GEORGIAN MEDICAL NEWS

ISSN 1512-0112

NO 12 (333) Декабрь 2022

ТБИЛИСИ - NEW YORK

ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

Monthly Georgia-US joint scientific journal published both in electronic and paper formats of the Agency of Medical Information of the Georgian Association of Business Press. Published since 1994. Distributed in NIS, EU and USA.

GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

GEORGIAN MEDICAL NEWS
No 12 (333) 2022

Содержание:

PATHOLOGIC FINDINGS IN GENDER-AFFIRMING MASTECTOMY: A SYSTEMATIC REVIEW

Alireza Hamidian Jahromi[1]*, Sydney Horen[2], Kelly Ho[3], Elizabeth Tran[3], Andrew Roth[3], Loren Schechter[2].

[1]*Division of Plastic and Reconstructive Surgery, Temple University Hospitals, Philadelphia, PA.*

[2]*Division of Plastic and Reconstructive Surgery, Rush University Medical Center, Chicago, IL, United States.*

[3]*Rosalind Franklin University of Medicine & Science, Chicago, IL, United States.*

Abstract.

Background: Following increased cultural awareness, expanded access to care, and decreased stigmatization, the number of transgender individuals seeking gender affirmation surgery such as gender-affirmation mastectomy (GAM) continues to rise. While post-mastectomy breast tissue is often sent for pathologic evaluation, few studies address the utility and standardization of this practice. This literature review evaluates the pathology findings in GAM specimens reported in the medical literature.

Methods: A systematic review following PRISMA guidelines was performed to evaluate all medical publications related to pathology reports following GAM. The overall type and incidence of benign and malignant breast lesions were analyzed to elucidate which patient characteristics significantly affect the pathology findings.

Results: Overall, eight of 488 identified studies met inclusion criteria (1278 patients). The incidence of pre-malignant lesions was 2.42%, including flat epithelial atypia (0.08%), atypical hyperplasia (0.23%), atypical ductal hyperplasia (1.33%), atypical lobular hyperplasia (0.39%), and lobular carcinoma in situ (0.39%).Patient age, hormonal therapy, and family / patient history of breast cancer were inconsistently reported among included studies. Lack of standardized pathologic classification did not permit further statistical analysis.

Conclusions: Although patients who undergo GAM are unlikely to have premalignant or malignant findings on breast pathology examination, pathologic evaluation of breast tissue remains common practice. Additional studies, which include a standardized method of pathologic evaluation, are necessary before practice guidelines can be recommended.

Key words. Gender affirmation surgery, gender-affirming mastectomy, pathology, breast cancer, transgender males.

Introduction.

In the United States, breast cancer is the second leading cause of cancer death in cisgender women (1 in 39) [1]. While the risk of developing breast cancer is multifactorial, sex (assigned female at birth) plays the most significant role [2]. Factors that increase the risk of breast cancer in cisgender women include age, genetic predisposition (BRCA gene, family history, and personal history of breast cancer), early menarche, late menopause, and nulligravid status [2]. Transgender men (individuals who are assigned female at birth whose gender identity is not aligned with their anatomy) are 80% less likely to be diagnosed with breast cancer than cisgender women [3]. Some research suggests that, by reducing the amount of glandular tissue in breasts, testosterone may reduce the risk of breast cancer. However, other research indicates potential increased risk of breast cancer due to peripheral conversion of testosterone to estrogen [4,5]. Gender affirming mastectomy (GAM) may lead to a decreased risk of breast cancer due to the removal of the majority of the glandular tissue, however, malignant transformation of the remaining breast tissue is still possible [5].

The prevalence of breast cancer in the transgender population is reportedly low [6]. However, following GAM, breast tissue is often sent for evaluation to assess for pre-malignant/malignant pathology. While this may identify occult or high-risk lesions, the utility of routine pathologic evaluation has not been proven in this population [6]. In low-risk individuals, the perceived benefits of pathologic evaluation versus the use of resources should be considered. This debate is heightened in resource-limited populations who require medically necessary GAM but may be responsible for additional procedural costs.

To the authors' knowledge, no prior study has provided a comprehensive literature review regarding the pathologic findings of breast tissue following GAM. Based upon the young age of most patients undergoing GAM (average age = 28.1 years old) [7], we hypothesize that the likelihood of occult or incidental malignancies will be rare; however, a family or personal history of breast cancer may be associated with an increased risk of malignant or pre-malignant lesions. The type, dose, and duration of hormone therapy may also play a role.

