الهيئة العامة للغذاء والدواء
Saudi Food & Drug Authority

POST-MARKET EVALUATION FOR THE SAFETY AND EFFECTIVENESS OF BREAST IMPLANTS

Background

The safety of textured breast implants has been evaluated extensively in the previous months by international regulatory offices and specialized societies, due to the unexpected risks that associate with this device. These risks were recognized first from the elevated adverse event reports that were submitted into governmental authority databases at the post-market phase, and followed by a broadly discussion in the global medical literature. Such discussion revealed a possible association between textured breast implants and the development of a special type of anaplastic large cell lymphoma (ALCL), known afterward as BIA-ALCL.

Clinical burden

Breast implants are medical devices that consist of a gel-like material in a flexible sac that take the shape of the female breast, as shown in figure 1. They are implanted surgically under the breast tissue (sub-glandular position) or under the chest muscle (sub-muscular position), where incision can be made under the breast fold (inframammary), under the arm (transaxillary), around the nipple (periareolar), or through the mastectomy scar, for reconstruction implantation, as shown in figure 1.A and 1.B. [1] Breast implant can be used to increase the breast size (breast augmentation), or to reconstruct the breast tissue, usually after mastectomy (breast reconstruction).

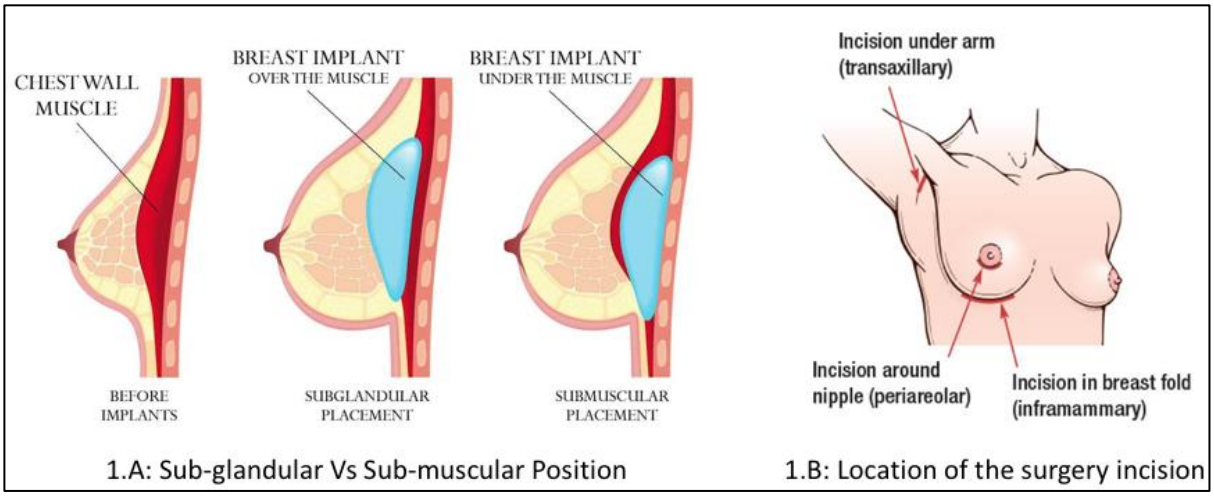

FIGURE 1: BREAST IMPLANTATION CLASSIFICATION IN ACCORDANCE TO THE IMPLANT (A) AND THE INCISION (B) POSITIONS.

Breast implant classifications

Breast implants are classified in accordance to the outer-shell surface into smooth and textured breast implants, as illustrated in figure 2. Textured breast implants are further sub-classified, based on surface area characteristics and measurements, into four types; nano-texture, micro-texture, macro-texture, and macro-texture-plus. [2]

The rationale behind texturing the outer surface of breast implant is to reduce the risk of capsular contracture (encapsulation of the implant by the body), through which the rough surface creates irregular surface to disrupt planar arrangement of cells in contact of the implant. [4] Also, it is believed that the integration between the body tissue and the pores can reduce the implant movement and rotation, as clarified in table 1.

