.

Note: Since the urinary component of the genitourinary syndrome in menopause (GSM) has 6 categories, 15 comparisons are necessary in order to determine the respective relationships. This makes it inconvenient to place the 15 calculated levels of significance (P-s). For this reason, we use only the letter symbols of the significant differences and non-differences.

Table 21. Comparative analysis of both types of castration relating to the urinary component of the genitourinary syndrome in menopause (GSM)

Type of castration	**Frequency**	**Urinary component of the genitourinary syndrome (GSM)**					
		Nocturia	Dysuria	Pollakiuria	Imperative incontinence ♦	Stress incontinence ♦	Mixed incontinence
Surgical	n	23	3	4	3	8	6
	%	60.5[a]	25.0[bce]	66.7[acf]	100.0[a]	100.0[df]	37.5[ae]
Chemical	n	15	9	2	0	0	10
	%	39.5	75.0	33.3	0	0	62.5

* repeating letters along the horizontal denote the lack of significant difference, and the varying ones – the presence of it ($p<0.05$)

** **P** values calculated for surgical castration are also valid for the chemical one

♦ these two categories cannot be compared statistically

V. INFERENCES

1. Removing the ovarian function (castration) in this study leads to a highly alkaline and alkaline pH in 82.1% of cases; in 60.2% of cases the vaginal cleanliness is of degrees III and IV; in 79.1% lactobacilli are reduced or highly reduced. The leading symptom in the urinary component of GSM is nocturia, and in the vaginal component – vaginal dryness.
2. Surgical castration is linked to a higher frequency of alkaline and highly alkaline pH, vaginal cleanliness degree IV and lack of lactobacilli compared to chemical castration;
3. Surgical castration is significantly linked todyspareunia and vaginal dryness;
4. Cervical cancer as a disease significantly leads to higher frequency of vaginal dryness; 84% of patients with breast carcinoma lack subjective vulva-vaginal symptoms;
5. The factors of age and type of oncological disease are not predictors for the presence of separate symptoms of the urinary component of GSM;
6. After surgical castration, nocturia and stress incontinence are encountered more often and dysuria – less often.
7. After chemical castration, dysuria is encountered more often and stress incontinence and nocturia – less often.
8. Both types of castration differ significantly with regards to the vaginal component of the genitourinary syndrome in menopause: with surgical castration dyspareunia and vaginal dryness dominate statistically reliably, whereas with chemical castration, there is no such component;
9. Both types of castrations differ significantly with regards to the urinary component of the genitourinary syndrome in menopause: with surgical castration stress and imperative incontinence, pollakiuria and nocturia dominate statistically reliably, whereas with chemical castration –dysuria and mixed incontinence do.

VI. CONCLUSION

Cervical cancer and mammary carcinoma are the most common oncological diseases, which can affect younger women with preserved ovarian function. The applied treatment of these diseases leads to castration (removal and discontinuation of the ovarian function) and to the development of various symptoms of the genitourinary syndrome in menopause. The study that was carried out proves that patients with surgical castration (double adnexectomy), as part of the surgical treatment of cervical cancer, develop the symptoms of vaginal dryness and dyspareunia. These symptoms can lower the quality of life by affecting the sexual function and partner relationships to a higher degree than after chemical castration in patients with mammary carcinoma. That is why, the recommendation that can be given is to preserve the ovaries when surgical treatment is given to younger women with cervical cancer – on one hand, and on the other – to avoid double adnexectomy (ovariectomy) in women with preserved ovary function and mammary carcinoma after chemo- and/or hormonal therapy.

