Review Article

Gynecomastia

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Abstract: This review article provides an overview of gynecomastia based on the current available literature. Despite being the most common breast condition in men, there is a paucity of quality data and a lack of consensus on diagnosis, classification, workup, and treatment options. True gynecomastia must be distinguished from pseudogynecomastia. While the etiology is often multifactorial, gynecomastia is often related to an elevated estrogen to androgen balance. Etiologic factors can often be divided into physiologic and nonphysiologic (pharmacologic, pathologic, and idiopathic) causes. While the majority of gynecomastia is asymptomatic, some develop breast pain or may palpate a retroareolar mass. There have been psychosocial ramifications of patients including reduced self-esteem, mood disorders and body dysmorphic disorders. A thorough history and physical exam remain the mainstay for diagnosis. True gynecomastia is detected on physical exam as a mobile concentric disk of firm tissue beneath the nipple-areolar complex. Laboratory testing, imaging, and biopsy are not routinely required except in cases where pathologic etiology, including breast cancer, cannot be ruled out. The treatment of choice for most cases involves sympathetic reassurance and observation as the majority of cases self-resolve within a few years. Recurrence rates are highly variable dependent on etiology. Select patients may be considered for treatment with medication, radiotherapy and/or surgical management. Adequate planning and alignment of patient expectations are imperative for optimal patient satisfaction.

Keywords: Gynecomastia; pseudogynecomastia; lipomastia

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Introduction

Gynecomastia, which stems from the Greek "gyne" meaning women and "mastos" meaning breast, describes excessive benign development of the male breast(s) due to proliferation of glandular tissue (1,2). Gynecomastia is the most common breast condition in males (3-5) with a prevalence ranging between 30–70% (1,4,6,7) of the population and occurs bilaterally in 50% of patients (3,7). There is lack of consensus on a standard grading scale for gynecomastia with multiple scales, based upon physical exam and fat versus glandular composition, currently being utilized which are summarized in *Table 1* (3,8-11).

Most gynecomastia is asymptomatic (6). Symptoms may include palpation of a retroareolar breast mass and/or enlargement of the breast(s). Breast pain and tenderness, most prevalent in adolescent gynecomastia, most commonly occurs in the first 6 months of gynecomastia during proliferation of the glandular tissue (7,12). Nipple discharge is very uncommon (13) and should prompt a diagnostic workup as nipple discharge is present in 10% of breast cancers (7). Psychological consequences include depression, anxiety, disordered eating, body dysmorphic disorder, and reduced self- esteem (1,4,14,15).

Traditionally, gynecomastia alone was not thought to have an elevated risk of breast cancer (12,13), however, factors

Table 1 Summary of gynecomastia grading scales

Grade	Description
1	Mild hypertrophy (10) <250 grams (8) limited to the areolar region (3,10)
A	Primarily glandular (9) with no skin redundancy (10)
B	Primarily fibrous (9) with skin redundancy
2	Moderate hypertrophy (10) between 250–500 grams (9) without ptosis (3) or above the IM fold (10)
A	Primarily glandular (9) without skin redundancy (8)
B	Primarily fibrous (9) with skin redundancy (8)
3	Severe hypertrophy >500 grams (9) with mild ptosis (11) and marked skin redundancy (3,10) or NAC located at or ~1 cm below the IM fold (10,11)
4	Severe hypertrophy >500 grams (9) with marked skin redundancy (3,10) and moderate to severe ptosis (1,3) or NAC more than 1 cm below the IM fold (10)

Table 1 provides a summary of available gynecomastia grading scales given lack of a consensus on grading in the current body of literature (3,8-11). Simon *et al.* describes gynecomastia in general terms of enlargement with or without skin redundancy (8). Rohrich *et al.* uses weight based determination of gynecomastia with the addition of (l) for glandular gynecomastia and (ll) for fibrous gynecomastia in grade I and II and the absence or presence of ptosis in grade III and IV (9). Cordova *et al.* utilized general terms of enlargement in reference to the nipple-areolar complex and inframammary fold to determine grading (10). Ratnam *et al.* utilized general terms of enlargement with presence or absence of the inframammary fold (11). NAC, nipple-areolar complex; IM, inframammary fold.

associated with increased incidence of gynecomastia, for instance estrogen exposure and androgen deficiency, may also increase the risk of breast cancer (13,16-18). Brinton *et al.* performed a meta-analysis indicating a significant association between male breast cancer and gynecomastia (OR 9.78; 95% CI: 7.52–12.71) (19).

