Breast Implant-associated Anaplastic Large Cell Lymphoma

An Evidence-based Systematic Review

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Objective: This evidence-based systematic review synthesizes and critically appraises current clinical recommendations and advances in the diagnosis and treatment of BIA-ALCL. This review also aims to broaden physician awareness across diverse specialties, particularly among general practitioners, breast surgeons, surgical oncologists, and other clinicians who may encounter patients with breast implants in their practice.

Background: BIA-ALCL is an emerging and treatable immune cell cancer definitively linked to textured-surface breast implants. Although the National Comprehensive Cancer Network (NCCN) consensus guidelines and other clinical recommendations have been established, the evidence supporting these guidelines has not been systematically studied. The purpose of this evidence-based systematic review is to synthesize and critically appraise current clinical guidelines and recommendations while highlighting advances in diagnosis and treatment and raising awareness for this emerging disease.

Methods: This evidence-based systematic review evaluated primary research studies focusing on the diagnosis and treatment of BIA-ALCL that were published in PubMed, Google Scholar, and other scientific databases through March 2020.

Results and Conclusions: The clinical knowledge of BIA-ALCL has evolved rapidly over the last several years with major advances in diagnosis and treatment, including en bloc resection as the standard of care. Despite a limited number of high-quality clinical studies comprised mainly of Level III and Level V evidence, current evidence aligns with established NCCN consensus guidelines. When diagnosed and treated in accordance with NCCN guidelines, BIA-ALCL carries an excellent prognosis.

Keywords: BIA-ALCL, breast implants, lymphoma, systematic review

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Breast implants are used extensively in the United States and throughout the world for breast augmentation and breast reconstruction. Textured-surface breast implants, a common type of breast implant, have been linked to breast implant-associated anaplastic large cell lymphoma (BIA-ALCL), an emerging non-Hodgkin type T-cell lymphoma.[1] Although BIA-ALCL shares morphologic and immunophenotypic characteristics similar to other ALCL, specifically anaplastic lymphoma kinase-negative ALCL (ALK$^-$ ALCL), its presentation, diagnosis, and clinical course represent a novel clinical entity with unique challenges for medical practitioners.

Since first being described in the mid to late 90s,[2–5] over 800 cases have been confirmed worldwide.[6] The majority of cases present with an acute onset, unilateral periprosthetic effusion, and follow an indolent clinical course when diagnosed and treated promptly.[7] When practitioners misdiagnose, fail to diagnose, or do not adhere to clinical guidelines, disseminated disease and death have resulted.[8] Reported cases of BIA-ALCL stratify equally between cosmetic and reconstructive patients, suggesting that history of a previous malignancy, such as breast cancer, is not an independent risk factor for the development of the disease. However, reports of implant-associated blood cancers continue to surface after reconstructive or cosmetic surgeries with textured devices,[9,10] implicating textured implants in the pathogenesis of this rare disease, while similarly raising concerns about the long-term safety of textured devices.[11,12] Despite some of these concerns, Tandon et al found that the use of textured breast implants for cosmetic indications is increasing.[13] In 2017, approximately 70,000 textured breast implants were placed in the US, accounting for 12.5% of the total market share.[14] In contrast, textured breast implants accounted for nearly 90% of device preference throughout Europe and Australia.[15] As such, there are currently millions of women worldwide with textured-surface breast implants, which poses a significant health risk for patients exposed to this type of device.

In 2011, the US Food and Drug Administration (FDA) issued a safety communication about the possible association between breast implants and BIA-ALCL.[16] Shortly thereafter, the World Health Organization provisionally classified BIA-ALCL as a distinctly challenging clinical entity.[17] Out of that concern, nearly forty different countries have banned the use of Allergan Biocell (Dublin, Ireland) textured-surface breast implants, and France has banned the use of macrotextured devices altogether.[18] After worldwide bans, the US FDA called for a Class 1 device recall. Subsequently, Allergan issued a voluntary, worldwide recall of their textured-surface breast implants and textured-surface tissue expanders.[19,20] Allergan's ''salt-loss'' manufacturing technique creates an exceptionally coarse macrotextured surface that maximizes tissue ingrowth to maintain breast pocket stability and improve aesthetic outcomes. However, this same process has come under scientific scrutiny, as Allergan carries the highest manufacturer-specific risk (1:355–2207 patients) for the development of BIA-ALCL.[21,22] Other device companies employ different texturing techniques that result in less rugged surfaces, including the Mentor corporation (Irvine, CA), which have allowed textured breast devices to remain commercially available in the US, despite their association with BIA-ALCL. Mentor specifically uses a negative-imprint stamping technique that carries significantly lower risk estimates (1:86,029 implants; 95% CI: 15,440–1,301,759) for the development of lymphoma in the Australia-New Zealand cohort which translates to an

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increased risk of 27.1:1 for Allergan Biocell implants compared to Mentor Siltex implants.[23] At this time, considerable clinical debate exists over the best course of action to both identify at-risk individuals with textured devices and adequately protect these patients from disease development while further preventing all future cases of BIA-ALCL. Despite recognition as a distinct clinical entity, BIA-ALCL remains underdiagnosed given its subtle clinical presentation and lack of physician awareness of the disease.

Evidence-based medicine is an applied methodology that utilizes the best, currently available evidence to guide clinical decision-making and care of individual patients to optimize patient outcomes. Although consensus guidelines and clinical recommendations have been put forth regarding diagnosis and treatment, the evidence supporting those recommendations has not been systematically studied. The purpose of this evidence-based systematic review is to detail and critically evaluate current practice recommendations for the effective diagnosis and management of BIA-ALCL to improve missed or misdiagnoses, increase reporting of affected individuals, and to determine if current treatment guidelines are supported by high-quality evidence. This study also aims to increase physician awareness of this emerging disease, particularly among breast surgeons, surgical oncologists, and other clinicians who may encounter patients with breast implants in their practice.

