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Surgical treatment for breast tumors in children

Хируршко лечење тумора дојки у дечјем узрасту

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SUMMARY

Introduction/Objective Fibroadenomas, often called “breast mice tumors” due to their mobility, are the most common breast tumors in pediatric population. Considering that some of tumors have a potential for rapid growth and breast tissue damage, and that an ideal diagnostic tool has not been found yet, complete mass extirpation might be the treatment of choice.

The aim of the study was to present our clinical experience in treating children with breast masses.

Methods A retrospective review (2011-2018) of patients treated for breast tumors at the Institute for Child and Youth Health Care of Vojvodina in Novi Sad was conducted.

Results In this study 29 girls (mean age 15.8 ± 1.8) were included. The majority of masses were located in the upper outer (27.6%) or lower inner (24.1%) breast quadrant. The mean mass diameter was 39.7mm. It has been observed that the mean mass diameter in group of girls with positive family history for breast diseases was significantly lower ($p < 0.05$) than in those with negative family history (27.5 vs. 43.2 mm). There were no proven malignant tumors and all tumors have been completely extirpated. The mean postoperative stay was 1.5 ± 1.02 days.

Conclusion An appropriate radical operative technique dependent on mass size and localization is still a “gold standard” for treating breast masses in pediatric patients. Cooperation with experts in field of oncologic breast surgery enables implementing these operative techniques in clinical practice of pediatric surgeons.

Keywords: breast fibroadenoma; phylloid breast tumor; surgery; children

САЖЕТАК

Увод/Циљ Фиброаденоми, услед своје изразите покретљивости звани и „мишеви дојке“, најчешћи су тумори дојке у дечјем узрасту. Узевши у обзир чињенице да тумори дојке могу својим растом да ремете развој њеног нормалног жлезданог ткива и да не постоји идеалан начин за дијагностиковање ових тумора, оперативно лечење са комплетном ресекцијом представља “златни стандард” у терапији. Циљ ове студије је да прикаже клиничко искуство Клинике за дечју хирургију у Новом Саду у лечењу ове патологије.

Метод Истраживање је конципирано као дескриптивно-ретроспективна студија. Анализиране су пацијенткиње лечене од тумора дојки на Институту за здравствену заштиту деце и омладине Војводине у Новом Саду у периоду од 2011. до 2018. године.

Резултати Студију чини 29 пацијенткиња, просечне старости $15,8 \pm 1,8$ година. Већина тумора је позиционирана у горњем спољашњем (27,6%) и доњем унутрашњем (24,1%) квадранту дојки. Тумори су били просечног дијаметра 39,7 милиметара. Уочено је како су код пацијенткиња са позитивном породичном анамнезом у правцу тумора дојке, тумори били мањих димензија у поређењу са оним код пацијенткиња са негативном породичном анамнезом (27,5 милиметара у поређењу са 43,2 милиметра). У студији није било малигнитета и код свих пацијенткиња начињена је тотална екстирпација тумора. Хоспитализација је у просеку износила један и по дан.

Закључак У зависности од величине и локализације тумора, одговарајућа радикална операција и даље представља “златни стандард” у лечењу тумора дојке код деце. Сарадња се експертима из области онколошке хирургије омогућава да ова патологија постане рутина у раду дечјих хирурга.

Кључне речи: фиброаденоми дојке; филодес тумори; оперативно лечење; деца

INTRODUCTION

When breast mass (lump) is detected, the most feared cause is breast cancer. Fortunately, malignant breast tumors are quite rare in children. When breast tumors are presented in adolescent girls, they commonly include hematological (cutaneous T-cell lymphoma) or metastatic diseases, chest wall malignancies, post radiation breast cancer,

sarcoma, primary breast cancer (invasive secretory carcinoma), and hereditary breast cancer (Cowden syndrome) [1, 2]. However, in the majority of patients the first causes of the lump to consider are benign tumors such as fibroadenoma [3]. The mass is most commonly found in the upper outer breast quadrant [4]. In 85-90% of cases, breast fibroadenomas are unilateral, but bilateral presentations as well as tumor multiplicity may be observed too [5].