Differential diagnoses include diabetic mastopathy (13), benign breast changes, and pseudogynecomastia. Male benign breast disease includes atypical lesions of the breast, dermoid cysts, duct ectasia, fat necrosis, hamartomas, hematomas, intramammary lymph nodes, lymphangiomas, lymphoplasmacytic inflammation, lipomata, mastitis, neurofibroma, sebaceous cysts, and papillomas (12,13). Pseudogynecomastia, also known as lipomastia refers to increased breast size due to fat deposition in the absence of glandular hyperplasia (13). Pseudogynecomastia may be bilateral with or without skin excess and most commonly occurs in obese patients (13).

Etiology

Cases of gynecomastia are usually multifactorial. Hormonal imbalance due to an elevated estrogen to androgen ratio may result in glandular breast proliferation (4,5). The etiology of gynecomastia is typically divided into physiologic and nonphysiologic categories with nonphysiologic gynecomastia further subdivided into pharmacologic, pathologic, and idiopathic causes (5,6,12,13,20). The diagnosis of physiologic and idiopathic gynecomastia, each accounting for approximately 25% of gynecomastia (5,6,12,13), should not be made until other underlying etiologies have been excluded (12).

Physiologic gynecomastia

The term physiologic gynecomastia refers to expected hormonal fluctuations that occur throughout development and aging. The prevalence of physiologic gynecomastia is felt to vary widely based on a trimodal distribution (12) with incidence between 60–90% in neonates (1,3,4), 50–60% in adolescents (1,3,4) and 60–70% in the elderly (also known as gynecomastia of senescence) (1,4,5,12). Neonatal transient breast hypertrophy (13) occurs in up to 90% (12) of newborns due to maternal placental estrogens (5,6,12). The work up of suspicious neonatal gynecomastia should be delayed until at least 1 year of age (4,5). Adolescent physiologic pubertal gynecomastia (7) most commonly occurs between 13 to 15 years old (7,13) and spontaneously regresses in up to 95% (13,21) of cases by 6 months to 2 years (12).

Nonphysiologic gynecomastia

Nonphysiologic gynecomastia encompasses pharmacologic,

Table 2 Pharmacologic causes of gynecomastia

Drug class	Agent
Antibiotics	Ethionamide, metronidazole, minocycline, anti-tuberculosis (isoniazid)
Antifungals	Ketoconazole*
Antiretrovirals	Protease inhibitors
Cardiovascular agents	Spironolactone*, calcium channel blockers (nifedipine£, verapamil£, amlodipine, diltiazem, felodipine), angiotensin converting enzyme inhibitors (captopril, enalapril, lisinopril), anti-arrhythmics (amiodarone, digitalis), digoxin, furosemide, methyldopa, reserpine
Chemotherapeutics	Alkylating agents£, methotrexate, cyclophosphamide, dasatinib, imatinib
Environmental exposure	Phenols, phthalates, phytoestrogens [lavender, tea tree oil, ginseng, hops (beer), tribulus terrestris, herbicides, licorice, black cohosh, red clover, dong quai and high dose soy products (>300mg/daily)], lead, meat or milk products of animals treated with estrogens
Gastrointestinal agents	Anti-acids [H2- receptor blockers (cimetidine*, ranitidine), proton pump inhibitors (omeprazole£, lansoprazole, rabeprazole)], prokinetics (domperidone, metoclopramide), misoprostol
Hormones	estrogens*, antiandrogens (bicalutamide*, flutamide*, cyproterone acetate*, nilutamide), 5α-reductase inhibitors (dutasteride*, finasteride*, epristeride, alfatradiol), human growth hormone (hGH)*, human chorionic gonadotropin (hCG)*, gonadotropin-releasing hormone (GnRH) analogs (goserelin*, leuprorelin*), anabolic steroids£, androgens, clomiphene citrate, corticosteroids, cyproterone, diethylstilbestrol
Miscellaneous	HIV medications [efavirenz£, nucleoside reverse transcription inhibitors (NRTI) (stavudine), protease inhibitors (indinavir, saquinavir)], ethanol/alcohol£, opioids (heroin£, methadone£), anti-convulsants (phenytoin, pregabalin, gabapentin), amphetamines, auranofin, benserazide, certirizine, diethylpropion, entecavir, etretinate, marijuana, mirtazapine, loratadine, phenytoin, penicillamine, anti-lipidemics [statins (atorvastatin, pravastatin, and rosuvastatin), fibrates (fenofibrate)], sulindac, theophylline, thiacetazone
Psychiatric agents	Risperidone£, first-generation neuroleptics (thioridazine, trifluperazine, prochlorperazine, perphenazine, sulpiride), atypical anti-psychotics (aripiprazole, clozapine, olanzapine, quetiapine, ziprasidone, haloperidol), anti-depressants [selective serotonin reuptake inhibitors/selective norepinephrine reuptake inhibits (SSRI/SNRI) (fluoxetine, paroxetine, venlafaxine, duloxetine)], benzodiazepines (diazepam), phenothiazine, tricyclic antidepressants