This study entailsa systematic review and meta-analysis of the medical literature to assess the pathology evaluations of transgender individuals undergoing GAM reported in the medical literature. The authors hope to elucidate whether universal guidelines for pathologic evaluation of breast specimens should be recommended in all transgender individuals seeking GAM.

Methods.

Literature Search:

A systematic search of articles related to pathologic findings in GAM specimens, was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [8]. The authors conducted a comprehensive search within the databases of PubMed, Cochrane, and Plastic and Reconstructive Surgery Journal archives on January 16, 2021.

The initial database search was performed by one of the authors [AR] using predetermined search terms and strategies (Appendix 1). Only English studies and those related to pathology specimen evaluation of the GAM were eligible for inclusion. No date limit

was applied. Animal studies were excluded. Search results were de-duplicated and then underwent primary screening by four authors independently [SH, AR, ET, KH]. Titles and abstracts assessment were performed to screen for articles that did not meet inclusion criteria. Eligible studies based on the titles and abstracts were subject to full-text evaluation by the same authors, independently. Eligibility criteria included retrospective and prospective case series, cohorts, and randomized controlled trials. No publication date restriction was applied. Reviews, commentaries, "letters to the editor" and experts' opinions were excluded. References of the publications that metinclusionmet inclusion criteria were assessed, and any relevant studies were included to ensure completeness.

Data Extraction:

Data extraction was performed by multiple authors [AR, ET, KH] using a data abstraction form created with Microsoft Excel. For relevant studies, the following data was included: year of publication, study time period, study design, study institution, sample size, average age of patients, number of patients taking hormones, number of patients with a personal or family history of breast cancer, and the reported pathologies (type and amount of benign, pre-malignant, and malignant lesions).

Results.

Overall, 484 studies were screened for inclusion, of which 452 were excluded after review of their titles and abstracts. Screening of the remaining 32 articles was performed through full-text review and yielded eight studies that were included in the final systematic review and meta-analysis (Figure 1). Characteristics of the included studies are presented in Table 1. Of the eight studies that met inclusion criteria, six were retrospective cohorts and two were prospective cohorts.

Analysis was performed to evaluate the number of benign and premalignant pathology reports in the included studies. In total, 1279 breast pathology results were reported, of which 31 contained a pre-malignant lesion (2.42%). Specimens considered premalignant included: flat epithelial atypia, atypical hyperplasia, atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH), ductal carcinoma in situ (DCIS), and lobular carcinoma in situ (LCIS). Analysis was also performed to evaluate for the presence of benign lesions in the six studies that reported such findings. An overall rate of 46.46% was calculated. Cysts, apocrine metaplasia, epithelial/ductal hyperplasia, gynecomastoid changes, pseudoangiomatous stromal hyperplasia, inflammation, columnar cell changes,

