

Special Topic

# NCCN Consensus Guidelines for the Diagnosis and Management of Breast Implant-Associated Anaplastic Large Cell Lymphoma

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## Abstract

Published case series demonstrate a lack of treatment standardization for breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) with a wide variety of therapeutic strategies being employed at all stages of disease. The National Comprehensive Cancer Network (NCCN) annually publishes Clinical Practice Guidelines for Non-Hodgkin Lymphomas. For the first time, BIA-ALCL management will be included which signifies an important and needed guideline addition. The new BIA-ALCL guideline was achieved by a consensus of lymphoma oncologists, plastic surgeons, radiation oncologists, and surgical oncologists. NCCN guidelines focus on the diagnosis and management throughout the stages of many lymphoma subtypes based upon the most current data available. This article summarizes the essential recommendations and optimal therapeutic strategies of the NCCN guidelines critical to the plastic surgery community. We encourage international adoption of these BIA-ALCL treatment standards by our specialty societies across the oncology and surgery disciplines.

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Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) is a rare T-cell lymphoma typically occurring in a delayed fluid collection around a textured implant or surrounding scar capsule.<sup>1,2</sup> In 2016, the World Health Organization for the first time provisionally classified BIA-ALCL as a newly recognized entity and highlighted the importance of surgical management of the disease.<sup>3</sup> However, recent case series demonstrate rare treatment standardization for BIA-ALCL with a wide variety of regimens such as surgery, chemotherapeutic agents, radiation therapy, and stem cell transplant being employed at all stages of disease.<sup>4-8</sup> The NCCN non-Hodgkin lymphoma (NHL) committee has developed a new consensus guideline for the diagnosis and treatment of BIA-ALCL included in the 2017 update. This article summarizes the essential recommendations and therapeutic strategies of the NCCN guidelines critical to the plastic surgery community.

NCCN is an alliance of 27 of the nation's leading cancer centers, which forms recommendations for the prevention, diagnosis, and management of malignancies.<sup>9</sup>

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) represent the authoritative oncology standards utilized worldwide, which apply to approximately 97% of cancer patients. Guidelines are intended to facilitate decision making by treating physicians, payers, and patients. NCCN guidelines on NHL focus on the diagnosis and management throughout the stages of many NHL subtypes based upon the most current data available and expert consensus, and are widely recognized as a standard for clinical practice. The new

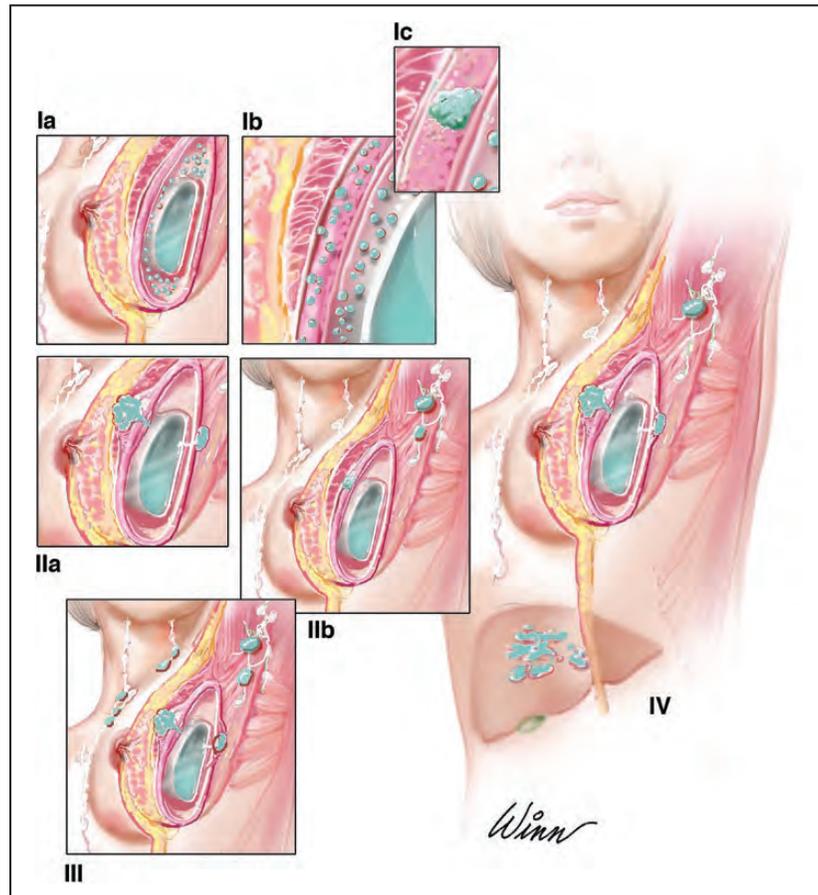
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**Figure 1.** Determination of clinical and pathologic BIA-ALCL staging is essential for treatment strategies. This figure represents a BIA-ALCL tumor, lymph node, metastasis (TNM) staging system modeled after the American Joint Committee on Cancer (AJCC) TNM staging system for solid tumors. Adapted from original illustration by Dave Arten, MA, CMI, in Clemens et al.<sup>5</sup>

BIA-ALCL guidelines were achieved by a consensus of lymphoma oncologists, plastic surgeons, radiation oncologists, and surgical oncologists from the NCCN member institutions. Due to copyright agreement, the actual NCCN BIA-ALCL algorithms cannot be reprinted in a journal, but can be found online ([www.nccn.org](http://www.nccn.org)). This manuscript represents a summary and explanation of the new guidelines.