METHODS

Search Strategy

A systematic review of PubMed (MEDLINE), EMBASE, Google Scholar, Web of Science, the Cochrane library, and the grey literature was conducted between March 1 and 15, 2020. The following search terms and Medical Subject Headings (MeSH) were used in combinations with Boolean operators: *breast implant associated-anaplastic large cell lymphoma, breast implant, breast implants, lymphoma, treatment,* and *diagnosis.*

Inclusion and Exclusion Criteria

Study inclusion criteria consisted of patient-oriented primary research related to the diagnosis and treatment of BIA-ALCL. Review articles were included on a case-by-case basis dependent on the ability to provided novel insights, including advancements or changes in diagnosis and treatment not discussed in a primary article. Editorials, discussions, and case reports were excluded. Citation chaining was performed on articles that met inclusion criteria using Web of Science. Two independent reviewers screened (R.C.D., M.W.C.) titles, abstracts, and the text of identified articles. Disagreement between reviewers was handled through discussion until there was 100% agreement. Only articles in the English language were reviewed. The search strategy was designed to capture articles focused on the diagnosis and treatment of BIA-ALCL. The list of references was reviewed for relevant studies, and no additional articles were discovered as a result. Each study was assessed for potential sources of bias. Levels of evidence were assigned, and articles related to current treatment recommendations (eg, en bloc resection, chemotherapy, radiation therapy, breast reconstruction) were ranked using the American Society of Plastic Surgeons (ASPS) Evidence-Based Rating Scales for Therapeutic Studies (see Table 1, Supplemental Digital Content, http://links.lww.com/SLA/C805). This systematic review was conducted in accordance with Preferred

TABLE 1. Cohort Studies and Consensus Guidelines of Breast Implant-associated Anaplastic Large Cell Lymphoma

Authors	Reference	Journal	Year	Study design	Focus of article	Level of evidence
Clemens et al	Complete Surgical Excision Is Essential for the Management of Patients with Breast Implant–Associated Anaplastic Large-Cell Lymphoma	*J Clin Oncol*	2016	Retrospective	Surgical Resection/ Adjuvant Therapy	III
Tevis et al	Stepwise En Bloc Resection of Breast Implant-Associated Anaplastic Large Cell Lymphoma with Oncologic Considerations	*Aesthet Surg J Open Forum*	2019	Retrospective cohort	Surgical Resection	III
Lamaris et al	Breast Reconstruction Following Breast Implant-Associated Anaplastic Large Cell Lymphoma	*Plast Reconstr Surg*	2019	Retrospective cohort	Breast Reconstruction	III
Clemens et al	How to Diagnose and Treat Breast Implant Associated Anaplastic Large Cell Lymphoma	*Plast Reconstr Surg*	2018	CME	Diagnosis and Treatment	V
Mehta-Shah et al	How I Treat Breast Implant Associated Anaplastic Large Cell Lymphoma	*Blood*	2018	Review	Diagnosis and Treatment	V
Clemens et al	2019 NCCN Consensus Guidelines on the Diagnosis and Treatment of Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL)	*Aesthet Surg J*	2019	Expert Consensus	Diagnosis and Treatment	V
Clemens et al	Finding Consensus After Two Decades of Breast Implant-Associated Anaplastic Large Cell Lymphoma	*Semin Plast Surg*	2019	Review	Diagnosis and Treatment	V

CME indicates Continuing Medical Education.

