

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.

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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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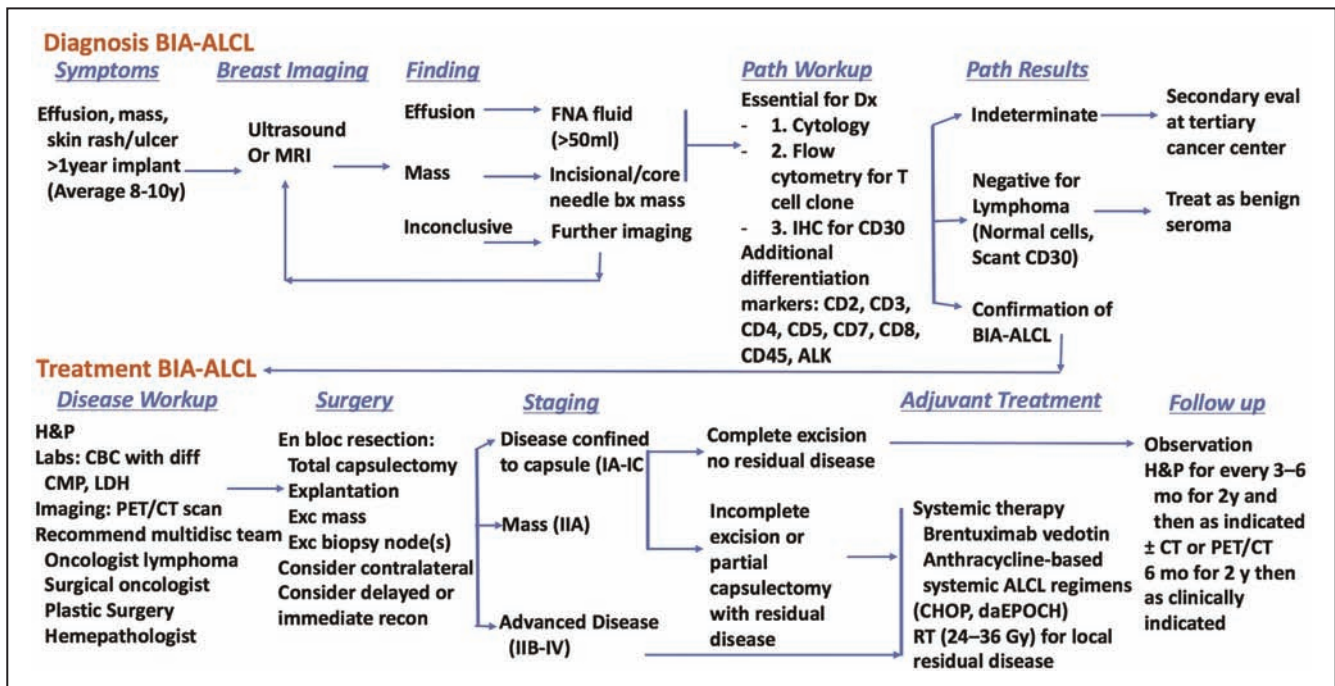


Figure 1. Breast implant-associated anaplastic large cell lymphoma disease algorithm. Current evidence-based algorithm for achieving diagnosis followed by treatment by stage of disease. Bx, biopsy; CBC, complete blood count; CHOP, cyclophosphamide doxorubicin vincristine prednisolone; CMP, complete metabolic profile; daE, dose adjusted etoposide; FNA, fine needle aspiration; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; PET/CT, positron emission tomography computed tomography; RT, radiation therapy.

For over 25 years, NCCN has created evidence-based algorithms to improve the quality of cancer care in the United States.⁸ 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. In addition to physician providers, NCCN guidelines also inform insurance providers to ensure needed patient care is indicated and approved. All NCCN guideline algorithms can be found at www.nccn.org, and this article represents a summary by NCCN lymphoma committee members.

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.^{9,10} In the last safety advisory on BIA-ALCL in March 2018, the FDA