Clinically, breast fibroadenomas may be completely asymptomatic. However, during physical examination they usually present as smaller or bigger “rubbery”, painless breast masses, and freely mobile under the skin. Because of their mobility, these tumors are often called “breast mice tumors” [5].

Histologically, fibroadenomas consist of of polyclonal epithelial and stromal cells. Therefore are considered to present hyperplastic masses, whose occurrence might be related to an aberrant maturation of the breast tissue [3, 6]. Tumor development is believed to be caused by MAD12 (mediator complex subunit 12) exon 2 somatic mutation [3].

Different radiological modalities may be used for assessment of breast diseases. MRI (magnetic resonance imaging) enables providing precise images without exposing patients to radiation, but its efficacy and accuracy in children with breast tumors has not been established yet. The modality of choice for the majority of pediatric patients may be ultrasound (US) [2, 7]. This diagnostic tool is capable of providing multiple images during a follow-up period, without a risk of causing any harm to a patient. Also, younger patients are not candidates for mammography, due to a predominantly glandular breast configuration and known dangerous effects that radiation exposure may cause. Fibroadenomas observed under ultrasound present as oval or round well-circumscribed hypoechoic masses with variable posterior acoustic alteration, and heterogeneous or homogeneous internal texture. These tumors are either avascular or with mildly increased blood flow on Color Doppler [7].

There are two subtypes of breast fibroadenoma, simple and complex. Tumor might be considered complex when containing at least one of the following characteristics: epithelial calcifications, apocrine metaplasia, sclerosing adenosis or cysts larger than 3 mm. Precise guidelines for making ultrasonographic distinction between simple and complex ones have not been established yet. This is really clinically important, knowing that their behavior is quite different. Simple breast fibroadenomas are not associated with increased risk of developing breast cancer. Also, these tumors may resolve spontaneously in up to 10%.

Therefore, conservative management may be feasible in many cases [4, 8]. On the other hand, patients with complex fibroadenomas are believed to have 3.1 times higher chances for developing breast cancer compared to general population [9].

Masses that are solid, non mobile, enlarging, tender, fixed to overlying skin or nipple-areolar complex, and/or associated with axillary or supraclavicular lymphadenopathy should be suspected for malignancy [4]. A risk factor for developing breast cancer in young patients may be radiation exposure during breast development. When it occurs, breast cancer in these patients tends to be of the secretory variety, with less metastatic potential [10].

Another type of tumor, which might clinically appear as fibroadenoma is phylloid breast tumor. It consists of the same cell types as fibroadenoma, but with stromal (connective) tissue predominance, as well as cellular atypia in some forms [11].

Clinically similar to these tumors, but often presented with serous or sero-sanguinous nipple discharge is intraductal papilloma. This tumor represents a benign proliferation of ductal epithelium. On ultrasound (US) it can be seen as an echogenic intraductal mass with internal vascularization on Doppler imaging. In some cases, ductal dilatation may be observed as well [12].

It is sometimes really hard to choose a proper therapeutic management for breast masses in young patients. In the first place, a risk of malignant disease must be estimated. However, only 0.02% of surgically removed pediatric breast masses are proven to be malignant [10]. There are some factors in patient's history which may indicate if observed mass requires specific attention, in order to exclude potential malignancy. The most important one is known breast cancer in a family member [13–16]. Patients with a clinical history of chest radiation (for example for childhood Hodgkin's disease) should also be carefully examined, due to the relatively high rates of breast cancer [17].

Considering specific (predominantly glandular) breast structure in adolescent girls, iatrogenic damage to the developing breast tissue must be avoided as much as possible. Also, generalized anxiety over having a breast lump, as well as cosmetic changes that may occur might be significant factors when determining appropriate management for young patients [4, 18].