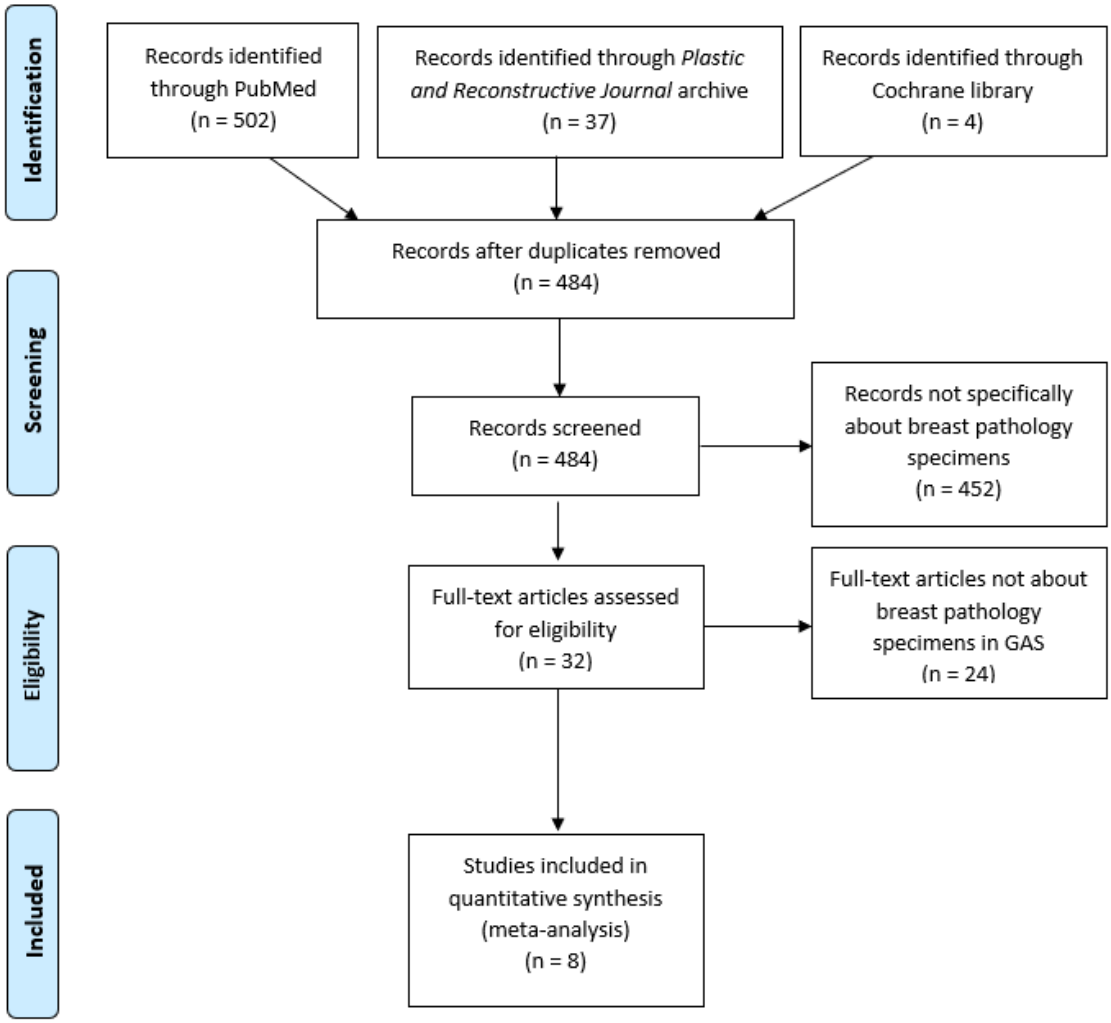

Figure 1. *Search strategy for our systematic review to find the currently published medical literature describing breast pathology findings in GAS mastectomy specimens.*

Table 1. *Characteristics of included studies related to gender mastectomy specimen evaluation.*

Publication (Reference)	First Author, Year, Study Type	Sample Size	Average Age*	# Patients taking Hormones	# Patients with FHx of Breast Cancer	# Normal pathology reports	# Benign pathology reports	# Premalignant or malignant pathology reports
Incidence of cancer and premalignant lesions in surgical specimens of transgender patients	Jacoby et al. 2021, RC	193	30.8± 12.3	161	1	176	11	6
Pathologic evaluation of breast tissue from transmasculine individuals undergoing gender-affirming chest masculinization	Hernandez et al. 2020, RC	211	28.1	142	30	205	n/a	6
Histopathologic findings in breast surgical specimens from patients undergoing female-to-male gender reassignment surgery	Torous et al. 2019, RC	148	28.4	130	1	n/a	n/a	6
Routine histopathological examination after female-to-male gender-confirming mastectomy	Van Renterghem et al. 2018, PC	344	25.8	113	1	178	166	7
An immunohistochemical study of the long-term effects of androgen administration on female-to-male transsexual breast: a comparison with the normal female brease and male breast showing gynecomastia	Burgess et al. 1993, PC	29	28.8	29	0	-	29	0
Clinicopathological findings in female-to-male gender-affirming breast surgery	East et al. 2017, RC	68	31.5	60	13	17	27	1
Histology of genital tract and breast tissue after long-term testosterone administration in a female-to-male transsexual population.	Grynberg et al. 2010, RC	100	28.9 ± 0.9	100	-	n/a	93	0
Clinicopathological study of breast tissue in female-to-male transsexuals.	Kuroda et al. 2008, RC	186	27.4	56	-	68	88	4

*RC: Retrospective Cohort; PC: Prospective Cohort; *:age reported in years, FHx: Family History.*

secretory/lactational changes, benign vascular lesions, cavernous hemangiomas, duct ectasia, microcalcifications or calcifications, fibroadenomatous changes, sclerosing adenosis, and intraductal papilloma were considered benign lesions. All reported lesions are described in Table 2. Due to inconsistency in reporting, further analysis was not performed to assess the impact of certain risk factors including hormone therapy, and family history.