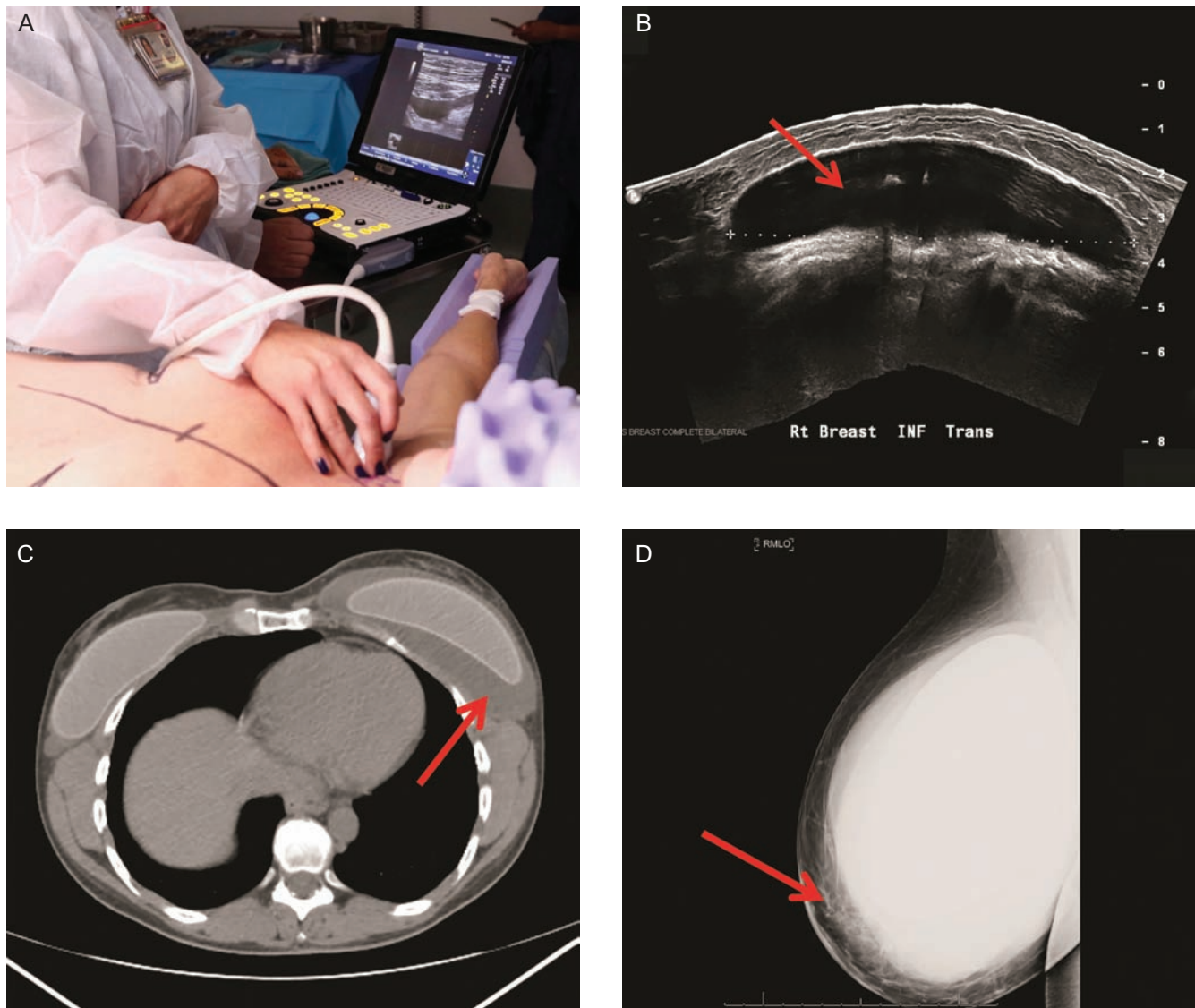


Figure 2. Imaging in suspected breast implant-associated anaplastic large cell lymphoma patients. Patients presenting with an enlargement of the breast more than 1 year after implantation should be evaluated with ultrasound. (A) Ultrasound should include implant, chest wall, regional lymph node basins, and contralateral breast implant. (B) Computed tomography scan or (C) magnetic resonance imaging may aid in diagnosis for soft tissue masses when ultrasound is indeterminate. Red arrows indicate periprosthetic fluid collections. Mammography is a poor imaging modality for breast implant-associated anaplastic large cell lymphoma and is less sensitive for effusions and/or masses that do not display calcifications. (D) Red arrow indicates a periprosthetic mass.

acknowledged receiving 414 adverse event reports on BIA-ALCL, of which 30 occurred in patients who received a smooth implant.⁵ 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 lymphadenopathy.^{3,7,8,11} 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.¹² 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

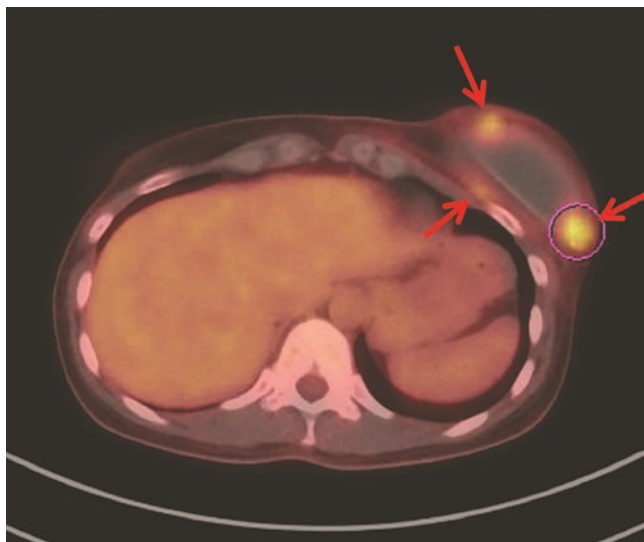


Figure 3. Imaging in pathology confirmed breast implant-associated anaplastic large cell lymphoma patients. After diagnosis of breast implant-associated anaplastic large cell lymphoma, oncologic workup should include imaging with a trunk positron emission tomography computed tomography scan to determine any associated capsular masses lymphadenopathy or any organ metastasis. The patient demonstrates infiltrative disease with 2 capsular masses, indicated by red arrows. positron emission tomography computed tomography scan can act as a surgical roadmap to guide surgical planning and resection.