Potential malignancy of tumor mass might be determined using less invasive techniques such as fine needle aspiration (FNA). It has recently been proven that this technique may not help making a precise differentiation between a fibroadenoma and phyllodes tumor, therefore it is not required [9, 19].

Considering that some of these tumors have a potential for rapid growth and breast glandular tissue damage, as well as that an ideal diagnostic tool has not been found yet, complete mass extirpation might be the treatment of choice [19]. Breast masses in children and adolescents require particular attention, both before and after surgical intervention. Of course, much more attention is paid if tumor is histologically proven to be complex fibroadenoma or breast cancer. On the other hand, some authors advocate that in benign diseases, such as simplex fibroadenoma, after tumor extirpation follow-up is not necessary any more [9].

The aim of the study was to present our clinical experience in treating children with breast masses, as well as to compare treatment options and outcomes with results recently published in studies worldwide.

METHODS

With the approval of the institutional ethical committee, a retrospective review of patients treated for breast tumors between years 2011 and 2018 was conducted. All the patients were diagnosed and treated at the Clinic of pediatric Surgery, Institute for Child and Youth Health Care of Vojvodina in Novi Sad. Diagnoses were made by taking history, performing physical and expert ultrasound examinations (standardly performed at the Diagnostic Imaging Center, Oncology Institute of Vojvodina, Sremska Kamenica). All extirpated masses were analyzed histologically at the Oncology Institute of Vojvodina in Sremska Kamenica, as well.

Recorded data were analyzed using Microsoft Office Excel 2007 and IBM SPSS 23 statistics programs. Data were described using frequencies, percentages, means, standard deviations and bivariant correlations where appropriate. Between-group differences were analyzed using the independent-samples T-test. Calculated differences lower than significance level of 0.05 were considered relevant.

RESULTS

In this retrospective chart review, 29 girls aged between 9 and 18 years (mean age 15.8 ± 1.8) were analyzed (Table 1).

The majority of masses were located in the upper outer (27.6%) or lower inner (24.1%) breast quadrant. In 13.8% of participants the tumor was in lower outer quadrant. Masses in both upper or in both lower quadrants were observed in 6.9% of patients each (Figure 1).

The mean mass diameter was 39.7mm (range 10-70mm) (Table 2). In 10 patients tumors were equal to or larger than 50mm in diameter.

The breast mass was painful in 34.5% of participants (Figure 2). There was no difference ($p > 0.05$) in diameter between painful and painless breast masses (Table 3, 4). One girl with painful mass was diagnosed with phylloid breast tumor, while in others fibroadenoma was proven.

There were no verified malignant tumors. Of all patients analyzed, just one was histologically proven with phylloid breast tumor, while all the others had breast fibroadenomas.

In majority of patients (79.3%) family history was negative for breast diseases (Figure 3). It has been observed that the mean mass diameter in group of girls with positive family history for breast diseases was significantly lower ($p < 0.05$) than in those with negative family history (27.5mm vs. 43.2 mm) (Table 5, 6).

Tumors have been completely surgically extirpated in all patients.

The mean postoperative hospital stay was 1.5 ± 1.02 days (range 1 to 5) (Table 7).

During postoperative follow-up period (7 months – 7 years) only one recurrent tumor was observed, 10 months after the initial operation of phylloid tumor. Histology confirmed diagnosis of fibroadenoma.

DISCUSSION

Fibroadenomas are quite common during reproductive period, approximately 25% of women, while incidence in adolescent girls is approximately 2% [5, 18]. These tumors may occur in any age of life, but the peak incidence is reported in the second and third decade [18, 20]. In our study, the mean age of patients was 15.8 (range 9 to 18).