Discussion.

Factors Affecting Cancer Development:

Age: The incidence of breast cancer in cisgender women increases with age, becoming significant after the age of 26 years [9]. In average risk individuals, the age at which breast cancer screening should begin is between 40-44 years old [10]. In cisgender women with a family history of breast cancer, screening is recommended beginning at 10 years before the earliest age of diagnosis in the family member.

Hellquist et al. found an 18% mortality reduction in cisgender women who were screened between 40-44 years old, and a 32% mortality reduction in cisgender women ages 45-49 [11]. Breast cancer risk continues to increase in cisgender women until the ages of 75-79, with only26% of deaths due to breast cancer diagnosed after the age of 74. Current recommendations include ongoing screening only if the life expectancy of an individual is at least 10 years or more [12]. Screening of cisgender women over than age 75 as well as those under the age of 40 raises concerns such as unnecessary radiation exposure [13].

In cisgender women undergoing reduction mammaplasty (RM), age is associated with increased pathologic findings on specimen analysis [14,15]. Sears et al., found that cisgender women who underwent RM under the age of 40 were more than five times less likely to have an incidental malignancy compared to those who underwent RM at 40 years and older (0.05-0.06% *vs.* 0.29-0.98%) [16]. Additionally, cisgender women who underwent RM under the age of 40 were nine times less likely to be diagnosed with dysplasia compared to those who underwent RM at 40 years or older (0.03-0.08% *vs.* 0.27-0.98%) [16].

In the present analysis, the average age of patients undergoing GAM was between the ages of 25.8 to 31.5 years [17,18]. While

Table 2. *Pathology specimen classification reported in papers including in meta-analysis.*

First Author, Year	Normal Acini	Normal Ducts	Fibrosis	Cysts	Apocrine Metaplasia	Epithelial/ Ductal Hyperplasia	Gynecomastoid Changes	PASH	Inflammation	Columnar Cell change	Secretory/ Lactational changes	BVL	Cavern-ous heman-gioma	Duct Ectasia	MC/C*	FA	Sclerosing Adenosis	Intra-ductal Papil-loma	ALH	LCIS	LCIS + ALH	FEA	Atypical Hyper-plasia	ADH
Jacoby et al., 2021																5	3	3	1	1				4
Hernandez et al. 2020																					1			5
Torous et al., 2019				62	47	38	60	28	36	5	6	12			32	44	1	3	3	1				3
Van Renterghem et al., 2018		178			83	57				102	13		1			13	11			2				5
Burgess et al., 1993	28	29	29	13	15	9									8									
East et al., 2017				22	16	3	22				2			12		11	5	1				1		
Grynberg et al., 2010			93				0									2		0		0	0	0		0
Kuroda et al., 2008				40	23											10	6			1			3	

this age group is not usually at a high risk for breast malignancy, cases have been reported that do not follow expected trends. Salibian et al. published a case report of a 29-year-old individual with no known high-risk genetic mutations who underwent GAM and was found to have DCIS [19]. The advantage of identification of incidental lesions includes the ability to access preventive care and/or intervene when necessary.

Familial History of Malignancy: Cisgender women with a family history of breast cancer have a significantly higher risk of developing breast cancer [20,21]. Nelson et al., found that the risk of breast cancer was highest in cisgender women with first degree relatives with breast cancer, the highest risk being in women with three or more first-degree relatives diagnosed with breast cancer [20]. This risk is further increased in cisgender women with a first-degree relative diagnosed with breast cancer under the age of 40 when compared to the risk of breast cancer in cisgender women with a first degree relative diagnosed at age 50 or older [20]. Similarly, Brewer et al. found that patients who had a relative with breast cancer diagnosed before 45 years were at a significantly increased risk of developing breast cancer themselves [21]. These findings highlight the importance of considering both family history and age of the family member at the time of diagnosis in determining patient risk of developing breast cancer.

