The following advisory represents a collaborative effort between the American Society for Aesthetic Plastic Surgery (The Aesthetic Society) and the American Society of Plastic Surgeons (ASPS) to provide biannual updates for members on recent disease developments, government regulatory communications, and consensus recommendations related to breast implant-associated anaplastic large cell lymphoma (BIA-ALCL).

UPDATES

Q: What does the latest Food and Drug Administration (FDA) statement say in regard to breast implant-associated anaplastic large cell lymphoma (BIA-ALCL)?

A: The FDA's February 2019 statement recognizes BIA-ALCL, a lymphoma that is associated with breast implants regardless of filling or texture. The FDA also acknowledged and agreed with the World Health Organization's classification of BIA-ALCL as a lymphoma, and the National Comprehensive Cancer Network (NCCN) treatment guidelines.*

The FDA noted surgical management for the majority of patients, and recommends all confirmed BIA-ALCL cases be reported to the **PROFILE registry**** for detailed tracking in addition to FDA's MDR reporting. The statement also affirmed that if a breast implant patient is not experiencing symptoms, there "is no need to change your routine medical care and follow-up."

The FDA states that while the majority of patients who develop BIA-ALCL have had textured implants, and cases reported in the literature describe individuals who have had textured implants, there have been reports of BIA-ALCL in patients with smooth-surfaced implants at the time of diagnosis. However, it is unclear whether or not these patients had a previous textured device. In addition, 30 percent of all cases reported to the FDA do not include the surface texture of the implant at the time of diagnosis.

Both organizations note that, to date, no pure smooth-only cases have been reported to the PROFILE registry, or been reported in case reports or case series.

On March 25-26, 2019, the FDA held an advisory committee panel on breast implant safety, which **reviewed data presented by surgeons, patients and manufacturers**. The panel specifically focused on 1. BIA-ALCL, 2. systemic symptoms described as Breast Implant Illness (BII), 3. creation of breast implant prospective registries, 4. use of surgical mesh in breast reconstruction, 5. MRI screening recommendations to detect silent rupture, 6. breast implant informed consent, and 7. Use of real-world data and patient perspectives in regulatory decision-making.

On May 2, 2019, the FDA Principal Deputy Commissioner Amy Abernethy, MD, released a statement on **new initiatives** to "protect women's health." This included a commitment to standardized informed consent, breast implant registries, and possible black box label warnings in the future.

**The NCCN is an alliance of 27 cancer centers in the United States which establishes consensus*

diagnosis and treatment recommendations for the majority of known cancers. The NCCN established evidence-based guidelines for BIA-ALCL in 2016, which are updated annually.

The PROFILE registry was created in 2012 by ASPS, The PSF and the FDA to prospectively track confirmed BIA-ALCL patients in the United States. PROFILE data is regularly updated and available by contacting* ***www.thepsf.org/PROFILE*.*

Q: How are other regulatory organizations worldwide handling BIA-ALCL?

In November 2018, the French regulatory body, National Agency for Medicines and Health Products Safety (ANSM), recommended against using macrotextured breast implants. On Feb. 7-8, 2019, the ANSM held breast implant safety hearings to review data presented by surgeons, patients and manufacturers.

In December 2018, the French Notified Body (GMED), which regulates medical devices in Europe, did not renew Allergan's CE mark* for Biocell and Microcell implants and tissue expanders. Subsequently, 38 countries (including 33 European nations, South Africa, Israel, Singapore and Colombia) have restricted further sales of these devices and, in some countries, Allergan has performed a voluntary recall of existing product stores. This recall does not apply to already implanted devices and importantly, there are NO recommendations for prophylactic explantation of breast implants. These regulatory decisions do not currently affect sales in the United States.

On May 28, 2019, Health Canada released an advisory stating that Allergan was notified of a suspension of its licenses for Biocell breast implants as a "precautionary measure."

**CE mark is a certification that indicates conformity to standards for products sold within the European Economic Area. Manufacturers must apply and obtain a CE mark to sell medical devices within the European Union.*

GENERAL

Q: What is BIA-ALCL?

A: BIA-ALCL is an uncommon lymphoma that has been reported most commonly in patients with a history of a textured breast implant device. When caught early, it is curable in most patients. BIA-ALCL is not a cancer of the breast tissue itself, but of the scar envelope that the body naturally forms around a breast implant – called the capsule. All government authorities and oncology organizations currently classify BIA-ALCL as a lymphoma.*

BIA-ALCL consists of a spectrum of disease stages that range from an indolent CD30+ fluid effusion within the capsule, to capsular tumors, to lymph node involvement and rarely distant metastases. BIA-ALCL is not considered benign at any stage. Ongoing research continues to strive to better understand and define BIA-ALCL.

**Lymph cells are part of the body's immune system that helps to protect and rid the body from*

noxious agents. A lymphoma is cancer of the lymph system. Lymph nodes are glands in many locations in the body that are part of the lymph system. Indolent refers to a cancer that is slow to progress.

