2019 NCCN Consensus Guidelines on the Diagnosis and Treatment of Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL)

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Abstract

National Comprehensive Cancer Network (NCCN) guidelines represent the consensus standard of care for diagnosis and management of the majority of known cancers. NCCN guidelines on breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) have been recognized by the US Food and Drug Administration and widely advocated by national specialty societies. Consensus guidelines have helped create a treatment standardization for BIA-ALCL at all stages of disease. NCCN guidelines are evidence-based where possible and utilize expert consensus opinion to fill in gaps that may exist. NCCN undergoes annual panel review by multidisciplinary faculty members, and this article represents the most up-to-date 2019 guidelines. Recommendations focus on parameters for achieving reliable diagnosis and disease management and emphasize the critical role for complete surgical ablation. Suggestions for adjunct treatments and chemotherapy regimens are included for advanced BIA-ALCL with lymph node involvement. BIA-ALCL recurrence and management of unresectable disease, and organ metastasis are addressed. Adherence to recognized BIA-ALCL guidelines ensures patients receive the most current efficacious treatment available.

In 2016, the World Health Organization provisionally classified breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) as a novel lymphoma.1 In the same year, the National Comprehensive Cancer Network (NCCN) established evidence-based consensus guidelines for the diagnosis and treatment of the disease, which was highlighted in this journal.2,3 NCCN guidelines on BIA-ALCL were subsequently recognized by the US Food and Drug Administration (FDA) as well as national plastic surgery societies to help physicians understand the disease and provide reliable diagnosis and treatment.4,5 A multidisciplinary team approach is essential for the management of this uncommon malignancy. BIA-ALCL is generally an indolent and localized disease with excellent prognosis when patients receive surgical excision. It remains unclear whether timely diagnosis can mitigate invasive disease or whether biologic variability of the tumor exists that affects prognosis. Advanced disease BIA-ALCL may require adjuvant treatments such as chemotherapeutic agents, radiation therapy, and stem cell transplant depending on pathology, stage of disease, and disease recurrence.6,7 This article will summarize the 2019 update of the NCCN Consensus guidelines on BIA-ALCL and highlight recommendations pertinent to a plastic surgery audience.

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For over 25 years, NCCN has created evidence-based algorithms to improve the quality of cancer care in the United States. The NCCN Clinical Practice Guidelines are based on the consensus of 27 member cancer centers and focuses on achieving optimal outcomes through prevention, accurate diagnosis, treatment, and provision of supportive services. Over 1200 clinician volunteers comprise the member committees for NCCN guidelines and are disease-specific subspecialists who have extensive experience in treating respective diseases. NCCN gives recommendations after evaluating the best evidence available at this time supplemented with expert consensus opinion to help fill gaps in evidence. As new data are published on BIA-ALCL, NCCN regularly updates recommendations to reflect new findings, current research, and clinical information that may change current standard of care. NCCN guidelines are the recognized standard in cancer care, and recommendations on BIA-ALCL have been adopted worldwide by government authorities and specialty societies. NCCN guidelines on BIA-ALCL focus on the diagnosis and management throughout the stages of disease based on the most current data available and expert consensus. BIA-ALCL guidelines undergo annual panel review among multidisciplinary faculty. The 2019 updated BIA-ALCL guidelines were achieved by a consensus of lymphoma oncologists, plastic surgeons, radiation oncologists, and surgical oncologists from the NCCN member institutions.