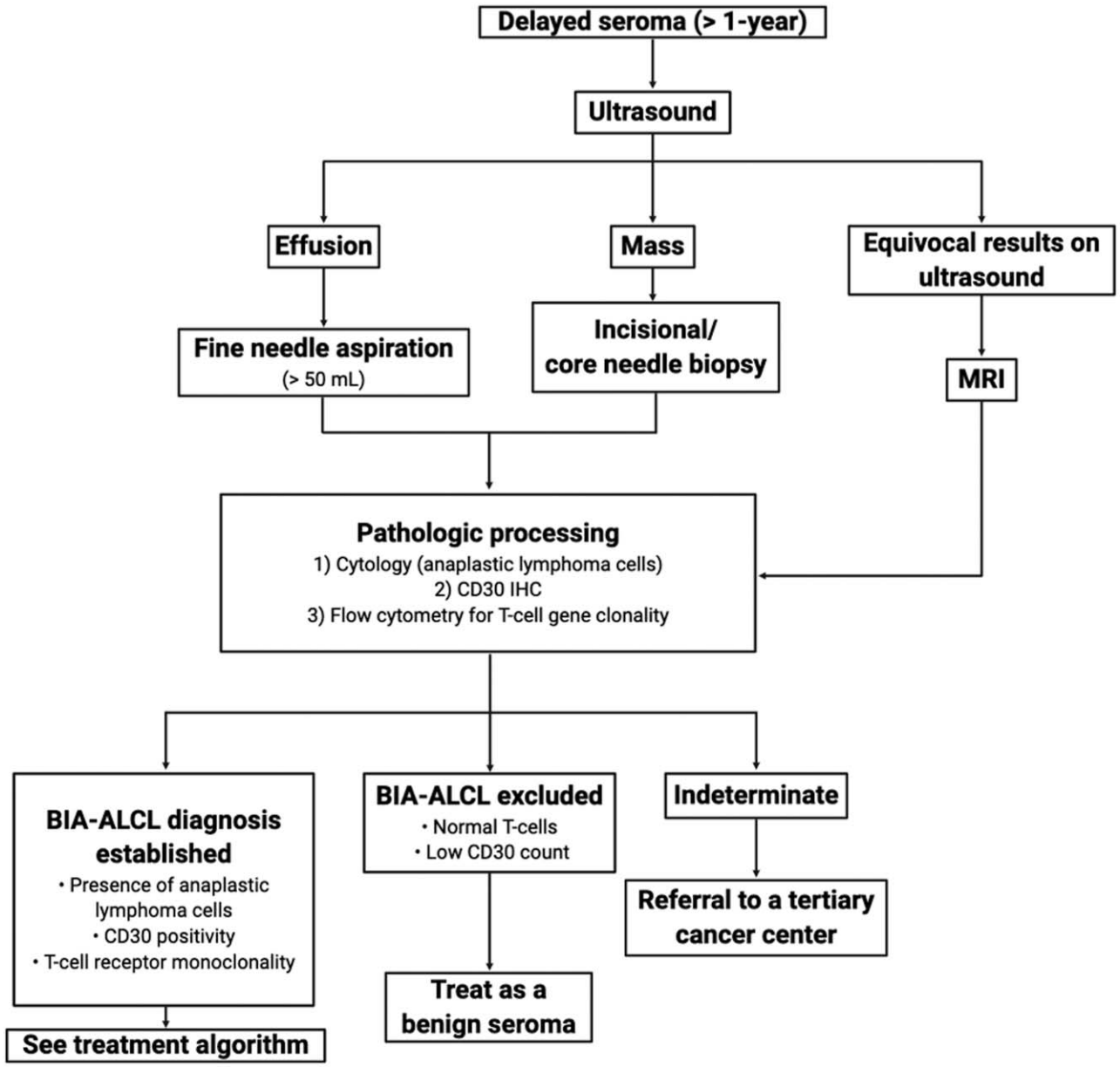

FIGURE 1. Evidence-based diagnostic algorithm for BIA-ALCL.

Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

RESULTS

An overview of the search strategy is provided in Figure 1, Supplemental Digital Content, http://links.lww.com/SLA/C804. The initial search yielded 511 articles. No other articles were identified from other sources. After removing duplicates found in the search ($n = 3$), 508 articles remained. Titles and abstracts were reviewed ($n = 508$) for relevance, and as a result, 501 articles were excluded on the basis of study design and lack of primary evidence related to diagnosis or treatment. The remaining articles ($n = 7$) were reviewed in their entirety and met inclusion criteria (Table 1) Studies were comprised of level III ($n = 3$) and level V ($n = 4$) evidence that focused on the diagnosis and treatment of BIA-ALCL. The limited number of available studies and heterogeneity in reported data precluded any meta-analysis.

EPIDEMIOLOGY

Historically, rare diseases present epidemiological challenges for investigators; precisely estimating the true incidence of disease remains an elusive task. With respect to BIA-ALCL, existing epidemiological studies are limited by a lack of global reporting and incomplete breast implant sales data, making it similarly difficult to quantify an accurate risk assessment.[24] The current lifetime risks associated with the development of BIA-

ALCL vary significantly according to geography and are also manufacturer specific.[25] The Australian Therapeutic Goods Administration estimates a lifetime risk of 1:2,500 to 1:25,000 patients with a textured breast implant.[26] More recent work by Doren et al estimates an average lifetime prevalence across manufacturers of 1:30,000 patients with a textured breast implant in the US.[23] Interestingly, the authors' reported a nearly 6-fold increase in the lifetime prevalence of BIA-ALCL cases attributable to Allergan textured devices compared to textured devices from other manufacturers. These data were later cited by the FDA as partial reasoning for issuing the Class 1 recall.[27] Allergan's unique manufacturing process highlights the texturing process as a critical regulator of disease pathogenesis. As such, investigators have focused on understanding the innate and adaptive immune response to implanted devices in hopes that their efforts will yield a clearer understanding of the cellular and molecular mechanisms driving disease development.

PATHOPHYSIOLOGY

BIA-ALCL is a subset of systemic ALCL (sALCL), which are a class of non-Hodgkin type peripheral T-cell lymphomas. Investigators stratify sALCLs by cellular and molecular markers that carry either favorable or less favorable clinical outcomes. The presence of ALK^+ occurs in 60% to 80% of sALCLs and carries a favorable 5-year progression-free survival. The other 20% to 40% of ALK^- sALCLs are characterized by specific gene rearrangements—*Dusp22, TP63,* or *Triple Negative* (ALK^-, *Dusp22*$^-$, *TP63*$^-$) and carry an overall survival rate of $\leq$50%.[28] BIA-ALCL cells isolated from patients are classified as *Triple Negative* ALCLs.[29] Although, reports exist of diffuse large B-cell lymphomas, marginal zone B-cell lymphoma, and plasmacytomas occurring adjacent to textured-surface breast implants, suggesting that the disease may have a broad spectrum of genotypic and phenotypic variations.[30,31] BIA-ALCL cells also carry the CD30 cell surface marker that traditionally marks activated B- and T-cells. Therefore, BIA-ALCL cells are pathologically classified as $CD30^+$, ALK^- lymphoma cells.

After 2 decades of investigation, the biological basis of the disease remains poorly understood.[32] Current evidence suggests BIA-ALCL arises from a novel antigenic stimulus that induces a chronic inflammatory state.[33,34] Consistent exposure to inflammatory cytokines in a genetically susceptible individual ultimately leads to unregulated immune-cell clonal expansion and lymphomagenesis. However, the specific antigenic stimulus remains a controversial topic and is the focus of our laboratory and others. Early investigations identified a gram-negative bacillus, *Ralstonia pickettii,* in establishing a subclinical, periprosthetic biofilm, leading to a lipopolysaccharide (LPS) endotoxin-induced carcinogenesis.[35] After a more careful examination, the Ralstonia data have since been refuted, and currently, no clear association between the breast microbiome and BIA-ALCL pathogenesis exists.[36] Other investigators have focused on allergen-driven carcinogenesis, either from particulate matter from the operating suite landing on implant surface or aberrant activation of the aryl hydrocarbon receptor by the contaminants residing on the implant surface itself.[37–39] Genetics, in combination with other factors, is also thought to be a major risk factor for the disease,[40,41] with oncogenic mutations in *TP53,*[42–45] *DNMT3A*,[43] and the JAK-STAT3 pathway being described.[29,43,46–48] Other proposed oncogenic drivers may include viruses or chronic trauma to the breast pocket.[49,50] Nevertheless, evidence to support a unifying theory has remained elusive, and the complex interplay between these factors remains largely unknown.