Considering that these tumors are estrogen dependent, their extremely rare occurrence in prepubertal girls, as well as their increased growth in periods when estrogen levels are high, such as puberty, pregnancy or lactation may be explained [8]. In pubertal girls, estrogen provides growth of lactiferous ducts, whereas progesterone stimulates differentiation of lobules and alveoli. Breast development may be clinically stratified into five Tanner stages. These clinical stages have their own specific ultrasound appearance, and must not be misunderstood for breast tumors [2].

There are various normal anatomical structures that might clinically appear as breast tumors, such as normal lymph nodes, breast bud asymmetry, prominent osseous structures (chest wall deformities or Poland syndrome). Physiological breast development might also be disturbed. As a result, ectopic breast tissue may be found, usually along the so called "milk line". If breast tissue fails to involute during male development, in pubertal boys gynecomastia may occur. In literature, it is reported in up to two thirds of boys aged 10-13. In our study there were no boys analyzed.

Non-neoplastic breast lesions are relatively common in children, and these include breast hematomas, cysts, galactoceles and abscesses [2].

Despite all these possible etiological factors, the most important causes of breast masses to consider are neoplastic lesions, benign and malignant. All but one patient (phylloid breast tumor) in our study had benign breast diseases (fibroadenomas).

In current literature, the most common localization of breast tumors is reported in to be in the upper outer quadrant of the breast, probably due to the highest concentration of glandular tissue in this area [4]. In our study, besides previously mentioned location, we found a large number of masses located in the lower inner breast quadrant.

Considering that breast malignancies are quite uncommon in children, as well as possibility of potential damage to developing breast tissue, we emphasize “first do no harm” in both diagnostic and therapeutic approaches [2]. For this reason, we have cooperated with our colleagues from the Institute of Oncology in Sremska Kamenica, whose experience in treating adult patients with breast pathology is great. Besides that, precise and gentle surgical technique enabled us to preserve noble glandular breast tissue undamaged.

Ultrasound (US) is the modality of choice for diagnosing breast diseases in majority of pediatric patients, and BI-RADS (Breast Imaging Reporting and Data System) lexicon is the gold standard for describing and stratifying these masses. Using this lexicon, seven different groups of masses (labeled 0-6) can be described. Masses categorized as BI-RADS 4 or above are suspicious for malignancy [2]. Characteristics considered as possible indicators that one mass is not a fibroadenoma (but e.g. phylloid tumor) include: maximum diameter greater than 4 cm, irregular borders, and heterogeneous echogenicity with intralesional cystic areas [21].

The mean tumor diameter in our study was 39.7mm (range 10-70mm). Fibroadenomas' size usually ranges from few millimeters to few centimeters. Rarely, these tumors may cause enormous and/or rapid breast enlargement. If fibroadenoma larger than 50 mm in diameter or replaces at least 80% of the breast, it is named giant fibroadenoma [19]. Giant fibroadenomas that present in adolescent patients are called juvenile fibroadenomas [9]. It occurs in approximately 4% of all adolescents with breast mass [21, 22, 23] and was present in 10 of our patients (37%). For juvenile fibroadenomas which are symptomatic or rapidly growing, prompt surgical excision is appropriate. When complete excision of this tumor is performed, specific reconstructive techniques might be required [4]. Although one of the members of our surgical team was a plastic surgeon, none of our patients needed reconstructive breast surgery.

Fibroadenomas are known to present as smaller or bigger “rubbery”, painless masses, freely mobile under the skin [2, 4, 5]. Despite that, 34.5% of our patients reported that the mass was painful. Our patient who was diagnosed with phylloid breast tumor was complaining of pain. This finding requires further investigation, in order to determine factors that might affect variances in clinical presentation of different types of breast tumors.

Phylloid breast tumor (cystosarcoma phylloides) is quite rare neoplasm, accounting for less than 0.5% of all breast tumors in all ages. High local recurrence rate as well as

sometimes malignant potential signifies its importance [11, 24, 25]. Phylloid tumors of the breast can be usually classified as benign, borderline or malignant [11]. In literature, benign forms have local recurrence rate in approximately 20% of cases, borderline in 14-25%, while malignant forms approximately 14-40%. Malignant phylloid breast tumors might cause metastatic disease in approximately 9-27%. Metastatic potential of borderline phylloid tumor is not certain, but few cases have been reported [11]. This is a reason why all extirpated masses were histologically analyzed at the facility which is highly experienced in this pathology.