Hartmann et al. looked at the impact of family history on the risk of developing breast cancer in patients with non-proliferative disease (cysts, apocrine metaplasia, mild hyperplasia without atypia), proliferative disease without atypia, and atypical hyperplasia. The study found an increased risk of breast cancer in cisgender women with a strong family history (i.e., at least one first-degree relative with breast cancer before 50 years of age or two or more relatives with breast cancer with at least one being a first-degree relative) of these pathologies, especially atypical hyperplasia and/or the occurrence of three or more foci of atypia [22]. Similar trends have been observed in women who undergo RM. Hernandez et al. defines significant pathologic findings as the presence of ALH, ADH, LCIS, DCIS, or invasive carcinoma [14]. In this study the authors found that 3 out of 41 (7.3%) patients with a family history of breast cancer had significant findings on their RM specimen [14]. This was higher than that of the transgender patient cohort in which only 1 out of 30 (3.3%) patients has a family history of breast cancer and significant findings. However, in a study by Fisher et al. of 155 patients who underwent RM, family history was positively correlated with significant pathology findings (p=0.026) [23].

Multiple studies of GAM pathology reported an association between patients with a first-degree relative with cancer and pre-malignant/malignant pathologic findings. Jacoby et al. reported one case of LCIS in a patient who had a family history of maternal breast cancer [23]. Torous et al. reported one case of DCIS in a patient who had a family history of paternal breast cancer [24]. Van Renterghem et al. reported that 1 patient with malignant pathologic findings of an invasive carcinoma surrounded by DCIS and LCIS had a positive family history of breast and endometrial cancer [17]. While these examples show that family history of breast cancer may increase the risk of pre-malignancy/malignancy found on pathologic evaluation, further investigation is required to determine the significance of

this variable in transgender men and compare these findings to those of cisgender women.

Hormones: The impact of testosterone on breast cancer risk is unclear. While multiple studies indicate that androgen administration has no impact on breast cancer [14,25,26]. Some limited research indicates that excess circulating levels of androgen may increase the risk of breast cancer in transgender men [18,23]. In their retrospective study of 148 transgender individuals undergoing breast reduction or mastectomy, Torous et al. reported that88% of patients underwent androgen therapy by the time of surgery (duration = 3 month – 5 years).They hypothesized that androgens may contribute to the development of malignancy, however noted a lack of significant atypical lesions found when compared to the age matched comparison group [24]. However, it is unclear which participants in this study [24] were receiving androgen therapy, and if high, normal or subtherapeutic levels of androgens were administered. Other researchers have also found that androgens do not impact the incidence of breast malignancy found on pathology [14,25,26]. Further study is necessary to assess the underlying pathophysiology and potential impact of androgen therapy on the risk of breast cancer development in transgender men.

Patient Evaluation Methods.

Pathology Assessment: Currently, in patients undergoing non-oncologic breast surgery, there is no standardized pathology assessment protocol for resection specimens [27]. Specimen evaluation may also vary by region (i.e., The United States and Europe). In addition, pathology specimens obtained from these procedures are fragmented due to the surgical technique, and or tissue plains are disrupted due to concomitant procedures i.e., liposuction making it difficult to assess margin status in the case of possible malignancy.

The lack of protocol standardization contributes to difficulty in interpreting results of pathology specimens in GAM as institutions varied significantly in the amount of tissue specimens submitted for histologic assessment and the protocols used for tissue sectioning. For example, some specimens may only be sent for gross or limited microscopic examination, potentially resulting in a lower threshold for discovering significant pathologic findings [23]. Similarly, the use of less tissue blocks per specimen may miss pathology. Hernandez et al. reported surveying 16 tissue blocks per specimen, Grynberg et al. surveyed between 2 and 10 sections per specimen, and Van Renterghem et al. reported surveying 5 tissue blocks per specimen [14,17,25]. Hernandez et al. also reported examining 2.8 times more slides for GAM cases compared to RM cases [14]. Similarly, of the remaining five studies included in this analysis, the number of blocks per specimen and the amount of tissue submitted for evaluation varied or was not reported. This variation in total specimens collected per patient may contribute to varying reports of premalignancy among each paper, resulting in a wide range of reported rates (0% to 4.05%) [24,25,28]. These inconsistencies highlight the need for standardization of protocols [27].