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.¹³ 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.¹⁴

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

Table 1. TNM Stage Classification of BIA-ALCL^a

| TNM classification | | TNM stage | |
|--------------------|--|-----------|--------------|
| T: Tumor extent | | IA | T1 N0 M0 |
| T1 | Confined to effusion or a layer on luminal side of capsule | IB | T2 N0 M0 |
| T2 | Early capsule infiltration | IC | T3 N0 M0 |
| T3 | Cell aggregates or sheets infiltrating the capsule | IIA | T4 N0 M0 |
| T4 | Lymphoma infiltrates beyond the capsule | IIB | T1-3 N1 M0 |
| N: Lymph node | | III | T4 N1-2 M0 |
| N0 | No lymph node involvement | IV | Tany Nany M1 |
| N1 | One regional lymph node (+) | | |
| N2 | Multiple regional lymph nodes (+) | | |
| M: Metastasis | | | |
| M0 | No distant spread | | |
| M1 | Spread to other organs/distant sites | | |

BIA-ALCL, breast implant-associated anaplastic large cell lymphoma; NCCN, National Comprehensive Cancer Network; TNM, tumor, lymph node, metastasis. ^aA solid tumor TNM staging of disease based on clinical and pathological evaluation was first proposed in 2016 by MD Anderson Cancer Center and is now included in the 2019 update of the NCCN guidelines.

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.^{15,16} 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.¹⁷ 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

