Plastic and Reconstructive Surgery Advance Online Article

DOI: 10.1097/PRS.0000000000003654

Breast implant associated Anaplastic Large Cell Lymphoma in Australia and New Zealand – high surface area textured implants are associated with increased risk

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Declaration

Professor Deva and Associate Professor Vickery have conducted research for Mentor(J&J), Allergan and Acelity

Dr. Magnusson is a consultant to Allergan.

Dr. Connell is a consultant to AirXpanders.

Abstract

Background: The association between breast implants and breast implant associated anaplastic large cell lymphoma (BIA-ALCL), has been confirmed. Implant related risk has been difficult to estimate due to incomplete or unknown implant histories and lack of clarity on the number of implants utilized.

Methods: All cases in Australia and New Zealand were identified and analyzed. Textured implants reported in this group were subjected to surface area analysis.

Sales data from three leading breast implant manufacturers (Mentor/Allergan/Silimed) dating back to 1999 were secured to estimate implant specific risk.

Results: 55 cases of BIA-ALCL were diagnosed in Australia and New Zealand between 2007 and 2016. The mean age of patients was 47.1 and the mean time of implant exposure was 7.46 years. There were 4 deaths in the series related to mass and/or metastatic presentation. All patients were exposed to textured implants. Surface area analysis confirmed that higher surface area was associated with 64 of the 75 implants utilized (85.3%). Biocell salt loss textured (Allergan/Inamed/McGhan) accounted for 58.7% of implants utilized in this series. Comparative analysis showed the risk of developing BIA-ALCL was found to be 14.11 times higher with Biocell textured implants and 10.84 higher with polyurethane (Silimed) textured implants as compared with Siltex textured implants.

Conclusion: This study has calculated implant specific risk of BIA-ALCL. Higher surface area textured implants have been shown to significantly increase risk of BIA-ALCL in Australia and New Zealand. We present a unifying hypothesis to explain these observations.

Introduction

Breast implant associated anaplastic large cell lymphoma (BIA-ALCL) is a CD30 positive, ALK negative, T cell derived lymphoma within the Non-Hodgkin lymphoma group. To date, all patients with BIA-ALCL have had prolonged exposure to textured implants[1,2].

There have been wide variations in estimation of risk for BIA-ALCL ranging from 1 in 3,000,000[3] to 1 in 50,000[4] implants. This is due to current limitations with accurately obtaining implant and clinical histories, variation in pathological diagnosis, under-reporting and missed diagnoses, duplication of case entries into registries and a lack of clear information on the total number of implants sold and implanted due to commercial sensitivities[5].

We sought to bring clarity to the implant related risk in our Australian & New Zealand population.

The objectives of this investigation were to:

1. Form a joint Australia and New Zealand task force to capture all reported BIA-ALCL cases (numerator)

2. To review and confirm pathological diagnoses

3. To lobby industry for release of sales data to calculate the true risk of BIA-ALCL in our population (denominator)

4. To study the association and risk of different textured implant surfaces with BIA-ALCL

Methods

The task force engaged with members of the Plastic Surgery, Breast Oncology, Hematology and Oncology and Cosmetic surgical societies. A proforma for reporting

cases was distributed electronically and by mail calling for notification of cases in October 2015. Human ethics approval was obtained from Macquarie University.

Clinical, operative and implant details were crosschecked with operative and clinical records where available.

Pathological diagnosis confirmed, where required, by secondary review of the pathology slides by independent pathologist (Dr Stephen Lade, Peter MacCallum Cancer Center). The TNM staging[6] was applied (See table 1).

Patient contact was made to confirm survival status.

The task force engaged the three major implant manufacturers in our region, (Mentor Worldwide LLC, Allergan Sales LLC, Silimed Inc.) to release sales data for implants from 1999 to 2015. The raw sales data were blinded to each manufacturer and clinicians and were used by an independent bio-statistician (KB, Macquarie University) for descriptive, risk and survival analysis.

Surface area determination

Surface texture of Silimed polyurethane, Biocell, Siltex, and smooth implants were visualized using ZEISS LSM 880 inverted Confocal Laser Scanning Microscope and Scanning electron microscope using previously published methods[7].

Three-dimensional (3D) reconstruction of confocal images was performed using Imaris v 8.4, ImarisXT, Bitplane. The 3D iso-surface area was measured by IMaris MeasurementPro.

Statistical analysis

Data on sales of respective implants were obtained on a yearly basis from Allergan, Mentor and Silimed from 1999 to 2015. For Silimed, the sales of implants did not increase significantly until after 2008, following Australian regulatory approval. For analysis, this was converted to integral years to allow a discrete time analysis, with

analysis restricted to subjects implanted during or after 1999 within Australia or New Zealand and who had been exposed to single type of texture only. For Silimed, we only included Australian cases. We did not include smooth implant exposure in our analysis. Incidence was calculated using the Poisson distribution and exact confidence intervals. The cumulative proportion of subjects with ALCL exposed to Biocell and Siltex texture was determined using the Kaplan-Meier estimate with confidence intervals obtained using a parametric bootstrap. Comparison between groups was performed using discrete-time survival analysis[8] using exact-like logistic regression. All calculations were performed using the R language[9] and packages boot[10] , elrm[11] and epitools[12] .