NATURAL HISTORY AND SPECTRUM OF DISEASE

Early reports suggested 2 distinct histologic subtypes of BIA-ALCL, in situ disease and *infiltrative* disease, each of which carried a significantly different prognosis. Over time, the knowledge of the disease has evolved to encompass a spectrum of disease that spans multiple diverse disease environments, including effusion-limited disease, superficial capsular involvement, a grossly identifiable lesion, lymph node extension, and finally, distant metastasis. In situ or effusion-limited disease is confined within the breast implant capsule and is characterized by a lymphomatous cell layer on the luminal capsular surface with or without suspension of anaplastic lymphoma cells in the serous fluid. The infiltrative subtype extends into or beyond the fibrous capsule and may be associated with locoregional or distant metastasis. The infiltrative subtype carries an inferior prognosis.

CLINICAL PRESENTATION

The majority (80%) of patients present with a spontaneous delayed seroma formation (greater than 1-year after implantation) but can also present with lymphadenopathy (4%–12%) or a palpable mass (8%–24%). Less frequently (<5%), the disease may present with local or systemic symptoms, including fever, capsular contracture, or cutaneous manifestations. The median interval time to presentation is 7 to 10 years (range 1–28 years) after textured device implantation for breast augmentation or reconstruction. Left untreated, scant $CD30^+$, ALK^- cells contained within the seroma fluid may coalesce and acquire characteristics of solid tumors[51,52]—including distant metastasis—underscoring the importance of early diagnosis and intervention.

DIAGNOSIS

The National Comprehensive Cancer Network (NCCN) guidelines for the diagnosis and treatment of BIA-ALCL were established based on the current understanding of the literature. In the subsequent paragraphs, we will discuss and critically appraise the clinical data that coalesced to form these essential guidelines while highlighting advances in diagnostic and therapeutic strategies and addressing current controversies not covered in NCCN guidelines or elsewhere in the published literature.

Differential Diagnosis and Diagnostic Work-up

Generally, BIA-ALCL follows an indolent clinical course and has an excellent prognosis when diagnosed and treated promptly. A proposed diagnostic algorithm is outlined in Figure 1. Briefly, suspicious seromas should be drained using ultrasound-guided fine-needle aspiration or in consultation with interventional radiology. It is important to note that the peri-implant space around most implants contains only a trace amount (5–10 mL) of fluid. Thus, an independent finding in an otherwise asymptomatic patient does not warrant further investigation. After excluding other differential diagnoses of delayed seroma (eg, infection, isolated trauma to the chest wall), aspirate (minimum 50 mL) should be sent for cytopathology with the request to ''rule out BIA-ALCL.'' A BIA-ALCL rule out requires 3 specific areas of investigation— $CD30^+$ cells by immunohistochemistry, cellular atypia as assessed with microscopy, and flow cytometry to assess for T-cell clonality.[53–56] Positive samples must typically satisfy all of the three requirements: $CD30^+$ cells in the aspirate; noted cellular atypia; and T-cell clonality (Fig. 2).

Although CD30 expression is a fundamental diagnostic element of BIA-ALCL, isolated expression is not pathognomonic for establishing the diagnosis, as CD30 is also expressed on other