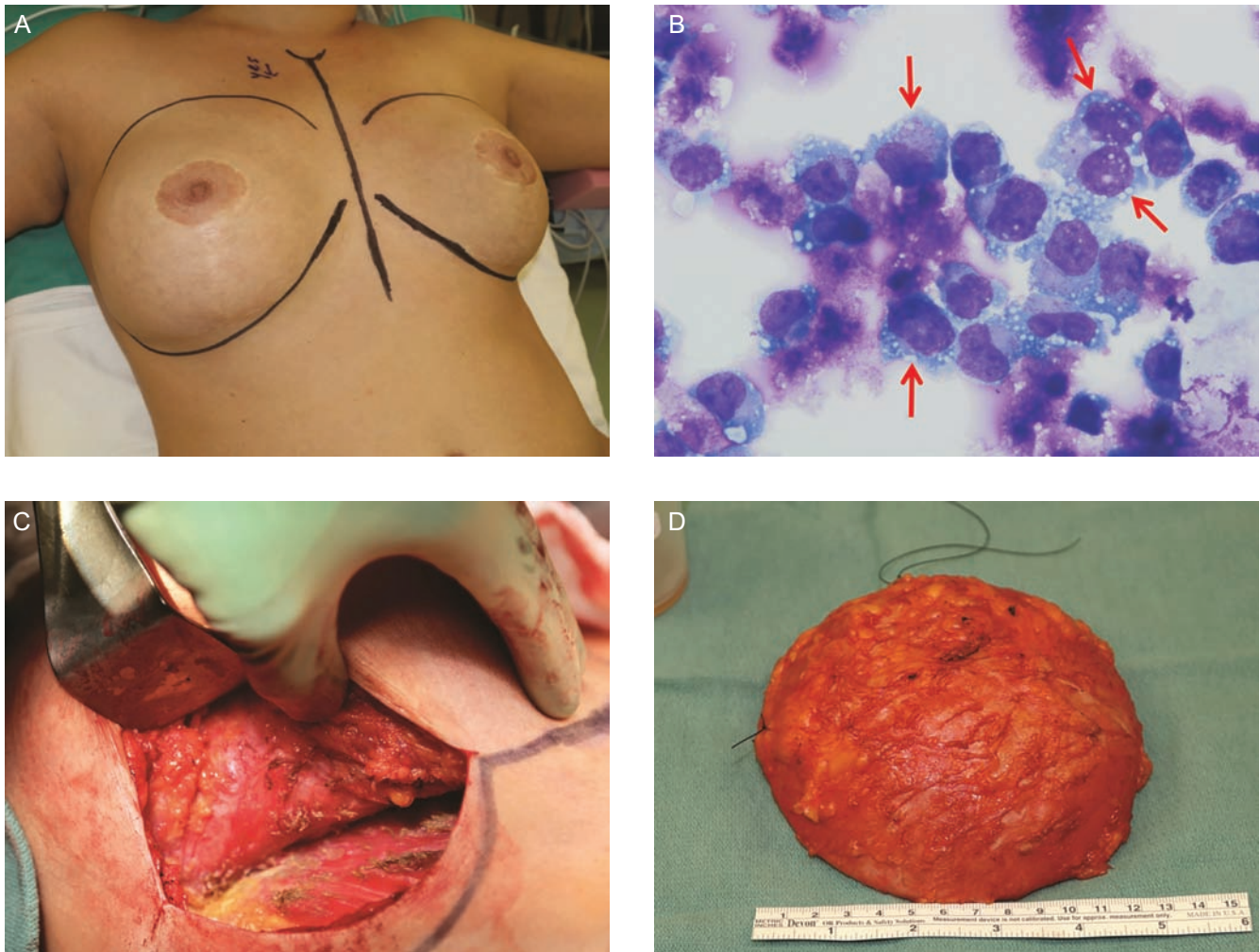


Figure 4. Breast implant-associated anaplastic large cell lymphoma case example. (A) This 32-year-old woman presented with rapid onset of a right periprosthetic effusion approximately 6 years following cosmetic augmentation mastopexy with a Silimed Polyurethane textured surface implant. Breast implant-associated 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.

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).¹⁸ 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.

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

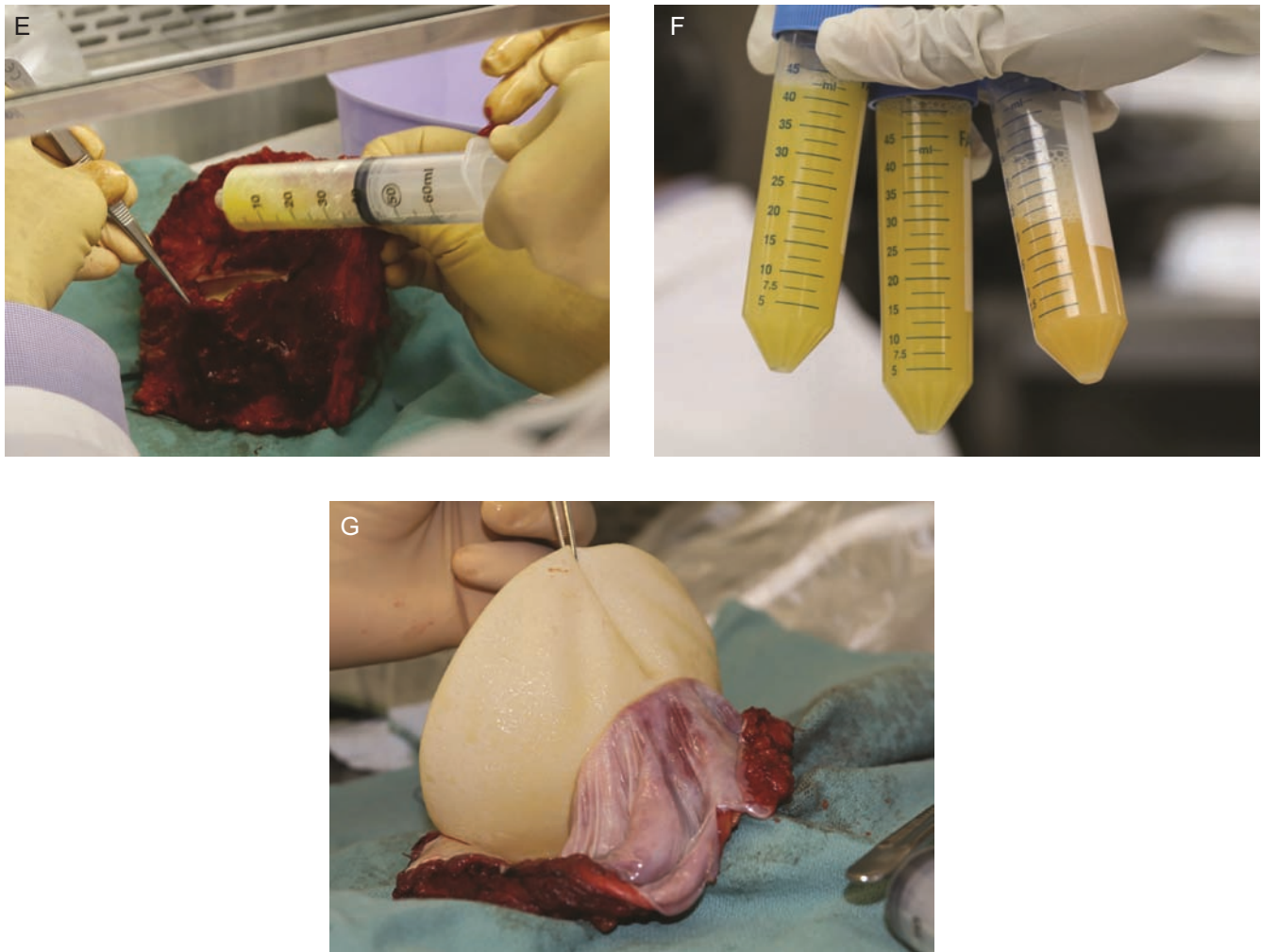


Figure 4. Continued

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).⁹ 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.¹⁹ 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%).^{4,7} 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.²⁰ 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%).^{7,14,21} 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.