Level of evidence of strength of correlation of medication with gynecology is indicated by * for good and £ for fair (3,5,7,9,12,13,18,20,22-25). The remaining medications have a limited or poor quality of evidence for association with gynecomastia.

pathologic and idiopathic etiologies. Nonphysiologic gynecomastia, in contrast to physiologic gynecomastia, can occur at any age (12). The most common cause of nonphysiologic gynecomastia is persistent pubertal gynecomastia and should prompt further workup if persistent beyond 2 years (12).

Another common cause is pharmacologic and the medications that cause this are numerous. These can include antiandrogens, antibiotics, antifungals, antihypertensives, antiretrovirals, chemotherapeutics, environmental exposures, hormones, gastrointestinal agents, psychiatric medications, and other agents. Even significant bilateral testicular trauma may lead to decreased testosterone production and resultant gynecomastia (12). A compilation of pharmacologic agents associated with gynecomastia, based on the quality of evidence in the literature, is listed in *Table 2* (3,5,7,12,13,18,20,22-25).

Pathologic causes of nonphysiologic gynecomastia have a broad differential (6) including chronic liver disease, chronic renal disease, diabetes, heart failure, thyroid disorders, gastrointestinal abnormalities, and neoplasms, among others. Diabetes, for instance, may lead to diabetic mastopathy characterized as a lymphocytic inflammatory infiltration of the mammary ducts in long-standing type 1 diabetes (13). Gynecomastia also occurs in 10–40% (12) of patients with hypothyroidism but may also occur in hyperthyroidism as well (5). Malnutrition is seen in up to 40% of renal failure patients and has been suggested to also contribute to gynecomastia (12). Meanwhile, primary (testicular) or secondary (central) gonadal failure, pseudohermaphroditism, true hermaphroditism, and androgen resistance syndromes are also causes of

gynecomastia (6), with gynecomastia occurring in up to 50–70% of patients with Klinefelter syndrome (47 XXY) (5,12,13) who carry a 20–50 times higher risk for breast cancer than men in the general population (4,13,26). Neoplasms account for the etiology of 3% (12) of gynecomastia cases including adrenocortical and testicular neoplasms. Testicular tumors (Leydig, Sertoli, human chorionic gonadotropin (hCG) producing and choriocarcinomas) are rare, with approximately 10% of these patients presenting with gynecomastia alone (12). Other pathologic causes are myriad, including cystic fibrosis, tuberculosis, hemochromatosis, metabolic syndrome, herpes zoster infection, and myotonic dystrophy.

Work up

History

A thorough history and physical is the mainstay for diagnosis of gynecomastia. This should include a detailed timeline of the patient's signs and symptoms, including the date of onset. A past medical history and family history, including a history of BRCA germline mutations and Klinefelter's syndrome (4), should be obtained. Medication, recreational drug, and environmental exposures should be reviewed. Any history of testicular trauma or pathology should also be elucidated (12).

Physical examination

A complete physical examination should be performed with attention paid to the breast, lymphatics, thyroid, abdominal and testicular findings. For patients with true gynecomastia, the breast exam will typically reveal a mobile, concentric disc of firm tissue, measuring at least 2 cm (1,2), located directly beneath the nipple-areolar complex (13). These classic exam findings can typically distinguish true gynecomastia from those patients with pseudogynecomastia or breast cancer. Breast cancer is typically distinguished on physical exam by a unilateral, hard, irregular mass that may be located anywhere in the breast which may have associated skin dimpling, fixation, nipple retraction and/or axillary lymphadenopathy (7,13). Any concern for malignancy, including suspicious lymphadenopathy and/or testicular masses, should prompt a diagnostic work up. Physical examination can differentiate pseudogynecomastia, typically found in obese patients, which typically lacks the discrete, focal, retroareolar firm tissue (13) noted in true gynecomastia.