Q: What is the risk of developing BIA-ALCL?

A: On Feb. 6, 2019, the FDA issued an open letter to physicians stating that it had received 660 adverse event reports of BIA-ALCL and that, after careful review, removal of duplicates and verification of pathology, there were 457 unique cases, including nine disease-related deaths. These reports were not limited to the United States. The FDA warns that this adverse event report data is "unverified." The ASPS/FDA PROFILE registry reports 282 unique U.S. cases to date. In the United States, approximately 300,000 breast augmentations and 150,000 breast reconstructions are performed annually. Less than 12 percent of these patients receive textured implants based upon published manufacturer sales data.

The lifetime risk of developing BIA-ALCL, from epidemiological studies and implant sales data from the U.S., Canada, Netherlands and Australia, ranges from 1:1,000 to 1:30,000 with textured implants. There appears to be some variability in risk depending on the type of implant texturing, with Allergan Biocell and polyurethane brands having disproportionately higher risks.

Q: Is BIA-ALCL a major concern?

A: A total of 282 distinct, suspected/confirmed cases of BIA-ALCL in the United States were reported to PROFILE from October 2011 to May 29, 2019. To date, complete case report forms have been submitted for 103 (37 percent) of these cases. Of this subset, 50 percent had a history of cosmetic breast augmentation; 49 percent had a history of post-mastectomy reconstruction. Worldwide, 717 suspected/confirmed cases have been reported, which includes 21 disease-related deaths.

The Aesthetic Society and ASPS provide online patient education tools that help breast implant patients put this disease in perspective. The relative risk of capsular contracture is approximately 100 to 3,000 times higher than BIA-ALCL. Though the risk is small, patient safety is the primary focus of the plastic surgery community, and we strive to educate and inform our members and the public about BIA-ALCL.

Q. Have there been any deaths attributed to BIA-ALCL?

A. There have been 21 confirmed deaths attributed to BIA-ALCL to date, which includes five U.S. cases. Disease-related deaths have been reported in Argentina, Australia, Brazil, Canada, France, Netherlands, New Zealand, Sweden, United Kingdom and the United States. In the 21 known deaths from the disease, all had either incomplete capsule removal or the disease spread prior to treatment (metastatic disease). In the majority of these cases, patients succumbed to disease progression into the chest wall and mediastinum.

PATHOGENESIS

Q: What causes BIA-ALCL?

A: The following are the current risk factors for BIA-ALCL based on compiled research:

1. Textured-surface device. Confirmed cases of BIA-ALCL have occurred in patients who either have or had a history of a textured implant(s).

2. Genetics. There have been two published reports that there may be a genetic predisposition (mutations in JAK1, STAT3 genes). Further investigation is required.

3. Inflammation. Chronic inflammation possibly triggered by an allergic response, bacteria, another as-yet-unknown factor, or some combination have all been theorized.

4. Time. BIA-ALCL typically presents several years (average 8 years, range 2-28 years) after the implants were placed.

ASPS, PSF*, The Aesthetic Society, ASERF* and the FDA are studying BIA-ALCL. Bacterial contamination, long-term allergic inflammation and/or irritation from implant texturing, and genetic factors have been theorized and are undergoing further study. Research is ongoing and cases are being monitored.

Concentrations of reported cases vary widely across the globe, with some geographic areas reporting very few cases. Ongoing data collection worldwide will help to determine any genetic propensities for this disease.

**Plastic Surgery Foundation (PSF); Aesthetic Surgery Education and Research Foundation (ASERF).*

Q: What are the differences in implant texture and how does this difference factor into BIA-ALCL research?

A: BIA-ALCL appears to develop predominantly in patients who have textured implants. There is a higher incidence of BIA-ALCL in higher surface area/roughness devices, such as Allergan Biocell and polyurethane coating*, compared to those that have less surface area. However, BIA-ALCL has been identified in patients with all types/brands of textured surfaces.

In both United States- and worldwide-reported cases of BIA-ALCL, there does not appear to be a difference in risk for silicone- versus saline-filled implants, nor between reconstructive or cosmetic use of breast implants.

**Polyurethane sponge covered implants have not been available in the United States since the early 1990s.*

PATIENTS CONSIDERING BREAST IMPLANTS

Q: What is important to discuss with patients considering breast implantation?

A: The FDA confirms that all breast implants carry a reasonable assurance of safety when used as indicated. Best practice requires plastic surgeons to discuss the known risks and potential complications associated with any procedure. It is important for the patient and her surgeon to frankly discuss all treatment options available, along with the benefits and risks of implants, both smooth and textured, including BIA-ALCL, capsular contracture, implant malposition and rates of reoperation. Any procedural risk that may lead to the death of a patient must be considered a major concern, albeit exceedingly uncommon. The patient must then make an informed decision based upon her own assessment of her needs and the risks involved.