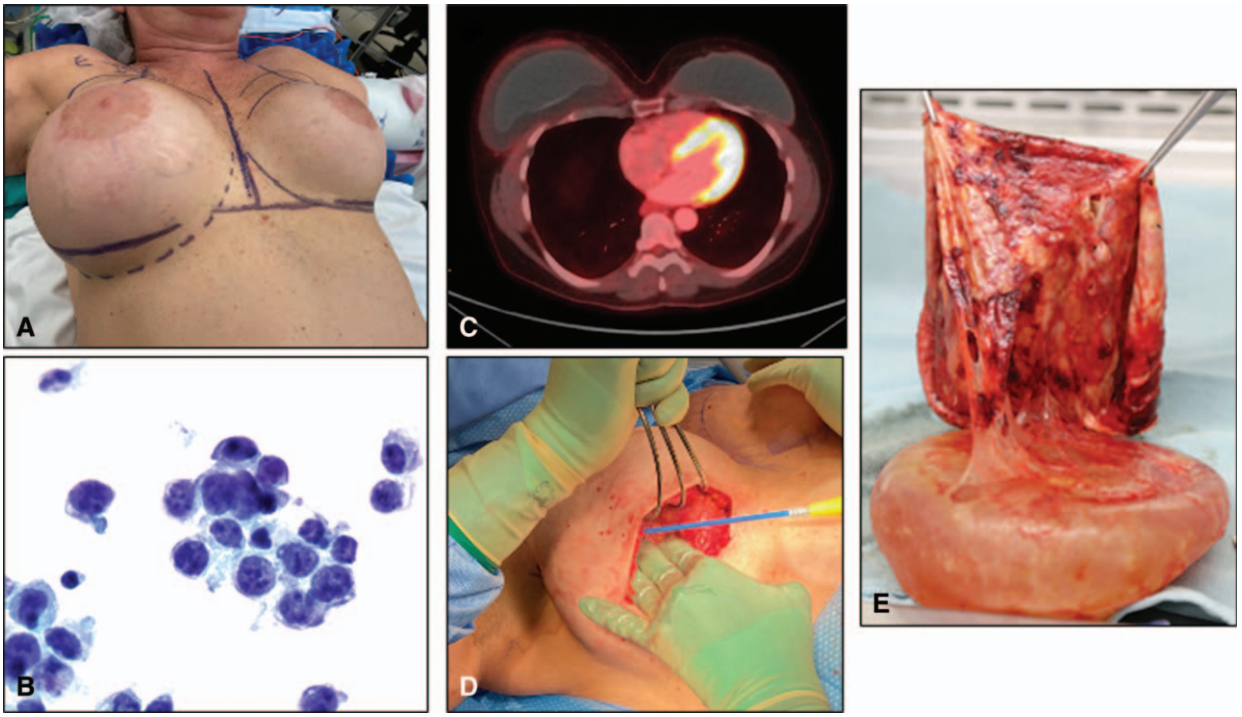

FIGURE 2. BIA-ALCL lymphoma cells. A malignant effusion in a BIA-ALCL patient demonstrates large pleomorphic anaplastic cells with prominent horseshoe-shaped nuclei and nuclear folding. (hematoxylin stain, 500X magnification) Positive anaplastic cytology, CD30 immunohistochemistry expression, and single T cell clonality demonstrated on flow cytometry are required for BIA-ALCL diagnosis. Reprinted with permission by Clemens, MW, DeCoster, RC, Fairchild et al, 2019. Finding Consensus After Two Decades of Breast Implant-Associated Anaplastic Large Cell Lymphoma *Semin Plast Surg.* 33(4):270–278, Thieme Medical Publishers, Georg Thieme Verlag KG.

immune cells, including activated T- and B-cells, eosinophils, and macrophages. Thus, $CD30^+$ lymphocytes with otherwise normal morphology do not require further investigation. Histologic experiments to assess cellular atypia focuses on identifying cells with anaplastic features—pleomorphic nuclei, either heterochromic or hyperlobulated, and abundant cytoplasm presenting in dense cellular sheets. These cells are often "hallmark" cells of ALCL. T-cell clonality suggests T-cell receptor gene rearrangement in response to a single antigenic stimulus. Thus, if a single peak seems in $CD30^+$ flow cytometry, further investigation is warranted. As referenced earlier, the combination of these 3 characteristics, $CD30^+$ cells, exhibiting cellular atypia, and T-cell receptor clonality, is highly suspicious for BIA-ALCL and should prompt clinical intervention.

Diagnostic Imaging

Ultrasound remains the imaging modality of choice for detecting a BIA-ALCL related effusion or mass. Adrada et al found that ultrasound conveys an 84% sensitivity and a 75% specificity for detecting an effusion and is 46% sensitive and 100% specific for detecting a mass.[57] Equivocal results on ultrasound should be further investigated with magnetic resonance imaging. The role of positron emission tomography-computed tomography (PET-CT) for preoperative workup and tumor surveillance is discussed in further detail below (see oncologic surveillance)

Pathologic Processing of Specimens

In a proposed update to the College of American Pathologist policy on surgical specimen collection, Lyapichev et al recently developed a standardized protocol for handling and processing BIA-ALCL tumor specimens.[58] Using mathematical modeling, the authors formulated an equation [minimum number of samples = $3.6 + 106.8/(\text{coverage}\%)$] that can be used to determine the minimum number of sections required to identify 95% of randomly distributed lesions in patients that do not have grossly identifiable lesions. The formula translates into a requirement of 12 biopsies per capsule, 2 for each side of the face of a cube. A more standardized protocol for the handling, sampling, and reporting of BIA-ALCL cases will continue to improve *diagnostic* accuracy and advance the collective understanding of the mechanisms underpinning this complex disease by providing more generalizability and statistical power to future studies.

Pathologic Staging and Prognosis

Although the Lugano modification (Ann Arbor staging system) has traditionally been used to stage non-Hodgkin lymphomas, BIA-ALCL displays behaviors most similar to solid tumors. Clemens et al demonstrated that the TNM staging system more accurately predicted overall survival and recurrence of BIA-ALCL than the Ann Arbor staging system ($P = 0.01$).[59] The TNM staging system for BIA-ALCL is summarized in Table 2. Furthermore, Clemens et al demonstrated a 91% 5-year overall survival rate and a 5-year event-free survival rate of 49%.[59] As previously mentioned, overall and event-free survival increase with the use of complete surgical excision when compared to other treatment modalities ($P < 0.001$). Additionally, when comparing prognosis according to stage, patients receiving complete surgical resection had an event rate of 0% for

TABLE 2. TNM Staging System for BIA-ALCL

TNM/Stage Classification	Description
Primary tumor (T)	
T1	Confined to effusion or a layer on luminal side of capsule
T2	Early capsule infiltration
T3	Cell aggregates or sheets infiltrating the capsule
T4	Lymphoma infiltrates beyond the capsule
Regional lymph nodes (N)	
N0	No lymph node involvement
N1	One regional lymph node (+)
N2	Multiple regional lymph nodes (+)
Distant metastasis (M)	
M0	No distant spread
M1	Spread to other organs/sites
Stage	
1A	T1N0M0
1B	T2N0M0
1C	T3N0M0
IIA	T4N0M0
IIB	T1-3N1M0
III	T4N1M0
IV	T (any) N (any) M1

stages T1, T2, and 14.3% at stage T4 ($P < 0.001$). Taken together, these data strongly suggest that en bloc resection combined with early detection yields a better early-term prognosis accompanied by a substantial survival benefit.

TREATMENT

Due to the emerging nature of this complex disease, a multidisciplinary team of plastic surgeons, surgical oncologists, and pathologists should be assembled after a definitive diagnosis of BIA-ALCL. The subsequent sections outline in detail evidence-based treatment strategies for achieving complete resolution. An overview of the treatment algorithm is provided in Figure 3.