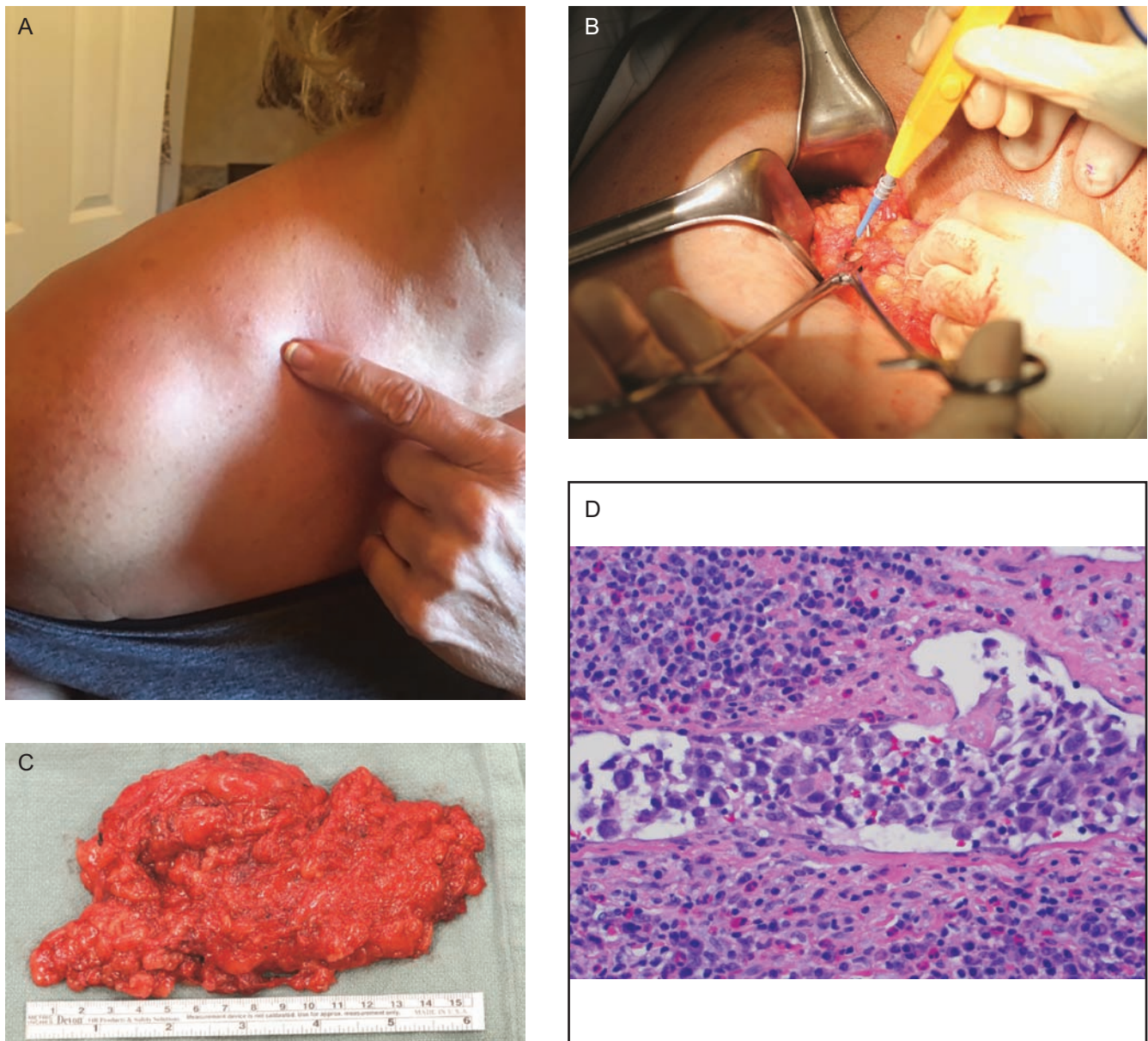


Figure 5. Breast implant-associated anaplastic large cell lymphoma lymph node metastasis. (A) This 57-year-old woman demonstrates a right supraclavicular lymph node metastasis as part of an advanced case of breast implant-associated anaplastic large cell lymphoma. In addition to surgical resection, the patient received chemotherapy. (B) A separate 46 year old female with multiple axillary lymph node metastasis is shown receiving a full axillary dissection in addition to an en bloc resection. (C) Pathology specimen ultimately demonstrated 16 positive lymph nodes for breast implant-associated anaplastic large cell lymphoma, and the patient was also recommended chemotherapy. (D) Histology from the 46 year old patient demonstrates characteristic sinusoidal pattern of lymph node infiltration of breast implant-associated anaplastic large cell lymphoma metastasis.