PATIENTS WITH BREAST IMPLANTS

Q: How does this impact those who already have breast implants?

A: The Aesthetic Society, ASPS, and the FDA advocate that all patients with breast implants follow their normal routine medical care and follow up, including mammography if indicated. Patients should immediately contact their physician if they sense any abnormalities within the breast or notice any significant changes. Fluid collections around implants within the implant capsules can occur and are usually not malignant. However, if the fluid collection around the implant is present one year or more after implantation, it MUST be aspirated to rule out for BIA-ALCL.

Q: Should healthy patients have their implants removed prophylactically?

A: The FDA does not suggest additional screening or removal of implants for patients who are not having symptoms.

Q: What is the recommended course of action for an asymptomatic patient with textured implants who wants his/her implants removed?

A: Physicians should thoroughly discuss the risks of prophylactic implant removal with their patients, adding that the risks associated with surgery are greater than the risk of developing BIA-ALCL. If the patient still would like her implants removed after this discussion, it is recommended to remove the implants and the capsules. However, physicians should let their patients know that removing the capsules is not always feasible.

Q: Should patients with breast implants be screened for BIA-ALCL?

A: The FDA advises that patients without breast changes do not require more than routine follow-up. If a patient experiences a change in her breasts – especially if there is swelling or a lump – she should see her surgeon and undergo examination, imaging and fluid testing, if present.

Q: Should patients with implants in place be followed on a routine basis, i.e., annually?

A: The FDA recommends patients with silicone-filled implants be screened post-operatively with MRI to diagnose implant rupture, but this may or may not detect BIA-ALCL. Periodic clinical examination

for implant patients is recommended, as one would do to screen for implant complications such as capsular contracture.

SYMPTOMS AND DIAGNOSIS

Q: What are the symptoms of BIA-ALCL?

A: The most common presenting symptom of BIA-ALCL is a swelling of the breast that develops several years (average 8 years, range 2 to 28 years) after the insertion of textured breast implants. The disease can also present as a lump in the breast or the lymph node in the armpit. Less common symptoms include overlying skin rash, and fever/weight loss (lymphoma B-symptoms).

Q: How is BIA-ALCL diagnosed?

A. Diagnosis of BIA-ALCL follows international recommendations by the National Comprehensive Cancer Network (NCCN). Prior to surgery, a swollen breast can be evaluated with ultrasound for either a fluid collection, capsular mass or lymph node swelling. Mammography is not useful in diagnosing BIA-ALCL.

Fluid collections should be sampled with a needle through the skin (aspirated percutaneously).

Aspirate (minimum 50ml) should be sent for:

1. CD30* immunohistochemistry, 2. Cell block cytology and 3. flow cytometry evaluation and labeled to "rule out BIA-ALCL." CD30 testing is critical to direct pathologists and efforts should be made to establish a diagnosis prior to any surgical intervention. “Rare” or “scant” CD30 staining (<2 percent of cells) is expressed normally and not considered BIA-ALCL.

**CD30 refers to a cell membrane protein that occurs normally on activated T-cell lymphocytes and abnormally in some lymphomas. CD30 immunohistochemistry is the screening test for BIA-ALCL and should be performed on all fluid collections developing more than one year after implantation. If CD30 is negative, BIA-ALCL is excluded. If CD30 is positive, it may or may not be BIA-ALCL and cell block cytology and flow cytometry are required to make the diagnosis.*

TREATMENT AND PROGNOSIS

Q. How is BIA-ALCL treated?

A. Treatment follows standardized guidelines established by the National Comprehensive Cancer Network (NCCN). (Algorithm available on ASPS and The Aesthetic Society websites). Current recommendations call for total capsulectomy, removal of the implant, as well as excision of any associated masses. Cases have been reported where both breasts are affected; therefore, surgeons may consider removing both implants and capsules. The majority of early-stage patients treated with total capsulectomy require no additional treatment. Chemotherapy is required for unresectable disease, lymph node spread or distant metastases.

Q: What is the prognosis of BIA-ALCL?

A: To date, all cases of BIA-ALCL with disease limited to the scar tissue around the breast capsule and treated with complete surgical excision have been cured. There have been 21 confirmed deaths attributed to BIA-ALCL to date, which includes 5 U.S. cases. These reports emphasize the importance of disease recognition and proper treatment in a timely fashion.

Q: Where can I find more information on BIA-ALCL?

A: Additional information, downloadable manuscripts, and resources on BIA-ALCL are available online at **www.thepsf.org/PROFILE** and at **www.plasticsurgery.org/alcl** – and in the Medical Professionals section of **www.surgery.org**, as well as by searching "ALCL" on RADAR.

Reporters seeking information or plastic surgeons contacted by a member of the media are encouraged to forward inquiries to:

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