It is hard to determine clear difference between breast fibroadenoma and phylloid tumor clinically. Masses that grow fast, as well as large masses are suspicious for phylloid tumors. There are authors who suggest that every breast mass larger than 30mm should be considered as phylloid tumor [21]. Larger tumor size and positive resection margin are well known to be risk factors for local tumor recurrence. Recurrence tumor can be lower or the same grade as the initial one, but in majority of cases more aggressive growth and enhanced malignancy are found on recurrence [26, 27, 28]. In our study, a girl which had been operated for phylloid tumor had recurrent tumor 10 months after initial surgery. Histology confirmed fibroadenoma.

In majority of girls included in the study, family history was negative for breast diseases. One girl (3,4%) had a positive family history for breast fibroadenoma, whereas another five girls (17.2%) had a breast cancer in their family history, which makes a total of six patients (20.6%) with known breast diseases in their families. In literature, positive family history for breast diseases is reported in approximately 8.6-24.4% of patients with breast masses [29].

Several genes, such as *TP53* (tumor suppressor protein 53), *BRCA1* and *BRCA2* (breast cancer genes), *PMS2* (post meiotic segregation increased 2 protein), *NFI* (neurofibromin protein 1 gene), *APC* (adenomatous polyposis coli gene), *RBI* (retinoblastoma associated protein 1) and *AML1* (acute myeloid leukemia protein 1 gene) are proven to be associated with breast cancer occurrence in some families [13, 14, 15, 16].

The mean tumor diameter at presentation in group of girls with positive family history for breast diseases was significantly lower than in those with negative family history (difference was approximately 15mm). Possible explanation might be in increased awareness

of breast pathology among girls who have a relative with breast tumor, as well as their justified fear of developing cancer themselves.

Choosing an appropriate management for breast tumors in young patients is a real challenge. Some authors advocate that probably benign masses up to 30-40mm in diameter might be safely followed-up, except when have tendency of rapid growth or cause significant clinical symptoms. These authors suggest that masses larger than 50mm must be biopsied [2]. However, biopsy isn't as harmless as it might appear, and iatrogenic damage of developing breast tissue has been reported [30]. On the other hand, there are also authors who believe that even tumors sized 30mm should be considered as phylloid breast tumors and surgically treated [21]. There is also important difference whether the breast fibroadenoma is simple or complex. Simple fibroadenomas may resolve spontaneously in up to 10% of cases, therefore may be treated non-operatively [4, 9]. However, in specific cases when these tumors cause anxiety in patient and/or patient's family, complete extirpation may be appropriate treatment [4, 18, 30].

At the beginning, our operations were performed in cooperation with colleagues from the Oncology Institute of Vojvodina in Sremska Kamenica.

Operative technique depends on the mass size and location, but generally speaking, complete tumor resection should be the main goal. In cases when phylloid tumor is proven (ex tempore) or suspected, R0 resection should be done due to its possible recurrence, rapid growth and/or metastasis [9, 11]. In all our patients, tumors have been completely surgically removed.

The optimal incision site (circumareolar or inframammary) which minimizes visible scarring is not always possible. When tumor location is further from the areolar border, its resection may be performed through curvilinear or semilunar incisions directly over the mass [4]. When treating giant fibroadenomas in young girls, it is important to make a proper reconstruction of the remaining tissue, in order to keep the breast shape acceptable. This also includes preserving the nipple-areolar complex in proper place, achieving the best possible aesthetic result, as well as enabling lactation in a regenerative period. Healthy breast tissue that had been compressed by expansive tumor lesion might appear diseased, but it has been proven that this tissue has a potential of filling the void left after surgical mass excision. This is the main reason why surgical breast reconstruction is rarely required in young patients

[19]. If needed, the precise timing for reconstructive surgery has not been established yet, but some authors recommend performing this operation minimally one year after the initial treatment and after skeletal maturation [18, 30]. None of our patients required breast reconstruction due to a complete “restitutio ad integrum”.