Laboratory testing

Routine laboratory testing, in the absence of suspicious history or physical examination findings, is not recommended (4,7,13). In significant or concerning cases, after elimination of physiologic causes of gynecomastia, a biochemical evaluation may be considered (5). Such an assessment may include liver function tests, serum creatinine, testosterone, estradiol (E2), follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin, thyroid stimulating hormone (TSH), free thyroxine (T4), sex hormone-binding globulin (SHBG) and beta (β-hCG) (5,12,13) to address many of the common causes noted above. Testosterone and LH, when drawn, need to be measured in the morning at their highest levels given normal circadian rhythm fluctuations (12,13). If total testosterone is borderline or low, then a free testosterone can confirm hypogonadism (7). Serum β-hCG, serum dehydroepiandrosterone sulfate, or urinary 17-ketosteroids can be used to evaluate for testicular, adrenal, and other tumors (12) as a potential cause. If serum estradiol or hCG are elevated then testicular ultrasound should be performed to rule out an underlying malignancy (4).

Imaging

Routine imaging studies are not typically recommended for clear cases of gynecomastia and the need should be guided by physical examination and clinical history (12). Breast imaging, diagnostic mammography, and diagnostic ultrasound, should be performed in those patients having questionable or suspicious physical features. Breast imaging should also be considered in those with a high familial risk, known deleterious BRCA mutation or those with Klinefelter's syndrome (13), who present with breast concerns. Diagnostic ultrasound is recommended as the initial imaging modality of choice in men less than 25 years of age with an indeterminate palpable mass by The American College of Radiology (18,27). Classic findings of gynecomastia that are pathognomonic include a hypoechoic retroareolar mass that, sometimes poorly defined, is typically flame-shaped as demonstrated in *Figure 1* (13). Diffuse glandular enlargement associated with prolonged anti-androgen use is depicted in *Figure 2*. Clinical suspicion should guide the need for testicular or abdominal imaging to evaluate for testicular or adrenal carcinoma, respectively (12).

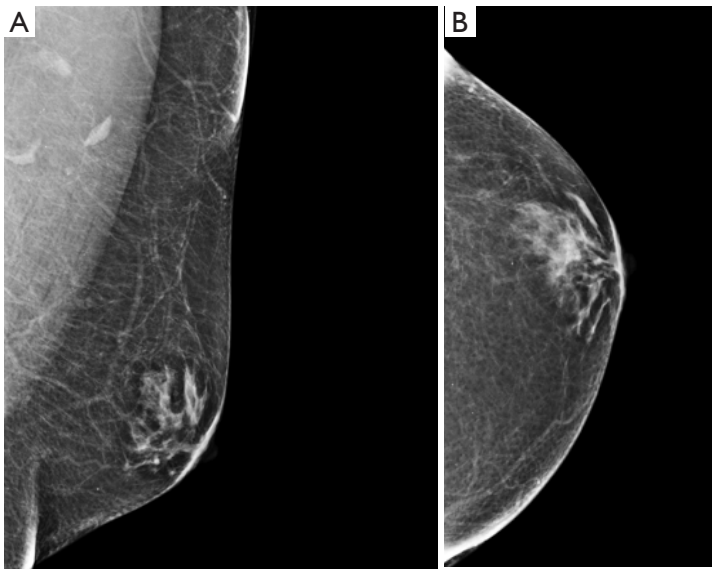

Figure 1 A 65-year-old man with retroareolar gynecomastia demonstrated on these mammogram images showing a classic flame-shaped retroareolar mass with indistinct borders blending into the surrounding adipose tissue on the left breast MLO (A) and left breast CC (B) view.

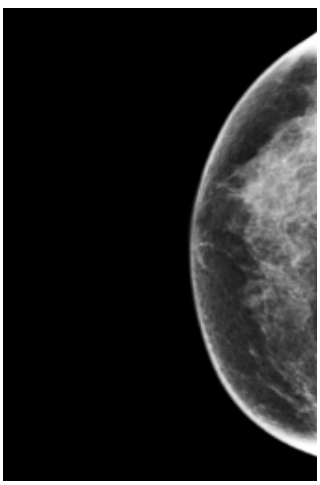

Figure 2 A 70-year-old man with a history of prostate carcinoma with gynecomastia on mammogram indicated by diffuse glandular enlargement consistent with prolonged anti-androgen use on the right breast CC view.