Classification Methods: Different classifications of pathology specimens were also reported, making comparison across studies difficult. Jacoby et al. included complex fibroadenoma, sclerosing adenosis, solitary papilloma, intraductal papilloma, ADH, ALH, DCIS, LCIS, and invasive malignancy as high risk and malignant lesions [24]. Hernandez et al. reported only ADH, ALH, DCIS, LCIS, and invasive carcinoma as high-risk pathology [14]. Van Renterghem et al. included columnar cell lesions (columnar cell changes and columnar cell hyperplasia), apocrine metaplasia (not assessed in subareolar area), sclerosing adenosis, lactational changes, fibroadenomas, usual duct hyperplasia, atypical duct hyperplasia, flat epithelial atypia, DCIS, LCIS and invasive carcinoma [17]. Grynberg et al. focused on intraductal hyperplasia and carcinoma and also included a marked reduction of glandular tissue and a proliferation of fibrous connective tissue, severe lobular atrophy, mildly atrophic or stromal changes, fibrocystic lesions and adenofibromas. East et al. included fibrocystic changes, simple cysts, apocrine metaplasia, adenosis, usual ductal hyperplasia, gynecomastoid changes, fibro adenomatoid change, duct ectasia, lactational changes, intraductal papilloma and flat epithelial atypia [18]. Torous et al. classified their findings as benign or significant. Significant findings included ADH, ALH, DCIS, LCIS and invasive carcinoma [24]. Kuroda et al. included carcinoma, ADH, ALH, mild to moderate hyperplasia, apocrine metaplasia, blunt duct adenosis, cyst, fibro adenomatosis, sclerosing adenosis [26]. Burgess et al. included normal acini, normal ducts, fibrosis, cysts, apocrine metaplasia, epithelial hyperplasia, microcalcification, and lymphocytic infiltration [28]. The lack of a standardized classification of findings may contribute to the range of incidences of pathologic findings in surgical specimens reported in the literature.

Preoperative Imaging: No standard pre-operative imaging protocols exist for patients undergoing RM or GAM. Many surgeons defer preoperative imaging or obtain imaging for high-risk patients only [29]. Others may obtain imaging according to pre-existing guidelines for cisgender women [30,31]. The American College of Radiology Guidelines says that women should undergo routine mammography no later than the age of 45 years old [32]. However, in some cases, routine screening protocols fail to detect malignancy when post-operative pathologic evaluation has found significant pathology. Ambaye et al. found that while the majority of patients with significant pathologic findings underwent screening mammograms within a year prior of RM, no findings were detected on preoperative screenings. Significant findings were only identified post-operatively [27]. Keleher et al. reported that pre-operative imaging may have prevented intra-operative diagnosis in three patients who did not undergo pre-operative mammography [32]. However, in another patient with intra-operative diagnosis, who did have pre-operative screening, no malignancy was found even with suspicion based on physical examination (firmness on palpation). Pre-operative diagnosis is beneficial in allowing for better surgical planning, as well as preparation for potential non-surgical treatments if necessary [33,34].

Cost: Sears et al. compared the total cost of RM with and without pathologic evaluation and found that the average total cost, defined as all diagnostic services including pathologic evaluation on the day of or up to seven days after surgery (included total reimbursement for facility and provider claims,

including insurer payments, coinsurance, copayment, and deductibles), was $12,387, compared to $11,469 without pathologic evaluation, with the mean cost of pathology claims totaling $307 [16]. Sears et al. also compared the cost benefits of pathologic evaluation between patients under and over the age of 40. In women under 40, screening of 1,747 specimens was required to detect a single new occult breast cancer [16]. This would result in an additional $536,000 in cost on average. In contrast, in women over 40, screening of 279 specimens was required to detect a single new occult breast cancer, resulting in an additional cost of $85,000 on average.

Limitations.

There are two limitations to this systematic review. First, although the authors of this article have attempted to perform a systematic review, there may have been reports missed in the published literature resulting by the inherent nature of a retrospective review. Other factors which may have contributed to this limitation is underreporting of cancer cases or incomplete reporting of cancer cases. Second, the conclusions made by the authors of this article were based on a limited number of cases with non-universally standard pathological evaluations, making a cohesive algorithm or guideline unachievable. The articles included in this study lacked appropriate patient follow up, had significant variability in their sample sizes, pre-operative imaging, pathology analytical methods, and use of occasional nonstandard classification methods among other key factors that would have allowed for a cohesive and detailed algorithm to be achieved.