Surgical Management

Preoperative Workup

After the establishment of a BIA-ALCL diagnosis, a team of multidisciplinary experts consisting of a medical oncologist, surgical oncologist, radiation oncologist, pathologist, and the plastic surgeon should be assembled. A list of suggested laboratory testing based on the current understanding of the reported cases is summarized in Table 3. PET-CT should be considered preoperatively to assess for capsular masses or extension into the chest wall and can serve as a ''roadmap'' to guide oncologic resection. However, the role of PET-CT in evaluating local disease immediately after (2–3 months) tumor extirpative surgery may be diminished as a result of surgery-induced inflammation.

En Bloc Resection

Clemens et al compared different therapeutic approaches and assessed oncologic outcomes in 87 patients with BIA-ALCL.[59] The authors found that complete surgical excision (eg, complete capsulectomy) demonstrated long-term, disease-free survival compared to all other therapeutic modalities ($P = 0.001$). As a result, current National Comprehensive Cancer Network (NCCN) consensus guidelines call for en bloc surgical resection of the surrounding capsule and removal of the implant (Fig. 4).[54] It is important to note that 2% to 4% of BIA-ALCL cases present with bilateral disease. Therefore, removal of the contralateral implant with complete capsulectomy should be considered should symptoms warrant. Tevis et al outlined the steps for en bloc resection and processing with all relevant oncologic considerations.[60] Given that BIA-ALCL does not involve the breast parenchyma, mastectomy is not indicated.

For asymptomatic patients concerned about the potential risk of developing BIA-ALCL, there is currently no evidence to support prophylactic implant removal as the risks associated with the required surgical procedure outweighs the current risk of BIA-ALCL development. This does, however, bring up an important issue not covered in NCCN guidelines or elsewhere. In the asymptomatic patient with a textured surface implant who wants the device removed out of concern of developing BIA-ALCL, is a total capsulectomy warranted? Complete capsulectomy remains an exceedingly challenging surgical procedure, which carries its own risks, such as additional bleeding and an increased risk of pneumothorax—specifically due to the strong adherence of the posterior wall of the capsule to the chest wall. Currently, there is insufficient clinical evidence to suggest the selection of subtotal versus total capsulectomy. Although the evidence supports a capsular origin of BIA-ALCL, there is not enough evidence at this time to definitively establish complete capsulectomy as a risk-reducing procedure in the asymptomatic patient. This concept marks an important distinction between complete capsulectomy and en bloc resection, where the goal of the latter is to achieve clear margins, something not obtainable in the patient where the disease is not clinically evident. Nevertheless, the patient and surgeon should engage in a meaningful discussion to consider the patient's desire as well as the specific risks and benefits for each approach on a case-by-case basis.

Indications for Adjuvant Therapies

The use of adjuvant chemotherapy or radiation in surgically unresectable or advanced disease is backed by Level III evidence.[59] Current NCCN guidelines advocate for the use of brentuximab vedotin, a monoclonal antibody directed against CD30 or a combination anthracycline-based chemotherapeutic regimen, CHOP (cyclophosphamide, adriamycin, vincristine, and prednisone), which is reserved for cases of residual or disseminated disease (MD Anderson Stage IIB-IV).[54] Radiation therapy (24–36Gy) should be considered for patients with local residual disease, positive margins, or surgically unresectable disease with chest wall extension and carries the same level clinical of evidence.

As mentioned, the current therapeutic regimen was born out of necessity to handle cases where en bloc resection is not achievable. The role of targeted therapies remains under consideration. For example, recent work from our group and others has identified aberrant JAK-STAT3 pathway involvement, which may serve as a novel therapeutic target for JAK-STAT inhibitors in the future. To that end, prospective studies are needed to further delineate the most effective chemotherapeutic regimen in the case of disseminated disease.

Breast Reconstruction after BIA-ALCL

Practitioners can reasonably offer immediate or delayed breast reconstruction after oncologic resection for BIA-ALCL to most patients, given the favorable prognosis of the disease with appropriate management. Methods of breast reconstruction after device explantation and complete surgical resection include implant replacement, autologous tissue transfer, mastopexy, or serial fat grafting. Given the known association of ALCL with textured implants, it is strongly recommended that implant-based reconstruction proceeds with smooth, round silicone implants should implant reconstruction, so be desired. Although patients may be reluctant to