Percutaneous biopsy

Percutaneous biopsy is not routinely required if history and exam are consistent with gynecomastia. However, percutaneous biopsy should be considered when carcinoma is unable to be ruled out based upon clinical and imaging findings alone (12,13). Histologic findings of gynecomastia include ductal epithelial hyperplasia with increased stromal and periductal connective tissues (5).

Treatment

The treatment of asymptomatic idiopathic and physiologic gynecomastia, in the absence of features suggesting underlying disease or malignancy, involves sympathetic reassurance and observation (1,12). Ninety percent of cases resolve on their own within a few years (1). Pharmacologic or surgical treatment may be considered in select cases of pubertal gynecomastia for cosmesis, analgesia, or for psychological well-being (12). Biannual follow up may be considered to monitor for resolution (12).

In cases of non-physiologic gynecomastia, treatment of the underlying cause is usually required. Pharmacologically inducted gynecomastia should be treated with discontinuation or substitution of inciting medications, whenever possible, and serial examination for resolution (6). For pathologic gynecomastia, early identification and correction of the suspected acute underlying medical cause can often resolve the gynecomastia in a period as short as one month (4,7). However, longstanding gynecomastia that has been present longer than one year is less likely to regress spontaneously with restoration of hormonal balance because fibrosis is typically present for such cases that will not regress spontaneously (4,7).

Medical treatment

Recommendations for pharmacologic treatment of gynecomastia is limited to studies with small sample sizes, inconsistent methodologies, and lacking control groups (1,3,13). There is no clear consensus on the drug of choice or optimal duration of treatment. Furthermore, the fact that the majority of gynecomastia resolves spontaneously, makes interpretation of these studies challenging (1,7). Longstanding gynecomastia, defined as that greater than 1 to 2 years, is often more refractory to pharmacologic treatment given the underlying hyalinization and fibrosis that occurs over time (3). Tamoxifen, with doses ranging from 10–40 mg, given for 2–4 months has shown improvement in pain scores with regression of gynecomastia in up to 80% of patients (6,7,12,13,28-31). Raloxifene, 60 mg for 3–9 months (32), has also been utilized in the treatment of both pubertal gynecomastia (12,32) and gynecomastia associated with antiandrogen therapy for prostate cancer (12). Anastrozole, given at 1 mg/day (12), has also been used, given its aromatase inhibition, but has not been shown to be more effective than tamoxifen or placebo (6,7,13,33-35) possibly because peripheral aromatization is not the only source of estrogen in the adult male; Leydig cells and germ cells both create estrogen *de novo* in the testes as well (5), which would not be impacted by aromatase inhibitors. For the treatment of gynecomastia in patients undergoing antiandrogen therapy for prostate cancer, anastrozole appears to be less efficacious than tamoxifen for both prevention and treatment (36,37). Use of dihydrotestosterone (7,38), testolactone (7), danazol (7,12,39-41) and clomiphene citrate (7,12) have been described but have limited supporting literature. Treatment of underlying hypogonadism with testosterone replacement often reduces breast tenderness and gynecomastia (5) in part because testosterone is felt to competitively compete with the estrogen binding to its receptor (42).

Radiotherapy

Radiotherapy has been described for pharmacologic gynecomastia resulting from antiandrogen therapy for prostate cancer (43-47). A randomized controlled trial comparing radiotherapy in a prevention arm to use in a treatment arm, suggests that radiotherapy is most effective if given prophylactically before the administration of antiandrogens (45). However, meta-analysis performed by Viani and colleagues (47) indicate that tamoxifen appears to be two times more effective in the prevention of gynecomastia due to antiandrogen therapy for prostate cancer than radiotherapy.

Surgical therapy

Surgical treatment of gynecomastia is not first-line therapy, and usually only considered in patients with longstanding gynecomastia which is less likely to regress spontaneously or respond to medical treatment given the associated stromal fibrosis (3,4,7). Surgery is also considered in patients who have developed symptoms, including pain or psychologic distress, or aesthetic concerns that have been refractory to initial medical or conservative management attempts. The goal of surgical therapy for gynecomastia is to restore the patient's ideal body image while minimizing scarring (13). Thorough preoperative counseling should occur to elucidate the patient's expectations and to help assist the surgeon in determining optimal surgical treatment. For instance, patients who desire chest wall contouring may have more surgical scarring as versus patients that prefer to minimize scarring and opt for a targeted resection (48). Barriers to surgical treatment include high cost and limited insurance coverage (1,49).