**Diagnosis and Workup of a Suspected Patient**

NCCN guidelines on BIA-ALCL are organized by the recommended approach for evaluating and treating a patient, specifically, symptoms, imaging, pathology and disease workup, surgery, staging, adjuvant treatments, and surveillance (Figure 1). The most common presentation of BIA-ALCL is a large spontaneous periprosthetic fluid collection occurring at least 1 year and on average 7 to 10 years following cosmetic or reconstructive implantation with a textured surface breast implant. To date, there have been no confirmed cases of a BIA-ALCL in a patient with only smooth devices. In the last safety advisory on BIA-ALCL in March 2018, the FDA...
acknowledged receiving 414 adverse event reports on BIA-ALCL, of which 30 occurred in patients who received a smooth implant. Importantly, the FDA noted that in all cases diagnosed in patients with smooth implants, the patients either had a mixed implant history of smooth and textured devices or no clinical history supplied to review. In addition to large fluid collections and delayed seromas, 8% to 24% of patients will present with an associated palpable mass and 4% to 12% with lymphade nopathy. Less commonly described (<5% of cases) are local and systemic symptoms including skin rash, fevers, and capsular contracture. Patients with a large fluid collection may have fluid levels around an implant and consequently may be misdiagnosed with an implant rupture. As a general rule, implant ruptures do not increase the overall volume of a breast. Other common etiologies for a delayed seroma are infection and recent trauma to the chest wall, which should be investigated and excluded. Every implant will likely have a scant or minimal amount (5-10 mL) of surrounding fluid, and this incidental finding in an otherwise asymptomatic patient does not require biopsy or further investigation. Initial
workup of an enlarged breast should include ultrasound evaluation for fluid collection, breast masses, and enlarged regional lymph nodes (Figure 2). Axillary (93%) lymph node involvement is most commonly followed by internal mammary and supraclavicular metastases, whereas involvement of nonregional lymph nodes is very uncommon. Adrada and colleagues investigated the diagnostic imaging findings of BIA-ALCL patients and reported the sensitivity and specificity of ultrasound for detecting an effusion (84% and 75%) or a mass (46% and 100%). In cases where ultrasound is equivocal, magnetic resonance imaging is recommended for further characterization.

Fine needle aspiration, in the clinic or by interventional radiology, is the optimal method to sample a periprosthetic fluid collection. At the time of aspiration, ultrasound may aid in implant displacement and protection. As much fluid as possible should be collected (minimum 50 mL) to aid in the diagnosis of disease. Fine needle aspiration (FNA) evaluation after previous serial drainages may artificially lower tumor burden, thus making diagnosis difficult. A suspicious mass requires tissue biopsy and evaluation. Specimens should be sent for cell morphology by cytology, CD30 immunohistochemistry, and flow cytometry for evaluation, quantification, and characterization of T cells within the specimen. CD30 immunohistochemistry is a fundamental part of the diagnostic tests for BIA-ALCL, but is not, by itself, pathognomonic because CD30 expression is nonspecific and CD30 can be expressed on benign inflammatory cells. Scant or rare CD30 positive lymphocytes with normal morphology is considered a normal finding and does not require further investigation. The diagnosis of BIA-ALCL requires careful clinicopathologic correlation, and physicians should include a relevant clinical history and directions to the pathologist to exclude BIA-ALCL. Quesada recently performed an in-depth pathology review of the stages of BIA-ALCL and emphasized the importance of excluding other malignancies or benign processes that may mimic BIA-ALCL. Additional biomarkers that may be required to establish the diagnosis and exclude other malignancies include CD2, CD3, CD4, CD5, CD7, CD8, CD45, and anaplastic lymphoma kinase (ALK) expression. BIA-ALCL is always ALK negative; however, because other systemic and cutaneous forms of ALCL are frequently ALK negative, this finding alone does not establish a diagnosis of BIA-ALCL.

Hematopathology consultation at a tertiary cancer center is strongly encouraged to establish or exclude a diagnosis of BIA-ALCL. Following exclusion of BIA-ALCL, benign...
seromas may be managed as appropriate by a plastic surgeon. The FDA recommends that all patients meeting the pathologic criteria for BIA-ALCL should be reported to the PROFILE registry of the American Society of Plastic Surgery (www.thepsf.org/PROFILE). As of December 1, 2018, the PROFILE registry had received reports of over 250 unique cases of BIA-ALCL, and the American Society of Plastic Surgery had tracked a total of over 650 unique cases in 33 countries worldwide.