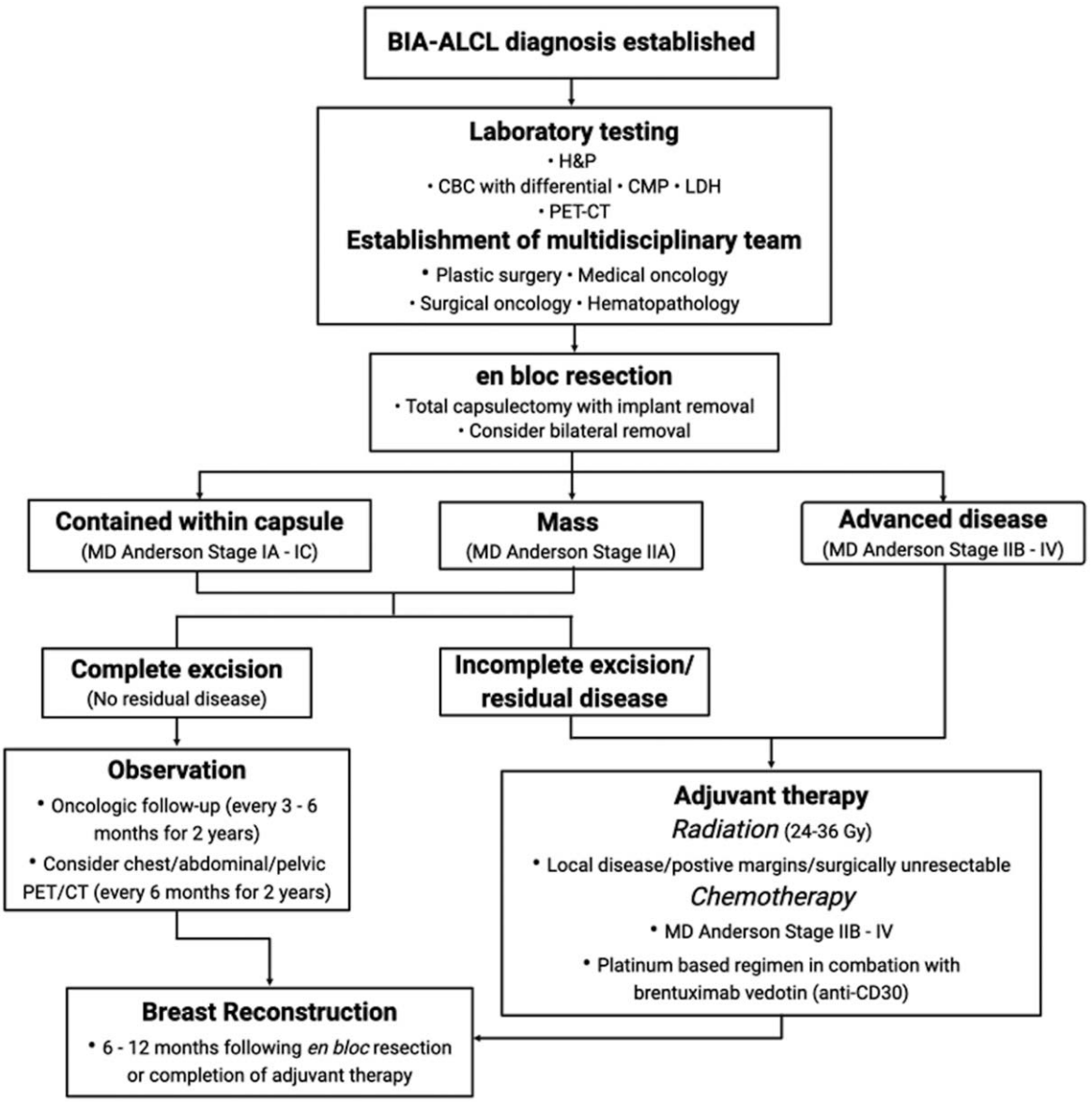

FIGURE 3. Evidence-based treatment algorithm for BIA-ALCL.

pursue implant-based reconstruction given the anxiety of device-induced recurrence, evidence has consistently demonstrated that all confirmed cases of BIA-ALCL have only occurred with textured devices.[61] However, psychologic fear should be explored preoperatively as the aforementioned options of autologous tissue transfer, mastopexy, or fat grafting demonstrate similar patient satisfaction and clinical outcomes in breast reconstruction and should remain as viable reconstructive options.

TABLE 3. Suggested Preoperative Laboratory Testing

Test	Comments
Complete blood count with differential	
Complete metabolic panel	
Lactate dehydrogenase (LDH)	Order LDH and Hep B if chemotherapy is being considered
Hepatitis B (Hep B)	
Bone marrow biopsy	Order if high suspicion of advanced disease (locally aggressive or lymph node metastasis)
PET/CT	Used to assess for chest wall involvement and to guide surgical resection

PET-CT indicates positron emission tomography-computed tomography.

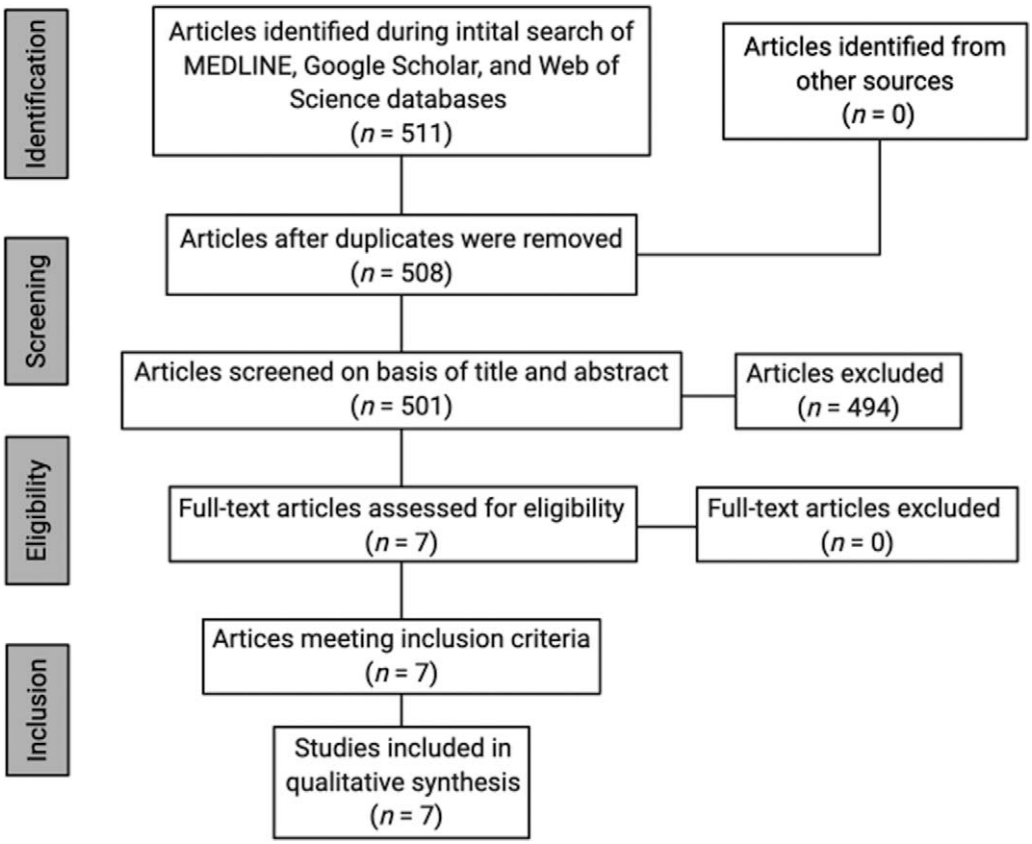

FIGURE 4. En bloc surgical resection and device explantation. The capsule and implant of a BIA-ALCL patient are shown during evaluation by pathology. Note the thickened surface of the capsule which had developed into a mass. Reprinted with permission by Clemens, MW, DeCoster, RC, Fairchild et al, 2019. Finding Consensus After Two Decades of Breast Implant-Associated Anaplastic Large Cell Lymphoma *Semin Plast Surg.* 33(4):270–278, Thieme Medical Publishers, Georg Thieme Verlag KG.