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 ($P = 0.01$).⁷

Surgical Treatment With en Bloc Explantation

Essential to the treatment of BIA-ALCL is timely diagnosis and complete surgical excision.⁷ The goals of surgery

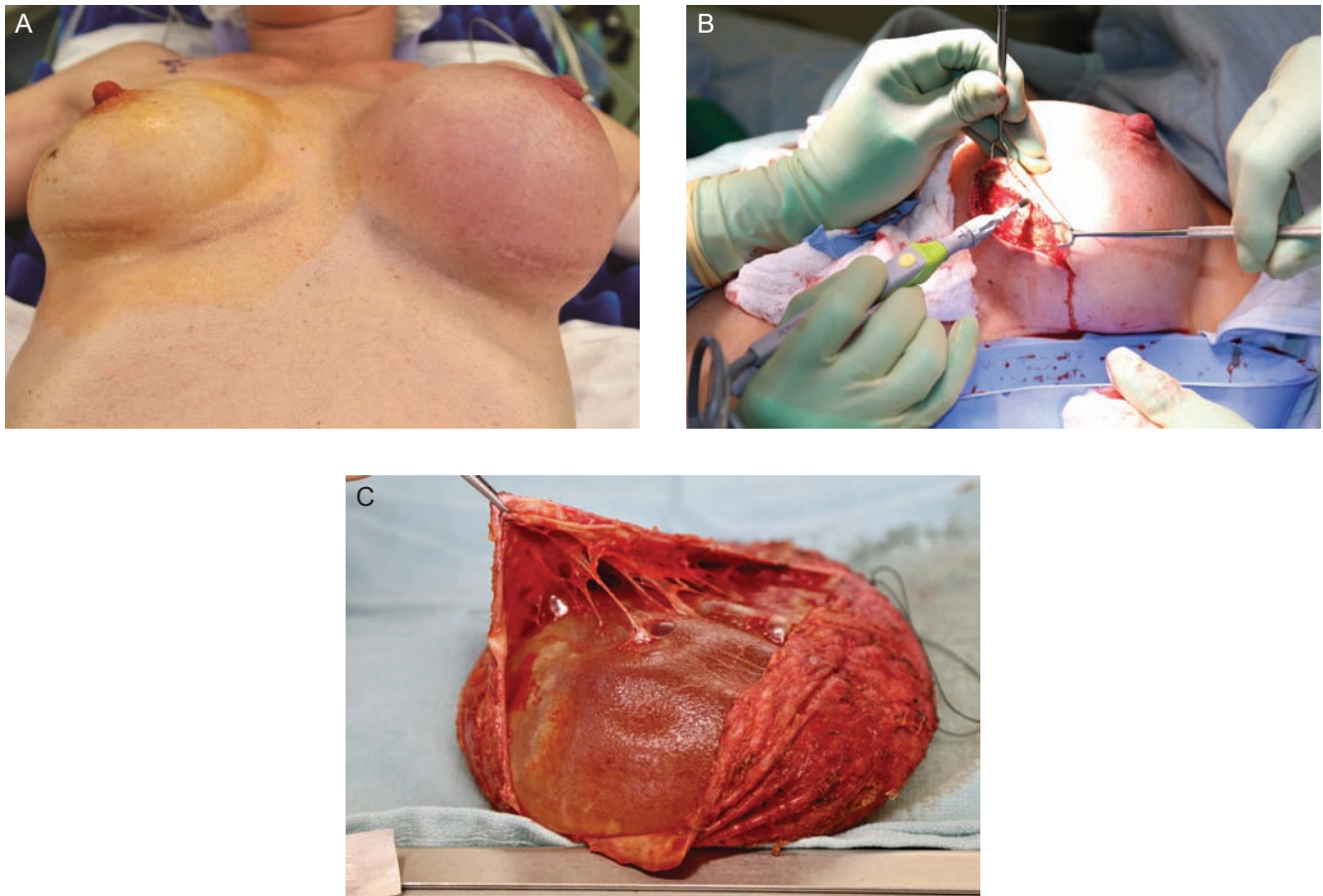


Figure 6. Surgical ablation of breast implant-associated anaplastic large cell lymphoma. (A) This 38-year-old woman presented with an outside misdiagnosis of left breast implant rupture and spontaneous capsular contracture. She had a periprosthetic effusion around an intact implant by ultrasound evaluation and was diagnosed with BIA-ALCL following fine needle aspiration. (B) Surgical en bloc resection was performed through her inframammary fold incision. (C) The implant is shown with double capsule formation and capsular adhesions. Disease was invasive into but not beyond the capsule, and she was a stage 1C and required no further treatment.

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.⁸ 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.⁷ 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 ($P = 0.001$).⁷ 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.