VII. CONTRIBUTIONS

1. A questionnaire is created to evaluate the subjective symptoms of the genitourinary syndrome in menopause – vaginal dryness, dyspareunia, pollakiuria, dysuria, nocturia, stress incontinence, imperative and mixed incontinence, for the studied sample of 67 patients of young age with oncological diseases, after surgical and chemical castration. (For the first time in Bulgaria).
2. "STUDY CARD" is created, which includes the encoded data of every patient, included in the study, according to their oncological disease (cervical cancer, mammary carcinoma, ovarian carcinoma), type of castration (surgical, chemical), number of lactobacilli, vaginal cleanliness, vaginal pH and subjective symptoms of the vaginal and urinary components of the genitourinary syndrome in menopause.
3. The vaginal secretion of 67 young patients with oncological diseases is studied after surgical and chemical castration with regards to the vaginal cleanliness, number of lactobacilli, vaginal pH. (For the first time in Bulgaria)
4. The frequency of the different symptoms of the vaginal and urinary components of the genitourinary syndrome in menopause in the studied sample was found. (For the first time in Bulgaria)
5. The predictive significance is foundfor the factors age, type of oncological disease and type of castration with regards to the separate manifestations of vaginal (dyspareunia, vaginal dryness, vaginal pH, number of lactobacilli) and urinary (nocturia, pollakiuria, dysuria, stress, imperative and mixed incontinence) components of the genitourinary syndrome in menopause for the studied sample. (For the first time in Bulgaria)
6. Comparative analysis is done for both types of castration (surgical) and chemical (chemo-/hormonal therapy) with regards to subjective and objective symptoms of the vaginal and urinary components of the genitourinary syndrome in menopause. (For the first time in Bulgaria)
7. It is found that the patients after surgical castration and cervical cancer have symptoms of vaginal dryness and dyspareunia, which affect their quality of life, significantly more than the patients with chemical castration and mammary carcinoma. (For the first time in Bulgaria)

VIII. PUBLICATIONS

1. Dobrev, P., St. Strashilov, A. Yordanov, Metastasis of malignant melanoma in ovarium simulating primary ovarian cancer: a case report. Gazetta Medica Italiana – Archivio per le Scienze Medicine,2021,180(0):000–000
2. Dobrev, P., A. Yordanov, St. Strashilov, Synchronous primary cervical carcinoma and ovarian fibroma: challenge in surgery. Gazzetta Medica Italiana-Archivio per le Scienze Mediche, 2020, 179(5),375–7.

Participation in the team of project No. 18/2013: Stress-hormonal response to open and mini-invasive (laparoscopic and robotic) surgery in obstetrics and urology.

IX. ATTACHMENTS

Attachment 1
STUDY CARD

STUDY CARD

1. INITIALS:……..

2. AGE……

3. Type of castration:
   1. Surgical –laparoscopic hysterectomy with adnexis (adnexectomy)
   2. Radiosurgery of the lesser pelvis
   3. Chemical castration – hormonal, chemotherapy

4. Main disease:
   1. Cervical cancer
   2. Ovarian cancer
   3. Breast cancer

5. Therapy
   1. Mammary surgery + chemical therapy (chemo- and/or hormonal therapy)
   2. Female reproductive system (FRS) surgery (adnexectomy with or without total/radical hysterectomy) + radiotherapy (RT) of the lesser pelvis
   3. FRS surgery (adnexectomy with or without total/radical hysterectomy) + chemotherapy (CT)
   4. FRS surgery (adnexectomy with or without total/radical hysterectomy)

6. Vaginal pH:
   1. Acidic pH (normal) –
   2. Alkaline (pH 5-7) –
   3. Highly alkaline (pH 7-9) –

7. Vaginal cleanliness
   1. Degree I
   2. Degree II
   3. Degree III
   4. Degree IV

8. Number of lactobacilli:
   1. Normal
   2. Reduced
   3. None

9. Subjective symptoms related to the urinary component of the genitourinary syndrome in menopause (GSM)
   1. Nocturia
   2. Dysuria

3. Pollakiuria
4. Imperative incontinence
5. Stress incontinence
6. Mixed incontinence

10. Vulva-vaginal symptoms:
    1. Dyspareunia
    2. Vaginal dryness
    3. Pruritus vulvae (dryness in the area of the outer sexual organs)
    4. None