Figure 4. Breast implant-associated anaplastic large cell lymphoma case example. (A) This 32-year-old woman presented with rapid onset of a right periprosthetic effusion approximately 6 years following cosmetic augmentation mastopexy with a Silimed Polyurethane textured surface implant. Breast implant-associated anaplastic large cell lymphoma was diagnosed by fine needle aspiration. (B) Demonstration of large anaplastic morphology consistent with breast implant-associated anaplastic large cell lymphoma (red arrows). Preoperative oncologic workup with positron emission tomography computed tomography scan demonstrated disease confined to the capsule with no signs of metastasis. She received surgical ablation with an en bloc resection of her implant and capsule and a contralateral explantation with capsulectomy. (C) Demonstration of a complete elevation of the implant capsule off the rib cage. (D) Demonstration of a specimen with pathology orientation sutures in place. (E) Demonstration of pathology evaluation of the capsule with removal of the malignant effusion, which is typically straw-colored, turbid, and viscous in nature (F) but may be clear, bloody, or absent. Patient’s polyurethane implant was grossly normal appearing with some adhesions to the surrounding capsule. Capsule was negative for evidence of disease invasion. (G) Patient was staged 1A and received no further treatment. She elected for no further reconstruction.

Preoperative Workup in Confirmed BIA-ALCL

Once the diagnosis of BIA-ALCL has been established, physicians are strongly encouraged to consult with a multidisciplinary team including oncologists, pathologists, surgical oncologists, and plastic surgeons. Suggested laboratory testing includes a complete blood count with differential, comprehensive metabolic panel, lactate
dehydrogenase, and hepatitis B testing (if adjuvant chemotherapy is being considered). We suggest a bone marrow biopsy for patients for whom there is a high suspicion of systemic ALCL such as patients with aggressive local invasion or lymph node metastasis. For any confirmed cases of BIA-ALCL, a preoperative positron emission tomography computed tomography (PET/CT) scan is optimal for demonstrating associated capsular masses and chest wall involvement and will serve as a “roadmap” for surgical excision (Figure 3). Due to significant surgery-induced inflammation, PET/CT scans are not reliable for evaluating local disease if performed within 2 to 3 months after surgery.

Non-Hodgkin lymphoma is traditionally staged utilizing the Lugano modification of the Ann Arbor staging system. Stage IE disease is limited to a single extranodal (E) site such as the breast or implant capsule, whereas stage IIE disease is defined as extranodal disease with spread to or involvement of local lymph nodes. Employing 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%). Due to the limited applicability of the Ann Arbor staging system for BIA-ALCL, which does not account for capsular invasion or penetration, NCCN guidelines now include the recently proposed tumor, lymph node, metastasis (TNM) solid tumor staging system modeled after the American Joint Committee on Cancer TNM (Table 1). Early manuscripts suggested that BIA-ALCL presentation is binary, either effusion limited or an invasive mass. However, the TNM classification describes BIA-ALCL as a spectrum of disease from IA (35-70%, effusion only), IB (3-11%), IC (8-13%), IIA (8-25%), IIB (3-5%), and III (3-9%) to stage IV (1-2%). Note that BIA-ALCL is classified as a lymphoma at all stages and presentations. Although indolent early on, BIA-ALCL is a malignancy and not considered benign at any stage.

Figure 4. Continued
In a study of 87 BIA-ALCL patients, Clemens et al reported an overall survival rate of 94% and 91% at 3 and 5 years, respectively. Within this study, solid tumor TNM staging predicted survival and recurrence for BIA-ALCL more accurately than Ann Arbor staging ($P = 0.01$).  

**Surgical Treatment With en Bloc Explantation**  
Essential to the treatment of BIA-ALCL is timely diagnosis and complete surgical excision. The goals of surgery
should be to remove the implant with the surrounding fibrous capsule and any associated capsule mass (Figure 4). Complete surgical excision prolongs overall survival ($P = 0.001$) and event-free survival ($P = 0.001$) compared with all other therapeutic interventions. Surgical specimens should be oriented and inked to allow for the anatomic location of the diseases. This is important for tumor site surveillance and in cases of recurrence requiring reexcision. At present, there is no clear role for radical mastectomy or sentinel lymph node biopsy. Full axillary dissection has been used rarely for gross involvement of multiple lymph nodes (Figure 5). An estimated 2% to 4% of patients develop bilateral disease, and therefore surgeons may consider removal of the contralateral implant and capsule. A surgical oncology consultation is not compulsory, but may be beneficial for plastic surgeons unaccustomed to optimal surgical resection of a malignancy.