Surgical treatment of gynecomastia involves removal of the hypertrophic retroareolar glandular tissue. Attention is given to the contour of the chest, elimination of the inframammary fold, correction of the nipple areolar complex position, removal of redundant skin, and creation of symmetry (13). There are a variety of approaches to the surgical management of gynecomastia which include minimal invasive options, a variety of mastectomy techniques, or a combination of approaches (50). It's important to remember that this is a contouring procedure and that the goal is not for complete excision of all breast tissue and fat. Removal of all such tissue is traditionally referred to as a subcutaneous mastectomy (7). Meanwhile, excision of the hypertrophic tissue in question may be performed in combination with liposuction to achieve a more cosmetically pleasing appearance (6). Additional considerations include the need to ensure adequate retroareolar tissue, typically a 1 cm even layer of fibrous tissue, in order to prevent contour defects and a saucer deformity (51). Mastectomy techniques can be divided into skin-sparing techniques, mastectomy with a component of skin resection, and simple mastectomy with free nipple grafts based on the severity of the gynecomastia and desired cosmetic outcomes (50). Mild cases of gynecomastia treated surgically can often be approached

through a periareolar incision for direct excision of glandular tissue via a crescent or circumareolar incision (Benelli type) (12,50,52). Moderate gynecomastia is often treated with direct excision with associated vertical or Wise pattern mastopexy incision (13), and an inframammary approach (6) for glandular excision with a pedicled nipple-areolar complex or a free nipple graft may be considered in cases of severe gynecomastia.

Minimally invasive approaches have also been described with the use of serial percutaneous biopsy techniques (53), endoscopic and vacuum assisted techniques (3,50,54-56), liposuction (5,50), or use of an ultrasonic scalpel (48). Liposuction is typically most effective for the treatment of adiposity associated with pseudogynecomastia rather than for the treatment of the fibrous glandular hypertrophy of true gynecomastia because of the density of the breast tissue that needs to be removed. However, minimally invasive options may be added to any of the mastectomy approaches outlined above for additional contouring (5,50). The Pull-Through technique involves a combination of minimally invasive incisions with resection of glandular tissue coupled with liposuction (50,52). Improved technology of radiofrequency-assisted liposuction (3) may further assist in removal of both fatty and more glandular tissue however direct excision of glandular tissue is often still required (6,13).

Given the breadth of surgical management options for gynecomastia, there is wide variation in published complications rates, ranging from 0 to 33% with an average of 13.1% (13,50,52). Factors including prolonged symptom duration and severity of gynecomastia have been associated with an increased surgical complication rate (12,48). Hematoma is the most common complication with an average of 5.8% while seroma rates average 2.4% (50). There have also been reports of infection, nipple necrosis and dehiscence (50). Hypoesthesia, which is often transient, ranging in incidence from 3–19% (13,50,52). Revision rates vary from 0–14.1% (50).

Recurrence and long-term outcomes

A study with a mean follow-up of 10.2 months has estimated recurrence rates of gynecomastia between 4.7–12.5% (57) with higher recurrence rates in those patients having lipomatous gynecomastia, defined as isolated adipose tissue hypertrophy, versus those with glandular gynecomastia (21). Long term recurrence rates, mean of 13.8 years, have been shown to be as high as 62.5% in those patients with lipomatous gynecomastia versus 12.5% in those with glandular gynecomastia with no statistically significant difference in BMI between the groups (21). Of note, the study design (21) of Fricke *et al.* highlights controversy within the current gynecomastia body literature as many studies would have excluded lipomatous gynecomastia as it may be more consistent with pseudogynecomastia. Recurrence may also occur if there is incomplete resection of mammary tissue at the time of surgery.