Conclusions.

Although analysis of studies evaluating the pathology identified in post-GAM breast specimens shows a 2.42%overall rate of pre-malignant / malignant lesions, there is not enough published evidence to create a guideline or algorithm for pathological assessment of GAM. However, complete, and standard tissue evaluation performed for breast cancer pathology protocol and radiology pre-op evaluation should be continued until enough published literature can conclude an algorithm. Certain patient demographics including an older age or a past medical and family history of breast cancer may justify routine pathologic evaluations, however, inconsistencies in data reported in the included studies prevented further analysis of these associations and their implications. While in most GAM specimens, pathologic evaluations do not yield significant findings, the non-zero rate of pre-malignant and malignant lesions should not be overlooked. Standardization in protocols, specimen classification, and pre-operative imaging procedures for high-risk transgender individuals should be encouraged in order to better define risk factors for malignancy and to identify trends. More research must be done in order to create a thorough guideline or algorithm for pathological assessment of GAM. With such data, a GAM evaluation algorithm which identifies premalignant and malignant lesions while efficiently using healthcare resources would be possible. With more patients desiring GAM, such guidelines will help increase health equity and provide the best care for transgender individuals in the future.

Conflict of interest statement.
All authors declared that there are no conflicts of interest

Authors' contributions.
All of the authors have contributed towards the preparation of the manuscript, have read, and approved the final version of the manuscript. Made substantial contributions to conception and design of the study and performed data analysis and interpretation: Hamidian Jahromi A; Horen S; Ho K; Tran E; Roth A; Schechter L.

Performed data acquisition, as well as provided administrative, technical, and material support: Horen S; Ho K; Tran E; Roth A

Availability of data and materials: Not applicable.

Financial support and sponsorship: None.

Ethical approval and consent to participate: Not applicable.

REFERENCES

1. American Cancer Society. How Common Is Breast Cancer? Breast Cancer Statistics. 2021.
2. National Breast Cancer Foundation. What is Breast Cancer? Risk Factors. 2020.
3. de Blok CJM, Wiepjes CM, Nota NM, et al. Breast cancer risk in transgender people receiving hormone treatment: Nationwide cohort study in the Netherlands. BMJ. 2019;365:l1652.
4. Slagter MH, Gooren LJG, Scorilas A, et al. Effects of Long-term Androgen Administration on Breast Tissue of Female-to-Male Transsexuals. J Histochem Cytochem. 2006;54:905-910.
5. Ray L, DNP. What trans men and nonbinary people need to know about breast cancer. 2019.
6. Brown GR, Jones KT. Incidence of breast cancer in a cohort of 5,135 transgender veterans. Breast Cancer Res Treat. 2014;149:191-198.
7. Lane M, Ives GC, Sluiter EC, et al. Trends in Gender-affirming Surgery in Insured Patients in the United States. Plast Reconstr Surg Glob Open. 2018;6:e1738.
8. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339:b2535.
9. Committee on Practice Bulletins—Gynecology, Pearlman M, Jeudy M, Chelmow D. Practice Bulletin No. 179 Summary: Breast Cancer Risk Assessment and Screening in Average-Risk Women. Obstetrics & Gynecology. 2017;130:241-243.
10. Oeffinger KC, Fontham ET, Etzioni R, et al. Breast Cancer Screening for Women at Average Risk. Journal of American Medical Association. 2015;314:1599.
11. Hellquist BN, Duffy SW, Abdsaleh S, et al. Effectiveness of population-based service screening with mammography for women ages 40 to 49 years: evaluation of the Swedish Mammography Screening in Young Women (SCRY) cohort. Cancer. 2011;117:714-722.
12. Howlander N, Noone A, Krapcho M, et al. SEER Cancer Statistics Review, 1975–2012. Bethesda, MD: National Cancer Institute. 2015.
13. Sima CS, Panageas KS, Schrag D. Cancer screening among patients with advanced cancer. JAMA. 2010;304:1584-1591.
14. Hernandez A, Schwartz CJ, Warfield D, et al. Pathologic Evaluation of Breast Tissue from Transmasculine Individuals