Our study had its limitations, mostly due to a small sample size. Therefore, many mentioned interesting findings should be checked in larger number of patients. Also, future studies might consider mechanical trauma as a possible etiological factor for developing breast tumor.

CONCLUSION

In this study, there were no verified malignant tumors. After carefully considering all the treatment options, an appropriate radical operative technique dependent on mass size and localization is still a “gold standard” for treating breast masses in pediatric patients. Cooperation with experts in field of oncologic breast surgery enables implementing these operative techniques in clinical practice of pediatric surgeons.

Conflict of interest: None declared

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Paper accepted

Table 1. The age of patients analyzed in the study

	n	Minimum	Maximum	Mean	Std. deviation	Skewness		Kurtosis	
	Statistic	Statistic	Statistic	Statistic	Statistic	Statistic	Std. Error	Statistic	Std. Error
Age	29	9	18	15.8	1.8	-2.1	0.4	6.8	0.8

Paper accepted

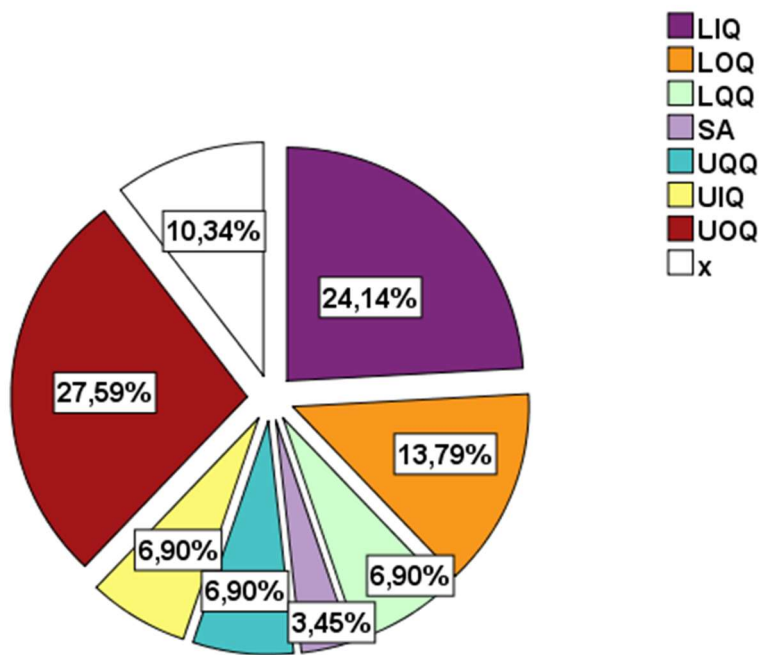


Figure 1. Localization of the mass in the breast

LIQ – lower inner quadrant; LOQ – lower outer quadrant; LQQ – both lower quadrants; SA – subareolar; UQQ – both upper quadrants; UIQ – upper inner quadrant; UOQ – upper outer quadrant; x – missing data

Table 2. The largest diameter of the breast mass in our patients

	n	Minimum	Maximum	Mean	Std. deviation	Skewness		Kurtosis	
	Statistic	Statistic	Statistic	Statistic	Statistic	Statistic	Std. Error		Statistic
Mass diameter (mm)	27	10	70	39.7	16	-0.5	0.5	-0.8	0.9