Adequate planning and alignment of the patient's expectations is imperative to achieve optimal satisfaction. Exploration of the patient's goals for surgery is crucial as it may guide treatment choices including use of medications or specific surgical techniques to balance optimal chest wall contouring while minimizing scaring (48). There are limited publications on quality of life data in patients after surgical treatment of their gynecomastia, which is further impacted by the fact that the majority of the existing data is from non-validated questionnaires administered by the patient's surgeon. Quality of life surveys administered to 47 patients by their plastic surgeons reveal that up to 98% of patients experience a significant improvement in their psychosocial satisfaction (3,58). While there is no validated quality of life questionnaire for post-operative gynecomastia patients, the Breast Evaluation Questionnaire (BEQ), has been altered for use in this patient population and administered to 74 patients by their plastic surgery team. This revealed 62.5% of patients were satisfied to very satisfied with their surgery (59). Davanco *et al.* utilized the Short-Form 36 (SF-36) in post-operative gynecomastia patients which showed improvement in multiple domains including mental health, general health, functional capacity, social aspects, and vitality (60).

Clinical scenarios

Adolescent gynecomastia

A 14-year of male presents to your clinic with complaints of a tender lump in the left breast which has been present the last several months. He denies any illicit drug use. His past medical and family history is otherwise noncontributory. On physical exam, he has a BMI of 22 kg/m^2. He has bilateral well circumscribed fibrous retroareolar masses noted with the left more prominent and more tender than the right. He has no other findings on his clinical breast exam and his complete physical exam is otherwise unremarkable.

Reassurance is provided that his history and clinical exam are consistent with adolescent gynecomastia. No laboratory or imaging workup is needed. Expected course

Table 3 Gynecomastia clinical pearls

Diagnosis is typically made based on clinical history and examination
Rule out pseudogynecomastia or breast cancer
Routine laboratory and imaging workup is not typically necessary although any suspicion for malignancy requires further evaluation
Physiologic gynecomastia is usually treated with reassurance and observation
Pathogenic causes of gynecomastia are addressed by treatment of the underlying causes
Pharmacologic gynecomastia is treated by discontinuation or conversion of the inciting drug
Medications, like tamoxifen, may be used to treat symptomatic or refractory gynecomastia or for gynecomastia associated with antiandrogen therapy for prostate cancer
Radiotherapy may be considered for prophylaxis or treatment of gynecomastia associated with antiandrogen therapy for prostate cancer
Surgical treatment may be considered in select cases typically involving chest wall contouring with direct excision, or those refractory to other treatments

of self-resolution within 2 years is discussed. Emotional support should be provided. A follow up exam in 6 months is recommended. Evidence of underlying psychosocial consequences with may prompt counseling and/or consideration of treatment. If persistent beyond 2 years and/or refractory to medical treatment, consideration can be given to surgical treatment after setting realistic expectations and a thorough discussion of the patient's goals.

Gynecomastia due to bicalutamide in prostate cancer

A patient presents to your clinic with complaints of bilateral breast enlargement after recently starting bicalutamide. Other than a recent prostate cancer diagnosis, his past medical and family history is unremarkable. His physical exam is notable for a BMI of 34 kg/m^2. His breast exam reveals bilateral, symmetric, dense retroareolar masses with no other suspicious masses or findings. His complete physical exam is otherwise unremarkable.

Reassurance should be provided that bicalutamide-induced gynecomastia due to androgen deprivation. No routine laboratory or imaging work up is needed in the absence of suspicious findings. He can be encouraged to follow up with his Urologist to discuss other treatment options for his prostate cancer as cessation of androgen deprivation or change is type of androgen deprivation medication. Watchful waiting is appropriate. However, if the gynecomastia is bothersome to the patient then medical treatment can be considered with Tamoxifen being utilized most commonly. If the patient has a contraindication these approaches or desires alternative treatment options, especially if pain is refractory to other interventions, subcutaneous mastectomy or, in extreme cases, referral to radiation oncology for discussion of therapeutic radiation can be considered.

Conclusions

The current body of literature on gynecomastia lacks consensus on definition, work up and treatment. This lack of standardization leads to significant heterogeneity in the literature and may fail to exclude patients with pseudogynecomastia. Furthermore, current research is limited by small sample size, lack of controls, and research methodologies. A summary of clinical pearls is listed in *Table 3*. A summary of gynecomastia review articles is listed in *Table 4* (1,3,5-7,12-15,20,24,49) while a list of additional articles on medical and surgical treatment of gynecomastia are listed in *Table 5* (6,8-10,28-41,47,48,53-56).

Despite these issues, we know that gynecomastia is a prevalent diagnosis which is based on clinical history and examination. Routine laboratory and imaging workup are often unnecessary except for cases where pathologic etiology or breast cancer cannot be ruled out. Treatment is often supportive in nature. However, use of medications and/or surgical intervention may be considered in select patients.