Undergoing Gender-Affirming Chest Masculinization. Arch Pathol Lab Med. 2020;144:888-893.
15. Clark CJ, Whang S, Paige KT. Incidence of Precancerous Lesions in Breast Reduction Tissue: A Pathologic Review of 562 Consecutive Patients. Plastic and Reconstructive Surgery. 2009;124:1033-1039.
16. Sears ED, Lu Y, Chung T, et al. Pathology Evaluation of Reduction Mammaplasty Specimens and Subsequent Diagnosis of Malignant Breast Disease: A Claims-Based Analysis. World Journal of Surgery. 2019;43:1546-1553.
17. Renterghem SM, Dorpe JV, Monstrey SJ, et al. Routine histopathological examination after female-to-male gender-confirming mastectomy. British Journal of Surgery. 2018;105:885-892.
18. East EG, Gast KM, Kuzon WM, et al. Clinicopathological findings in female-to-male gender-affirming breast surgery. Histopathology. 2017;71:859-865.
19. Salibian AA, Axelrod DM, Smith JA, et al. Oncologic Considerations for Safe Gender-Affirming Mastectomy: Preoperative Imaging, Pathologic Evaluation, Counseling, and Long-Term Screening. Plastic Reconstr Surg. 2021;147:213e-221e.
20. Nelson HD, Zakher B, Cantor A, et al. Risk Factors for Breast Cancer for Women Aged 40 to 49: A Systematic Review and Meta-analysis. Annals of Internal Medicine. 2012;156:635-648.
21. Brewer HR, Jones ME, Schoemaker MJ, et al. Family history and risk of breast cancer: An analysis accounting for family structure. Breast Cancer Research and Treatment. 2017;165:193-200.
22. Hartmann LC. Benign Breast Disease: Toward Molecular Prediction of Breast Cancer Risk. New England Journal of Medicine. 2009.
23. Fisher M, Burshtein AL, Burshtein JG, et al. Pathology Examination of Breast Reduction Specimens: Dispelling the Myth. Plastic and Reconstructive Surgery - Global Open. 2020;8:e3256.
24. Torous VF, Schnitt SJ. Histopathologic findings in breast surgical specimens from patients undergoing female-to-male gender reassignment surgery. Modern Pathology. 2019;32:346-353.
25. Grynberg M, Fanchin R, Dubost G, et al. Histology of genital tract and breast tissue after long-term testosterone administration in a female-to-male transsexual population. Reprod BioMed Online. 2010;20:553-558.
26. Kuroda H, Ohnisi K, Sakamoto G, et al. Clinicopathological study of breast tissue in female-to-male transsexuals. Surg Today. 2008;38:1067-1071.
27. Ambaye AB, Goodwin AJ, Maclennan SE, et al. Recommendations for Pathologic Evaluation of Reduction Mammoplasty Specimens: A Prospective Study with Systematic Tissue Sampling. Archives of Pathology & Laboratory Medicine. 2017;141:1523-1528.
28. Burgess HE, Shousha S. An immunohistochemical study of the long-term effects of androgen administration on female-to-male transsexual breast: A comparison with normal female breast and male breast showing gynaecomastia. The Journal of Pathology. 1993;170:37-43.
29. Klement KA, Hijjawi JB, Neuner J, et al. Discussion of preoperative mammography in women undergoing reduction mammaplasty. Breast J. 2019;25:439-443.
30. Sears ED, Lu Y, Swiatek PR, et al. Use of Preoperative Mammography During Evaluation for Nononcologic Breast Reduction Surgery. JAMA Surg. 2019;154:356-358.
31. Campbell MJ, Clark CJ, Paige KT. The role of preoperative mammography in women considering reduction mammoplasty: A single institution review of 207 patients. Am J Surg. 2010;199:636-640.
32. Keleher AJ, Langstein HN, Ames FC, et al. Breast Cancer in Reduction Mammaplasty Specimens: Case Reports and Guidelines. Breast J. 2003;9:120-125.
33. https://documents.cap.org/protocols/cp-breast-invasive-resection-20-4400.pdf
34. https://www.acr.org/Clinical-Resources/Breast-Imaging-Resources.