FIGURE 2: BREAST IMPLANT CLASSIFICATION IN ACCORDANCE TO THE OUTER-SHELL SURFACE: SMOOTH (LEFT) AND TEXTURED (RIGHT).

TABLE 1: SMOOTH AND TEXTURED BREAST IMPLANT BENEFITS AND LIMITATIONS, AS REVEALED BY CALOBRACE ET AL. [4]

BI surface	Benefits	Limitations
Smooth	Smaller incisions, softer, less wrinkling, more natural shape and feel.	Great mobility, expected to have higher rate of capsular contraction.
Textured	Stronger adhesion to the tissue, more stable, minimal risk of rotation	Require large incision, higher rate of wrinkling, higher risk of seroma, double capsule and BIA-ALCL.

Risks and complications

Breast implants are reported to be associated with some complications, which include, but not limited to, implant rupture, capsular contracture, wrinkling, asymmetry, connective tissue disease, breast pain, and infection, among other adverse events. Table 2 summarizes and characterizes the serious complications as reported by the literature, where complications were listed based on the degree of severity, as revealed by Mentor and Allergan core studies that monitored the device safety and performance over 10 years.

TABLE 2: LONG TERM COMPLICATIONS AND ADVERSE OUTCOMES OF SILICON-FILLED BREAST IMPLANTS.

Complication	Description	Long term study >8 yrs follow-up 1723 cases*
Safety complications		
Capsular Contracture	Encapsulation of the implant by the body	**17.4%**
Device Rupture	A tear or hole in the implant's outer shell.	**13.3%**
Sensation Changes	Change in the feeling of the nipple and/or breast.	**6.0%**
Breast Pain	Pain in the nipple or breast area	**6.0%**
Hematoma	Collection of blood near the surgical site.	**2.1%**
Infection	Mostly appear within days, but possible any time.	**2.0%**
Performance complications		
Re-operation	The need to revise the surgery	**35%**
Implant removal	Implant removal with or without replacement	**20%**
Asymmetry	Uneven appearance of size, shape or breast level.	**6.1%**
Implant malposition	Incorrect position of implant is not in the breast.	**3.6%**

* Data were retrieved by combining Mentor and Allergan statistics, were the actual numbers obtained by manipulating each category considering its percentage and size number.

** **DATA WERE EXTRACTED FROM [5], [10], AND [16]**

Breast implant anaplastic large cell lymphoma (BIA-ALCL)

Breast implants associate also with the development of anaplastic large cell lymphoma (ALCL), which is a rare T-cell lymphoma. [11] In 2011, the US FDA developed a registry to gather information about such association, and as of Feb 2019, the registry announced some findings that include the characterization of 457 reports, with an association of breast implants and ALCL, including nine deaths, [11] following another announce by the Australian Therapeutic Goods Administration (TGA) of 76 confirmed cases of breast implant-ALCL in Australia, including 4 deaths. [12] and 57 cases in the UK, as reported by Medicines and Healthcare products Regulatory Agency (MHRA), where the majority of cases have associated with texture silicon breast implants [13]

Evaluation Outcomes

A) Clinical Paper Review for the Safety of Textured Breast Implants

A-1 Search criteria

A literature search was conducted to review the safety of textured breast implant as compared to the smooth type via the Google Search engine and PubMed. We included both grays (eg., Government and non-governmental agencies) and academic literature sources. **In order to satisfy the scope of this review, common complications that appears in both smooth and textured breast implants were excluded, and the search focuses in those complications that only associate with one type**. A number of 65 articles were acquired, and screened considering defined inclusion criteria and quality measures. Lastly, 18 recent and specific articles were included in the review, as summarized in in table 4.

A-2 Summary of the literature findings:

- The included studies were limited to those who derived their conclusion utilizing real-world data, and all were with good or strong level of evidences.
- There is almost an absolute agreement among researchers that support the association between BIA-ALCL and textured breast implant. (14 articles)
- Other articles demonstrated an association between textured breast implants and the formation of bacterial biofilm, as revealed by various lab testing. (4 articles)
- Limitation: There might be a repetition in the provided data at the different studies, but this issues will be tackled in the next section, and what can be concluded here is that the decision was interpreted by different study groups.