Paper accepted

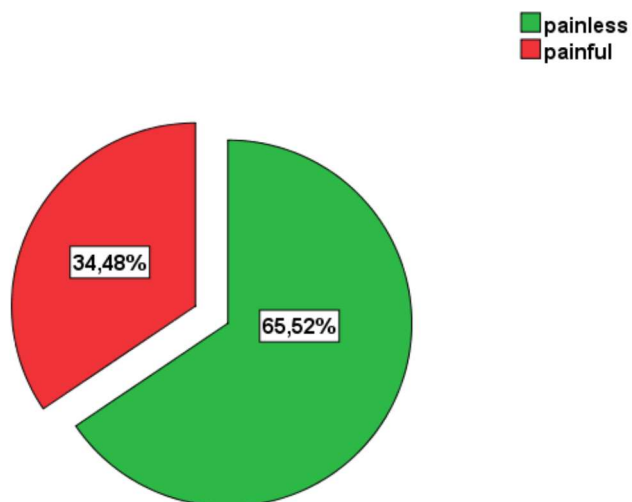


Figure 2. Pain presentation in our patients

Paper accepted

Table 3. The mean mass diameter in patients with pain at presentation and in those without it

	Pain	n	Mean	Std. deviation	Std. error mean
Mass diameter (mm)	painless	17	39.7	15.8	3.8
	painful	10	39.7	17.05	5.4

Paper accepted

Table 4. Comparison of mass diameters in patients with painful and painless breast masses

		Levene's test for equality of variances		t-test for equality of means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean difference	Std. error difference	95% confidence interval of the difference	
									Lower	Upper
Mass diameter (mm)	Equal variances assumed	0.2	0.7	0.001	25	0.99	0.006	6.5	-13.3	13.4
	Equal variances not assumed			0.001	17.8	0.99	0.006	6.6	-13.9	13.9

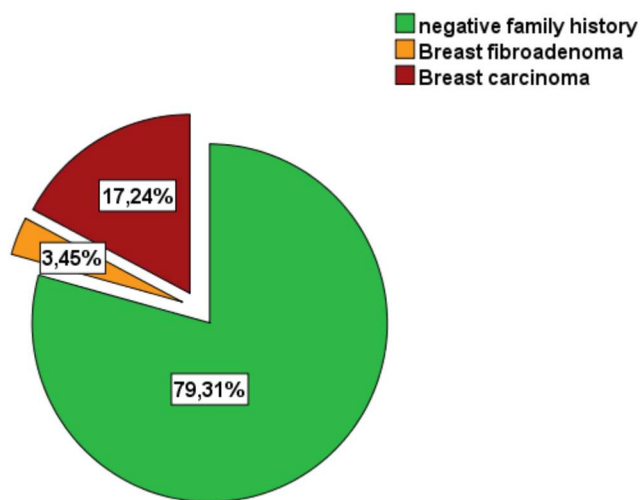


Figure 3. Family history of breast tumors

Paper accepted

Table 5. The mean mass diameter in patients with positive family history of breast diseases and in those without it

	Family history	n	Mean	Std. deviation	Std. error mean
Mass diameter (mm)	negative	21	43.2	14.6	3.2
	positive	6	27.5	15.4	6.3

Paper accepted

Table 6. Difference in the mean mass diameter in patients with positive family history of breast diseases and in those without it

		Levene's test for equality of variances		t-test for equality of means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean difference	Std. error difference	95% confidence interval of the difference	
									Lower	Upper
Mass diameter (mm)	Equal variances assumed	0.01	0.9	2.3	25	0.03	15.7	6.8	1.6	29.8
	Equal variances not assumed			2.2	7.8	0.06	15.7	7.06	-0.7	32.04



Figure 4. Giant breast fibroadenoma extirpation

Table 7. Days spent in hospital after the surgery

	N	Minimum	Maximum	Mean	Std. deviation	Skewness		Kurtosis	
	Statistic	Statistic	Statistic	Statistic	Statistic	Statistic	Std. error	Statistic	Std. error
Postoperative stay (days)	29	1	5	1.5	1.02	2.2	0.4	4.6	0.8

Paper accepted