The timing of reconstruction after treatment has been highly debated and depends on disease severity at presentation. NCCN guidelines for breast reconstruction after breast cancer are well-defined but are currently nonexistent for BIA-ALCL. Recently, Lamaris et al proposed a treatment algorithm based on their experience reconstructing 18 consecutive patients after treatment for BIA-ALCL.[61] Patients with surgically resectable disease (stage IA-IC) can be offered either immediate reconstruction or delayed reconstruction after surveillance PET-CT in 3 to 6 months. Complete capsulectomy can result in devascularized tissue and must be considered in any patient undergoing immediate reconstruction. Those patients with advanced disease (stage IIA-IV) should be offered delayed reconstruction after surveillance imaging, which generally occurs 6 to 12 months after completion of surgical resection and any adjuvant chemotherapy. In subsequent updates, NCCN guidelines should reflect best evidence-based practices as outlined above for breast reconstruction after complete resolution of BIA-ALCL.

Oncologic Surveillance

Patients that have been successfully treated should be followed by an oncologist every 3 to 6 months for a period of 2 years.[62] Follow up should include a physical examination, and physicians may elect to use CT or PET-CT of the chest/abdomen/pelvis to monitor for tumor recurrence.

TABLE 4. Relevant International Classification of Diseases, Tenth Revision, and Current Procedural Terminology Codes for Suspected and Confirmed BIA-ALCL Cases

Code	Description
ICD-10 diagnostic codes	
C84.79	Anaplastic large cell lymphoma kinase-negative, extranodal, solid organ sites
N63	Unspecified lump in breast, nodule, mass, or swelling of the breast
R59.9	Enlarged lymph node
N64.4	Other specified disorders of the breast
CPT procedural codes	
10022	Fine needle aspiration with imaging guidance
19101	Breast biopsy, open, incisional
19260	Excision of chest wall tumor
19328	Removal intact mammary implant
19371	Breast periprosthetic capsulectomy
38525	Biopsy/excision, lymph node; open or deep axilla

CPT indicates Current Procedural Terminology; ICD-10, International Classification of Diseases-10th Revision.

Insurance Coverage

Insurance coverage for BIA-ALCL is provided by some major carriers, including Blue Cross and Aetna. Coverage includes removal of the implant with capsulectomy out of medical necessity, one indication being BIA-ALCL. A comprehensive list of ASPS Insurance Coverage Criteria for Third-Party Payers-BIA-ALCL may be found on the following web site: (https://www.plasticsurgery.org/documents/Health-Policy/Reimbursement/Insurance-2017-BIA-ALCL.pdf). Relevant diagnostic and procedural codes are included in Table 4.

DISEASE REPORTING

All suspected or confirmed cases should be reported to the American Society of Plastic Surgeons/Plastic Surgery Foundation Patient Registry and Outcomes For Breast Implants and Anaplastic Large Cell Lymphoma Etiology and Epidemiology (PROFILE) registry (https://www.thepsf.org/research/registries/profile/case-submission). The PROFILE registry now recognizes 288 confirmed or suspected cases in the US, bringing the total worldwide cases to 871 as of December 6th, 2019.[63]

CONCLUSIONS

The clinical knowledge of BIA-ALCL has advanced rapidly over the last several years. This evidence-based systematic review critically evaluated current NCCN consensus guidelines and clinical recommendations while highlighting advances related to the diagnosis and treatment of BIA-ALCL and emphasizing issues not covered by NCCN. Despite a limited number of high-quality studies, current clinical recommendations and NCCN consensus guidelines are supported by evidence and represent best clinical practices. As reinforced throughout this article and in conjunction with NCCN guidelines, early diagnosis, and strict adherence to clinical guidelines maintain an excellent prognosis for patients diagnosed with the disease. The diagnostic modality of choice to evaluate a delayed onset seroma is ultrasound. Suspicious seromas should be drained under using fine-needle aspiration with or without ultrasound guidance or in conjunction with interventional radiology and sent for cytopathology. Equivocal results on ultrasound should be further investigated using magnetic resonance imaging. When diagnosed preoperatively, en bloc resection is now the standard of care for the majority of cases (MD Anderson Stage I-IIA). Importantly, en bloc resection is an oncologic procedure that includes complete/total capsulectomy and obtaining clear margins, while incomplete resection or partial/subtotal capsulectomy increases the risk for locoregional recurrence. Adjuvant therapy is reserved for patients with refractory disease or those unamenable to initial surgical resection (MD Anderson Stage IIB-IV). PET-CT may be used preoperatively to assess for chest wall involvement. For the asymptomatic patient with a textured breast implant, there is currently no evidence to support prophylactic implant removal, as performing explantation in conjunction with complete capsulectomy may not be a risk-reducing procedure. Although high-risk Allergan textured surface breast devices, which are the subject of a Class I recall from the FDA, have been removed from the market, surgeons and other healthcare providers should expect to see cases more frequently over the next 7 to 10 years. As the incidence of BIA-ALCL is expected to increase, a heightened awareness and thorough knowledge of current evidence-based guidelines and recommendations is needed to ensure timely diagnosis and prompt management, which are essential to ensuring patient safety.

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