Table 4: A comparison for the complications in textured versus smooth breast implants

Ref.	Study Design	BI associated complications	Number of cases	Relation to the BI surface
Wilkinson et al[4]	Retrospective study.	BIA-ALCL	55	100% T-BI
Brody et al [5]	Systematic review.	BIA-ALCL	173	100% T-BI
Haioun et al [6]	Retrospective study.	BIA-ALCL	39	100% T-BI
de Boe et al [7]	Case-control study.	BIA-ALCL	32	100% T-BI
Dashevsky et al [8]	Retrospective study.	BIA-ALCL	11	100% T-BI
Kricheldorff et al [9]	Systematic review.	BIA-ALCL	7	100% T-BI
Gallardo et al [10]	Meta-analysis study.	BIA-ALCL	80	100% T-BI
Leberfinger et al [11]	Systematic review.	BIA-ALCL	95	100% T-BI.
Johnson et al [12]	Systematic review.	BIA-ALCL	23	100% T-BI
Pompeo et al [13]	Retrospective study.	BIA-ALCL	4	100% T-BI
Clemens et al [14]	ASPS report.	BIA-ALCL	457	95% T-BI
Srinivasa et al [15]	Retrospective study.	BIA-ALCL	363	92.3% T-BI
Ezekwudo et al [16]	Case report study.	BIA-ALCL	1	T-BI
Doren et al [17]	Retrospective study.	BIA-ALCL	100	A significant association with T-BI
James et al [18]	In-vitro examination.	Bacterial biofilm formation	5 brands	Greater biofilm load in T-BI
Jones et al [19]	In-vitro examination.	Bacterial biofilm formation	11 brands	Greater biofilm load in T-BI
Jacombs et al [20]	In-vitro & in-vivo testing.	Bacterial biofilm formation	121 BI in 16 adult female pigs	72-fold biofilm increase in T-BI.
Giot et al [21]	Lab testing study.	Bacterial biofilm & double capsule	10 samples	All samples were macro-textured BI and revealed a similar mechanism.

A-3 An analysis of BIA-ALCL risk factors as revealed by 712 confirmed and unique cases

Referring to the reviewed articles and the governmental databases, a number of 712 BIA-ALCL were analyzed to define the disease risk factors. The cases are confirmed as revealed by the authors, and unique because the data were extracted from governmental sites, as referenced in each data set. The rationale behind collecting all these cases is to better estimate the risk factors and characteristics of BIA-ALCL. Below is a summary of the main search findings:

- Up to Feb 2019, there exist 712 confirmed BIA-ALCL
- Most of the cases were detected in North America (67%), followed by Europe (22%) and Australia (11%).
- These cases associate with a mortality rate of 3.1%.
- The median age of patient who are affected by BIA-ALCL is 52.9 year, and the mean interval from implantation to diagnosis is 9.2 years.
- Nearly all known cases were associated with textured BI.
- In most of the cases BIA-ALCL is detected by seromas in early stage (61%), which is curable by surgery alone and the removal of the implant. However, in 20% of the cases BIA-ALCL was presented with a solid tumor mass, which preserve a more challenging prognosis.
- However, this analysis is limited by two factors. First, nearly all reported data were extracted from governmental registries, which make a room of duplication. For instance, and as revealed by Srinivasa et al, 59 from the cases reported by the US database were for international cases, and thus this would give a possibility of double entries. [26] Secondly, results were acquired by calculating the mean of means, which may result in a minor deviation in the results accuracy.

B) Clinical Experience Review for the Safety of Textured Breast Implants

In order to get a better understanding of the actual practice of breast implantation in the Saudi market and to report the experts' opinion regarding the safety of these devices, requests of consultation were sent into members of:

- The Saudi Scientific Association of Plastic Surgery and Burns, and
- Saudi Plastic Surgery Care Society

Experts of these societies generously provided significant efforts to reflect the breast implantation practice and the associated incidents in the local market, and to review the SFDA recommendations that are listed below.