Complete resection of disease is associated with excellent, long-term, disease-free survival (Figure 6). Disease localized to the capsule (Lugano IE, MD Anderson Cancer Center [MDA] IA-IIA) may be treated with surgery alone in most cases if complete surgical excision is possible, though a slightly higher rate of recurrence is noted with invasive disease. The rate of disease events and recurrence is 2.6-fold higher for stage II disease and 2.7-fold higher for stage III disease compared with stage I disease. The rate of disease events following complete surgical excision is 14.3% for patients with T4 disease compared with 0% for patients with T1-T3 disease ($P = 0.001$). Local recurrence is most common following incomplete resections or partial capsulectomies (Figure 7). Radioactive seed localization can facilitate surgical resection. All attempts should be made to gain complete surgical resection because retained or unresectable disease likely indicates the need for adjuvant treatments.
Figure 7. Management of breast implant-associated anaplastic large cell lymphoma with local disease recurrence. A 52-year-old woman developed a left delayed seroma of the right breast 9 years following cosmetic augmentation with Biocell textured surface implants. After repeated aspirations, she elected for explantation and received a partial anterior strip capsulectomy during implant removal. Pathology from the case demonstrated BIA-ALCL with capsule invasion, however no further treatment was performed at this time. Eleven months following surgery, the patient developed a 2cm medial breast mass adjacent to her previous capsule, which is shown on (A, red arrow) positron emission tomography computed tomography scan and (B, red arrow) magnetic resonance imaging. (C, Red arrow) Ultrasound-guided radioactive seed placement was performed to aid in surgical localization, and preoperative seeds (D, red arrow) within the mass are shown in a mammogram. (E) Radiograph was performed intraoperatively to confirm complete excision of the mass and radioactive seeds which defined the boundaries of the mass (red arrows), with adequate surrounding margins. The patient remains disease-free after 2 years.
**Adjuvant Treatments**

There are no prospective trials to guide the management of patients with disseminated disease, and treatment paradigms are generally extrapolated from the treatment experience of primary cutaneous and systemic ALCL. Local or involved site radiation therapy with 24 to 36 Gray (Gy) is suggested for patients with local residual disease, positive margins, or unresectable disease with chest wall invasion. Systemic therapy is warranted in patients with Lugano stage II-IV or MDA stage IIB-IV disease. Oncologists can consider either a standard approach for systemic ALCL (NCCN guidelines for first-line therapy of a peripheral T-cell lymphoma) such as combination anthracycline-based chemotherapy or, alternatively, a combination with brentuximab vedotin. Case reports have demonstrated favorable activity of brentuximab vedotin in BIA-ALCL, and the combination of anthracycline-based chemotherapy and brentuximab vedotin demonstrated an overall survival advantage compared with chemotherapy alone in the first-line treatment of CD30 expressing peripheral T-cell lymphomas in the ECHELON II trial. Based on the results of the ECHELON II trial, the addition of brentuximab is now considered “preferred” first line therapy for peripheral T-cell lymphomas. The treatment plan must also consider the patient’s comorbidities, previous chemotherapy exposure, and overall goals of care.

**Disease Surveillance**

Patients who have a complete response with treatment can be monitored with history and physical every 3 to 6 months for 2 years and then as clinically indicated. The role of routine radiographic surveillance is unclear, but either a chest/abdominal/pelvic CT scan with contrast or PET scan could be considered every 6 months for 2 years then only as clinically indicated.

**CONCLUSIONS**

The 2019 update to the NCCN BIA-ALCL guidelines represents the most evidence-based approach to the disease based on the most current research. Symptomatic peri-prosthetic effusions greater than 1 year after implantation should be tested for BIA-ALCL. BIA-ALCL presents as a spectrum of stages from an effusion-limited lymphoma to invasive disease, and metastasis. This is considered a malignancy at all stages and presentations. When diagnosed early, BIA-ALCL is commonly indolent and slow growing with an excellent prognosis, particularly when treated with surgery. NCCN guidelines remain the recognized standard for diagnosis and treatment and ensure that patients are managed in a timely and appropriate fashion.

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