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Table 4 Gynecomastia review articles

Article	Description	Number of studies
Braunstein, *N Engl J Med* 2007 (7)	Clinical presentation and work up	–
Dickson, *Am Fam Physician* 2012 (12)	Comprehensive review	–
Barros, *Sao Paula Med J* 2012 (13)	Comprehensive review out of Brasil	–
Deepinder, *Expert Opinion on Drug Safety* 2012 (25)	Systematic Review	150
Nuzzi, *Plast Reconstr Surg* 2013 (49)	Psychosocial aspects in adolescent GM	–
Ladizinski, *South Med J* 2014 (20)	Comprehensive review	–
Ordaz, *Body Image* 2015 (1)	Body image and psychological function	–
Fagerlund, *J Plast Surg Hand Surg* 2015 (3)	Systematic review	17
Fagerlund, *PLoS One* 2015 (24)	Systematic review in prostate cancer	11
Rew, *J Adolesc* 2015 (14)	Psychosocial systematic review	10
Sansone, *Endocrine* 2017 (5)	GM with a focus on hormonal factors	–
Baumann, *Breast Care* 2018 (6)	Medical and surgical treatment review	–
Solli, *Gland Surg* 2018 (15)	Psychosocial changes after surgery	6
Holzmer, *Plastics and Reconstructive Surgery-Global Open* 2020 (50)	Comprehensive review of surgery	17

GM, gynecomastia.

Table 5 Articles on the treatment of gynecomastia

Article	Description
Medical	
Buckle, *Postgrad Med J* 1979 (41)	Danazol
Parker, *Metabolism* 1986 (29)	Tamoxifen
Eberle, *J Pediatr* 1986 (38)	DHT-hp in persistent pubertal GM
Jones, *Ann R Coll Surg Engl* 1990 (4)	Danazol *vs.* placebo in adult idiopathic GM
McDermott, *South Med J* 1990 (30)	Tamoxifen in idiopathic GM
Ting, *Am Surg* 2000 (39)	Tamoxifen *vs.* danazol in idiopathic GM
Saltzstein, *Br J Urol* 2002 (37)	Tamoxifen *vs.* anastrozole in bicalutamide induced GM
Lawrence, *J Pediatr* 2004 (32)	Raloxifene *vs.* tamoxifen in pubertal GM
Plourde, *J Clin Endocrinol Meta*b 2004 (33)	Anastrozole in pubertal GM
Riepe, *Horm Res* 2004 (34)	Anastrozole in pubertal GM
Perdona, *Lancet Oncol* 2005 (31)	Tamoxifen & radiotherapy in bicalutamide induced GM
Boccardo, *J Clin Oncol* 2005 (36)	Tamoxifen *vs.* anastrozole in bicalutamide induced GM
Hanavadi, *Breast* 2006 (28)	Tamoxifen
Mauras, *J Clin Endocrinol Metab* 2009 (35)	Anastrozole in pubertal GM
Viani, *Int J Radiat Oncol Biol Phys* 2012 (47)	Tamoxifen *vs.* radiotherapy in prostate cancer

Table 5 (*continued*)

Table 5 (*continued*)

Article	Description
Surgical	
Simon, *Plast Reconstr Surg* 1973 (8)	Surgical treatment
Colombo-Benkmann, *Am J Surg* 1999 (48)	Indications for surgery
Rohrich, *Plast Reconstr Surg* 2003 (9)	Ultrasound-assisted liposuction
Prado, *Plast Reconstr Surg* 2005 (5)	Arthroscopic-endoscopic cartilage shaver
Cordova, *J Plast Reconstr Aesthet Surg* 2008 (10)	Algorithm for surgical treatment
Benito-Ruiz, *Aesthet Surg J* 2009 (6)	Minimally invasive surgery
He, *J Laparoendosc Adv Surg Tech A* 2011 (3)	Vacuum-assisted biopsy
Li, *Ann Plast Surg* 2012 (51)	Surgical treatment
Cao, *Exp Ther Med* 2013 (54)	Endoscopic subcutaneous mastectomy
Holzmer, *Plastics and Reconstructive Surgery-Global Open* 2020 (50)	Comprehensive review of surgery
Medical & surgical	
Baumann, *Breast Care* 2018 (6)	Review of conservative and surgical management

DHT-hp, dihydrotestosterone heptanoate; GM, gynecomastia.

Footnote

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