SFDA actions

a. Allergan macro-textured Biocell silicone breast implants are recalled from the Saudi market, due to the susceptible risks that outweigh the benefits, as revealed by the literature review and as suggested by international and local experts. (Action date: Feb, 2019)
https://www.sfda.gov.sa/sites/default/files/2019-10/%28SG-1902-08-H%29.pdf

b. Manufacturers of textured breast implants were ordered to initiate a post-market clinical follow-up study, as guided by MDS-G31 (Guidance on Post-Market Clinical Follow-Up Studies) in a design of a clinical registry to prove the benefits and risks of their textured silicone breast implants as compared to the smooth type and to report their findings to the SFDA. This is applicable for all macro-textured breast implants. (Action date: May 2019)
https://www.sfda.gov.sa/sites/default/files/2019-12/MDCirculation2352019.pdf

c. Manufacturers of textured breast implant were requested to provide a clarification about the level of texturization in the product labeling. (Action date: May 2019)

https://www.sfda.gov.sa/sites/default/files/2019-12/MDCirculation2352019.pdf

d. Manufacturers of all breast implants in the Saudi market were inspected to check the availability of tracking systems for their products in the market. (Action date: March 2019)

SFDA recommendations

Recommendations for Healthcare Providers

SFDA highly recommends healthcare providers to:

- **a.** Discuss BIA-ALCL with their patients at the initial consultation, and they are greatly encouraged to include the association between BIA-ALCL and textured implants in the informed consent, especially those having, or planning to have, textured breast implants.
- **b.** Discuss BIA-ALCL signs and symptoms with patients who decide to select textured breast implant.
- **c.** Provide patients with the implant ID card for future references.
- **d.** Facilitate routine follow-up visits with their patients, every two years, for the first 6 years, and in a yearly basis afterwards.
- **e.** Follow the recommended diagnostic procedures, including the ultrasound guided aspiration and cytological analysis, with any suspected BIA-ALCL case, especially those cases that demonstrate a sudden and unexplained seroma AND/OR a sudden asymmetry in the patient breast. Note: when sending fluid for cytology, healthcare providers should consider asking for identification of cytological markers CD30-positive and ALK-negative T-cell lymphocytes.
- **f.** Keep in mind that most experts advise using a smooth or micro-textured implant for new implant recipients.
- **g.** Track their patients to be able to reach them for any sudden warning that relate to their implants.

Recommendations for Patients

- **a.** Breast implant is not a lifetime device, but the longer you have the implant, the most likely you are to experience local complications and adverse outcomes. However, the new generation of breast implants preserve safer products that could last for a longer time with minimal risks.
- **b.** BIA-ALCL is a rare disease, but studies show that its symptoms appear in a period of 8-10 years (median interval from implantation to diagnosis is 9.2 years). Therefore, the longer you have the implant, the more caution you should be to do a routine medical follow-up regarding any sudden pain, lumps, swelling or recent asymmetry in the breast.
- **c.** Educate yourself about breast implants before agreeing to surgery, and upon your agreement to have a breast implantation, plan for a routine follow-up for a long period of time, considering the suggested period of replacing the device as per directed by your healthcare provider.
- **d.** BIA-ALCL is believed to be developed more frequently in individuals with textured implants than in people with smooth-surfaced implants. Before getting breast implants, make sure to talk to your health care provider about the benefits and risks of both textured-surface and smooth-surfaced implants.
- **e.** In case you have a breast implant, there is no need to panic or to change your routine medical follow-up. Also, keep in mind that you should expect swelling and pain right after the surgery. However, if you noticed changes in the way your breast looks or feels after your recovery, or at any time afterward, make sure to talk to your healthcare provider.
- **f.** Remember to keep your implant ID for future references.
- **g.** Make sure to report any adverse event you notice regarding your implant through the National Center for Medical Devices Reporting (NCMDR) system: https://ncmdr.sfda.gov.sa or Saudi Vigilance System https://ade.sfda.gov.sa/

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- Saudi Plastic Surgery Care Society

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For inquiries related to this study, you may reach us through this email: cia.md@sfda.gov.sa

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