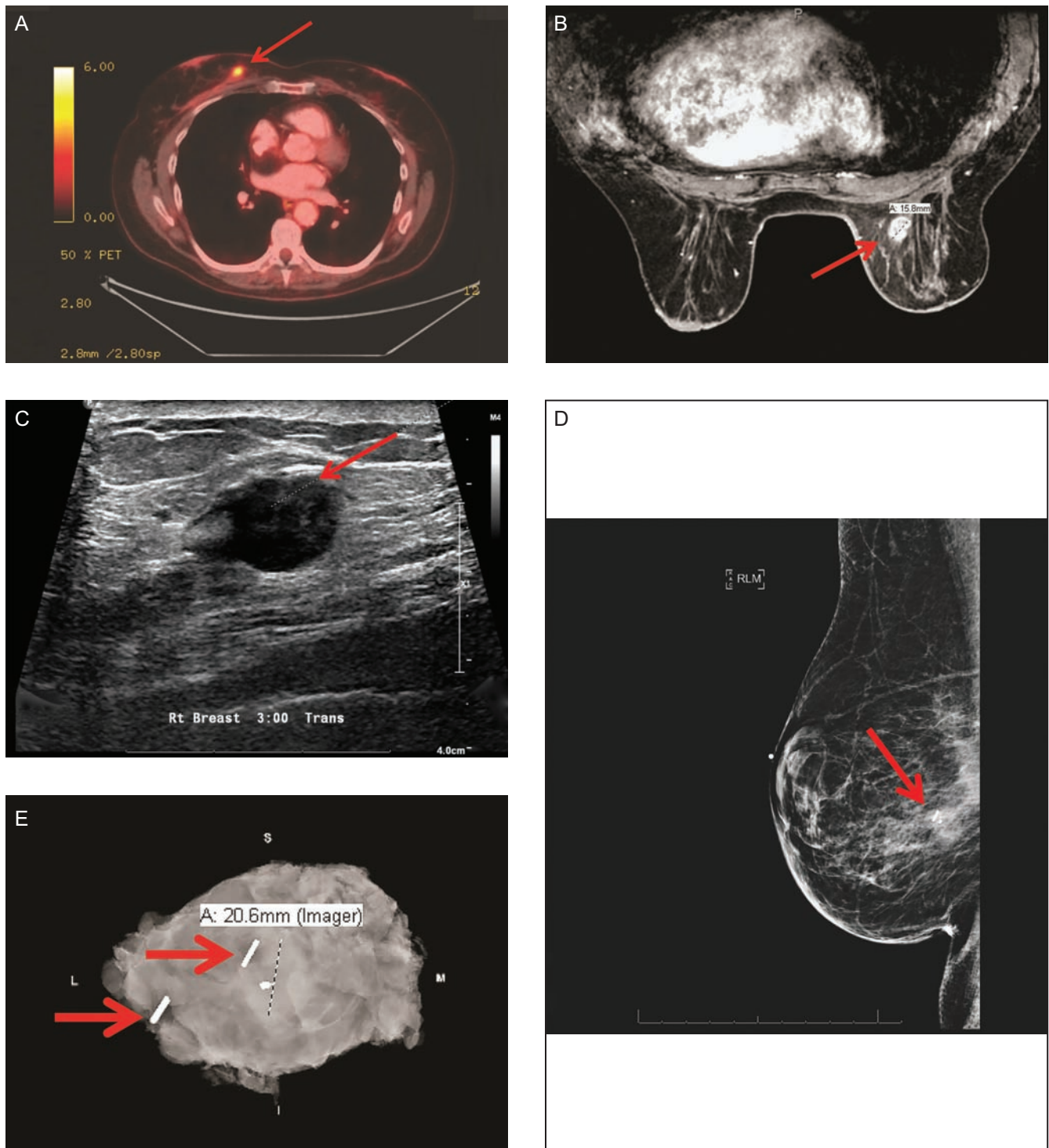


Figure 7. Management of breast implant-associated anaplastic large cell lymphoma with local disease recurrence. A 52-year-old woman developed a left delayed seroma of the right breast 9 years following cosmetic augmentation with Biocell textured surface implants. After repeated aspirations, she elected 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.²²⁻²⁷ 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 periprosthetic 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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Disclosures

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REFERENCES

1. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood*. 2016;127(20):2375-2390.
2. Clemens MW, Horwitz SM. NCCN consensus guidelines for the diagnosis and management of breast implant-associated anaplastic large cell lymphoma. *Aesthet Surg J*. 2017;37(3):285-289.
3. Clemens MW, Brody GS, Mahabir RC, Miranda RN. How to diagnose and treat breast implant-associated anaplastic large cell lymphoma. *Plast Reconstr Surg*. 2018;141(4):586e-599e.
4. US Food & Drug Administration. Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL). <https://www.fda.gov/medicaldevices/productsandmedicalprocedures/implantsandprosthetics/breastimplants/ucm239995.htm>. Accessed September 1, 2018.
5. ASAPS and ASPS BIA-ALCL Advisory Update. <https://surgery.org/sites/default/files/BIA-7-31-18.pdf>. Accessed August 15, 2018.
6. Miranda RN, Aladily TN, Prince HM, et al. Breast implant-associated anaplastic large-cell lymphoma: long-term follow-up of 60 patients. *J Clin Oncol*. 2014;32(2):114-120.
7. Clemens MW, Medeiros LJ, Butler CE, et al. Complete surgical excision is essential for the management of patients with breast implant-associated anaplastic large-cell lymphoma. *J Clin Oncol*. 2016;34(2):160-168.
8. National Comprehensive Cancer Network. www.nccn.org/about Accessed January 1, 2019.
9. Brody GS, Deapen D, Taylor CR, et al. Anaplastic large cell lymphoma occurring in women with breast