## INITIAL DIAGNOSIS AND PATHOLOGIC WORKUP

BIA-ALCL patients most commonly present with a spontaneous peri-prosthetic fluid collection or capsular mass at an average of eight to ten years following implantation with a breast implant for either cosmetic or reconstructive indications. A vast majority of cases were encountered with a clinical history of a textured implant.<sup>10</sup> Other described symptoms have included breast enlargement, skin rash, capsular contracture, and lymphadenopathy.

Initial workup of an enlarged breast should include ultrasound evaluation for fluid collection, breast masses, as well as enlarged regional lymph nodes (axillary, supraclavicular, and internal mammary). For BIA-ALCL patients, the sensitivity and specificity of ultrasound for detecting an effusion (84% and 75%) or a mass (46% and 100%) were found to be similar or better than computed tomography or magnetic resonance imaging (MRI).<sup>11</sup> If ultrasound is indeterminate or requires further confirmation, physicians may also utilize an MRI or positron emission tomography (PET) scan in select cases.

Peri-prosthetic fluid collections should undergo fine needle aspiration. At time of aspiration, ultrasound may aid in implant displacement and protection, and aspiration can be performed either in a clinic setting or by interventional radiology. A suspicious mass requires tissue biopsy and evaluation is best made by a hematopathologist. Specimens should be sent for cytology. Essential to the diagnosis of BIA-ALCL is immunohistochemistry and flow cytometry for T-cell markers, specifically CD30 cell surface protein is highly expressed in

**Table 1.** BIA-ALCL Tumor, Lymph Node, and Metastasis (TNM) Staging and Stages. Adapted from Clemens et al.<sup>5</sup>

Staging				
Tumor size	T1	T2	T3	T4
T	Confined to effusion	Early capsule invasion	Mass aggregate, confined to capsule	Tumor locally invasive out of capsule
Lymph Nodes	N0	N1	N2	
N	No lymph node involvement	One regional lymph node	Multiple regional lymph nodes	
Metastasis	M0	M1		
M	No distant spread	Other organs/distant sites		
Stages				
Stage IA: T1N0M0	Stage IIA: T4N0M0		Stage III: TanyN2M0, T4N1M0	
Stage IB: T2N0M0	Stage IIB: T1-3N1M0		Stage IV: TanyNanyM1	
Stage IC: T3N0M0				

ALCL as well as some lymphoproliferative disorders<sup>12-14</sup> and is necessary to establish the diagnosis of BIA-ALCL. As BIA-ALCL is a rare disease at most medical centers, inclusion of a clinical history and directions to the pathologist to “rule out BIA-ALCL” is beneficial and suggested. If after pathology evaluation, diagnosis of lymphoma is indeterminate, secondary hematopathology consultation is recommended at a tertiary cancer center with experience in this disease. If the pathology is negative, the patient should be referred to a plastic surgeon for management as a benign seroma. In accordance with the United States Food and Drug Administration (FDA) recommendation,<sup>15</sup> histologic confirmation of BIA-ALCL should be reported to the BIA-ALCL PROFILE registry ([www.thehsf.org/profile](http://www.thehsf.org/profile)) of the American Society of Plastic Surgeons.

## LYMPHOMA WORKUP AND STAGING

Following confirmation of BIA-ALCL diagnosis, a multi-disciplinary team is recommended for managing patients. Routine laboratory blood tests include a complete blood count (CBC) with differential, comprehensive metabolic panel, lactate dehydrogenase (LDH), and Hepatitis B testing (if adjuvant chemotherapy is being considered). Women of child-bearing age should be tested for pregnancy prior to embarking on oncologic treatment. For BIA-ALCL confirmed cases, a bone marrow biopsy may be performed but is most often not necessary except in select cases with evidence or suspicion of systemic spread, and can be left to the oncologist’s discretion. For confirmed cases of BIA-ALCL, a PET scan is often beneficial for demonstrating associated capsular masses, chest wall involvement, and is the preferred test to evaluate