- implants: analysis of 173 cases. *Plast Reconstr Surg.* 2015;135(3):695-705.
10. Doren EL, Miranda RN, Selber JC, et al. U.S. epidemiology of breast implant-associated anaplastic large cell lymphoma. *Plast Reconstr Surg.* 2017;139(5):1042-1050.
 11. Loch-Wilkinson A, Beath KJ, Knight RJW, et al. Breast implant-associated anaplastic large cell lymphoma in Australia and New Zealand: high-surface-area textured implants are associated with increased risk. *Plast Reconstr Surg.* 2017;140(4):645-654.
 12. Bengtson B, Brody GS, Brown MH, et al.; Late Periprosthetic Fluid Collection after Breast Implant Working Group. Managing late periprosthetic fluid collections (seroma) in patients with breast implants: a consensus panel recommendation and review of the literature. *Plast Reconstr Surg.* 2011;128(1):1-7.
 13. Ferrufino-Schmidt MC, Medeiros LJ, Liu H, et al. Clinicopathologic features and prognostic impact of lymph node involvement in patients with breast implant-associated anaplastic large cell lymphoma. *Am J Surg Pathol.* 2018;42(3):293-305.
 14. Adrada BE, Miranda RN, Rauch GM, et al. Breast implant-associated anaplastic large cell lymphoma: sensitivity, specificity, and findings of imaging studies in 44 patients. *Breast Cancer Res Treat.* 2014;147(1):1-14.
 15. Chott A, Vonderheid EC, Olbricht S, Miao NN, Balk SP, Kadin ME. The dominant T cell clone is present in multiple regressing skin lesions and associated T cell lymphomas of patients with lymphomatoid papulosis. *J Invest Dermatol.* 1996;106(4):696-700.
 16. Kadin ME, Deva A, Xu H, et al. Biomarkers provide clues to early events in the pathogenesis of breast implant-associated anaplastic large cell lymphoma. *Aesthet Surg J.* 2016;36(7):773-781.
 17. Quesada AE, Medeiros LJ, Clemens MW, Ferrufino-Schmidt MC, Pina-Oviedo S, Miranda RN. Breast implant-associated anaplastic large cell lymphoma: a review. *Mod Pathol.* 2018. doi: 10.1038/s41379-018-0134-3. [Epub ahead of print]
 18. US Food & Drug Administration. Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL). <http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/BreastImplants/ucm239995.htm>. Accessed July 6, 2016.
 19. Cheson BD, Fisher RI, Barrington SF, et al; Alliance, Australasian Leukaemia and Lymphoma Group; Eastern Cooperative Oncology Group; European Mantle Cell Lymphoma Consortium; Italian Lymphoma Foundation; European Organisation for Research; Treatment of Cancer/Dutch Hemato-Oncology Group; Grupo Español de Médula Ósea; German High-Grade Lymphoma Study Group; German Hodgkin's Study Group; Japanese Lymphoma Study Group; Lymphoma Study Association; NCIC Clinical Trials Group; Nordic Lymphoma Study Group; Southwest Oncology Group; United Kingdom National Cancer Research Institute. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol.* 2014;32(27):3059-3068.
 20. Roden AC, Macon WR, Keeney GL, Myers JL, Feldman AL, Dogan A. Seroma-associated primary anaplastic large-cell lymphoma adjacent to breast implants: an indolent T-cell lymphoproliferative disorder. *Mod Pathol.* 2008;21(4):455-463.
 21. de Boer M, van Leeuwen FE, Hauptmann M, et al. Breast implants and the risk of anaplastic large-cell lymphoma in the breast. *JAMA Oncol.* 2018;4(3):335-341.
 22. Johnson L, O'Donoghue JM, McLean N, et al. Breast implant associated anaplastic large cell lymphoma: the UK experience. Recommendations on its management and implications for informed consent. *Eur J Surg Oncol.* 2017;43(8):1393-1401.
 23. Duvic M, Tetzlaff MT, Gangar P, Clos AL, Sui D, Talpur R. Results of a phase II trial of brentuximab vedotin for CD30+ cutaneous T-cell lymphoma and lymphomatoid papulosis. *J Clin Oncol.* 2015;33(32):3759-3765.
 24. Kim YH, Tavallaee M, Sundram U, et al. Phase II investigator-initiated study of brentuximab vedotin in mycosis fungoides and sézary syndrome with variable CD30 expression level: a multi-institution collaborative project. *J Clin Oncol.* 2015;33(32):3750-3758.
 25. Prince HM, Kim YH, Horwitz SM, et al.; ALCANZA study group. Brentuximab vedotin or physician's choice in CD30-positive cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial. *Lancet.* 2017;390(10094):555-566.
 26. Younes A, Bartlett NL, Leonard JP, et al. Brentuximab vedotin (SGN-35) for relapsed CD30-positive lymphomas. *N Engl J Med.* 2010;363(19):1812-1821.
 27. Pro B, Advani R, Brice P, et al. Brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large-cell lymphoma: results of a phase II study. *J Clin Oncol.* 2012;30(18):2190-2196.