for systemic spread to regional or distant lymph nodes, and/or organ involvement.<sup>11</sup> Active BIA-ALCL is positive on PET scan. Staging of BIA-ALCL may be performed either by a lymphoma or solid tumor staging system. The Lugano revision to the Ann Arbor staging system is a lymphoma staging with stage IE disease limited to a single extranodal site such as breast or capsule involvement only, with stage IIE disease defining spread to local lymph nodes.<sup>16</sup> Using this system, nearly all BIA-ALCL patients have early-stage disease, either stage 1E (83%-84%) or stage IIE (10%-16%) vs stage IV disease (0%-7%).<sup>4,5</sup> An MD Anderson (MDA) solid tumor BIA-ALCL tumor, lymph node, metastasis (TNM) staging system has been proposed and modeled after the American Joint Committee on Cancer (AJCC) TNM (Tumor, lymph Node, Metastasis). (Figure 1, Table 1) Using this system, BIA-ALCL patients have a spectrum of disease from IA (35.6%, effusion only), IB (11.5%), IC (13.8%), IIA (25.3%), IIB (4.6%), III (9.2%), to stage IV (0%).<sup>5</sup> In the same study of 87 BIA-ALCL patients, the overall survival (OS) rate was 94% and 91% at 3 and 5 years, respectively, and the 3-year and 5-year event free survival (EFS) rates were both 49%. Complete surgical excision prolonged OS ( $P = .001$ ) and EFS ( $P = .001$ ) compared with all other therapeutic interventions. Patients with stage I disease have better EFS than those with higher stages ( $P = .003$ ), and the rate of disease events is 2.6-fold higher for stage II disease and 2.7-fold higher for stage III disease compared with stage I disease.<sup>5</sup> The rate of disease events following complete surgical excision was 14.3% for patients with T4 stage and was 0% for patients with T1 and T2 stages ( $P = .001$ ). Within this study, the MDA TNM staging system predicted OS for BIA-ALCL patients more accurately than did the Ann Arbor Lymphoma staging system ( $P = .007$ ).<sup>5</sup>

## SURGICAL AND ADJUVANT TREATMENT

The new NCCN BIA-ALCL guidelines confirm that timely diagnosis and complete surgical excision of lymphoma, implants, and the surrounding fibrous capsule is the optimal approach for the management of patients with this disease. Disease localized to the capsule (Lugano IE, MDA IA-IIA) may be treated with surgery alone in the majority of cases. Surgical goals are a total capsulectomy with removal of the breast implant with excision of any associated capsular mass and excisional biopsy of suspicious lymph node(s). At present, there is no clear role for radical mastectomy, sentinel lymph node biopsy, or full axillary dissection. Surgeons may consider removal of the contralateral implant as approximately 4.6% of cases have demonstrated incidental lymphoma in the contralateral breast.<sup>5</sup> Consultation with a surgical oncologist may be beneficial for plastic surgeons unaccustomed to surgical ablation of a malignancy. For patients with localized and resected disease the outcomes have been excellent with the great majority remaining long term progression free.

There is limited data to guide an optimal approach for patients who are unable to have a complete excision or who present with disseminated disease. Those with local residual disease, positive margins, or unresectable disease with chest wall invasion may benefit from radiation therapy. Extended disease with lymph node involvement warrants systemic therapy (Lugano II-IV, MDA IIB-IV). While data is limited, physicians may consider either a standard approach for systemic ALCL (see NCCN guidelines for first line therapy of a peripheral T-cell lymphoma) such as combination anthracycline-based chemotherapy, or alternatively Brentuximab vedotin for which promising anecdotal activity has been observed for BIA-ALCL, and reported in clinical trials for systemic ALCL.<sup>17,18</sup> Brentuximab vedotin is an antibody-drug conjugate consisting of a chimeric anti-CD30 monoclonal antibody attached to a microtubule inhibitor exerting a potent antitumor activity. Prospective trials of BIA-ALCL patients at major referral centers may help delineate chemotherapeutic sensitivity and efficacy of novel agents. Outcomes of chemotherapeutic regimens in BIA-ALCL are from small retrospective case series and a treatment plan must take into account the patient's comorbidities, previous chemotherapy exposure, and overall goals of care. NCCN believes that the best management of any patient with cancer is in a clinical trial, and therefore participation in clinical trials, when available, is especially encouraged.

## DISEASE SURVEILLANCE

Patients are observed with a clinical follow-up, history, and physical every three to six months for two years and then as clinically indicated. Physicians may include chest/

abdominal/pelvic computerized tomography (CT) scans with contrast or PET scan every 6 months for 2 years then only as clinically indicated.

## CONCLUSIONS

In summary, key points for NCCN guidelines on BIA-ALCL include:

- Symptomatic peri-prosthetic effusions greater than one year after implantation should be aspirated and screened for CD30 immunohistochemistry and flow cytometry.
- BIA-ALCL localized to the capsule may be treated with surgery alone in the majority of cases.
- Extended BIA-ALCL with lymph node involvement warrants adjuvant chemotherapy.
- Local residual or unresectable disease may require radiation therapy treatment to the chest wall in the salvage setting.
- Distant organ metastasis follows established NCCN guideline regimens for systemic ALCL treatment.

BIA-ALCL is a rare peripheral T-cell lymphoma and a standardized diagnosis and treatment approach helps ensure patients are appropriately managed in a timely fashion. BIA-ALCL NCCN guidelines include the most recent important advances in our understanding of the disease that directly impacts our diagnostic approach and therapeutic strategies. New insights into the biology of BIA-ALCL have allowed for more targeted and effective therapies. We encourage international adoption of these BIA-ALCL treatment standards by our societies across the oncology and surgery disciplines.

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