Results

Patient and implant characteristics

A total of 55 patients were identified between 2007 and August 2016. Eleven women had multiple implant exposure whilst the remaining 44 had a single implant exposure with a total of 75 implants pairs being deployed in this cohort. The mean age of patients was 47.1 years (range 22.4 to 69.6 years). The mean time to develop BIA-ALCL from time of last implantation was 7.46 years (range 0.2 to 27.0 years).

All implant histories were obtained and the frequency of different implant types associated with the BIA-ALCL positive breasts in these 55 patients is reported in table 2. All patients were exposed to textured implants at some point in their implant history. On 4 occasions smooth implants were used early in these patients implant history (implanted prior to 1999) reflecting a change to use of textured implants in the Australia/ New Zealand market.

In 38 (69.1%) patients, the indication for breast implants was for cosmetic augmentation. In the remaining 17, the indication for implants was for post-mastectomy reconstruction for both cancer and prophylaxis.

Eleven patients had multiple implants for revision either for rupture, infection or capsular contracture (See table 3). Of the reconstructive patients, 10 had textured tissue expanders utilized prior to insertion of the definitive implant.

BIA-ALCL diagnosis/presentation and pathology

Table 4 summarizes the clinical presentation of BIA-ALCL. Forty-two (76.4%) patients presented with a unilateral breast swelling due to seroma (See figure 1) (see Video, which shows the appearance of BIA-ALCL intraoperatively on patient, available in the "Related Videos" section of the Full-Text article on PRSJournal.com or, for Ovid users, available at INSERT LINK)(Video Graphic 1). In 2 patients, the seroma was associated with contralateral capsular contracture. A total of 10 patients (18.2%) presented with a mass. One patient presented with concurrent metastatic axillary disease. Three patients presented with concurrent seroma and mass (4.3%).

Geographic location of implant insertion

Of the total of 75 implants placed into patients that developed BIA-ALCL, 65 implants were placed in Australia and 8 implants were placed in New Zealand. In two patients, implants were placed outside of Australia and New Zealand (1 Mexico and 1 Thailand).

Pathology, staging, treatment and survival

All patients underwent total capsulectomy and removal of implants both on the diseased and non-diseased side. All samples were CD30 positive and ALK negative.

Thirty-two patients (58.2%) had no evidence of BIA-ALCL on histopathological examination of the capsule indicating the disease was confined to the peri-implant

malignant effusion. In 3 of these patients, there was an intense associated (benign) lymphocytic hyperplasia in the capsule. In a further 10 patients (18.2%), tumor cells were seen to populate the inner lining but did not invade into the capsule. These patients represent early stage disease and 6 of them were treated with adjuvant postoperative chemotherapy early in the series. The remainder were treated with surgery only.

Twelve patients (21.8%) had evidence of tumor infiltrating the capsule with associated mass lesions present in 5 of these patients. One patient had tumor deposits within the pectoral muscle as an incidental finding during revision surgery. Two of these patients had evidence of metastatic spread to axillary/mediastinal lymph nodes on presentation. Table 5 summarizes TNM staging[6] of patients in this series.

Ten of these 12 patients were treated with adjuvant chemotherapy and 9 of them also received adjuvant radiation. One patient was treated with neoadjuvant chemoradiation prior to surgery. One patient was treated with an autologous bone marrow transplant.

Fifty-one patients (92.7%) remained alive, well and disease free at the conclusion of this study. The median disease free survival for all non-deceased patients was 2.62yr for this series (range 0.1-8.2yr).

Five patients had local recurrence of disease treated with adjuvant therapy. Of these, 2 patients had positive tumor margins on histopathology. Three patients survived and remain disease free.

Mortality

There were 4 patient deaths in this series. One patient presented with a clinical seroma and three others presented with mass and/or metastatic disease. Two cases followed cosmetic augmentation and 2 followed cancer reconstruction. Their mean age was 49.7 (range 44.5-58.0) and 3 were following single implants with Allergan Biocell

implants and 1 had multiple implants (smooth then Allergan Biocell x 2). The mean time to developing this disease was 7.35 years. All patients had mass disease extending beyond the capsule on histological staging. Two of these patients had spread to lymph nodes (ipsilateral axilla/axilla and mediastinum) at the time of presentation. Two patients had recurrence (1 had incomplete resection on histology) following treatment (surgery/adjuvant therapy) with subsequent spread to mediastinum and distant metastases. They died from obstructive respiratory failure. Two other patient deaths were related to complications of adjuvant therapy (sepsis post chemotherapy/bone marrow transplantation). A multi-center analysis of poor outcomes following BIA-ALCL presentation and treatment is currently in progress and will report these cases in more detail.

Implant related risk

The odds ratio for developing BIA ALCL for Biocell implants compared to Siltex implants was 14.11 (95% CI 1.20,561.46) p = 0.0005. The odds ratio for developing BIA-ALCL for polyurethane (Silimed) implants compared to Siltex implants was 10.84 (95% CI 1.00,566.34) p = 0.05. This shows the risk of developing BIA-ALCL was 14.11 times higher for Biocell and 10.84 times higher with (Silimed) polyurethane and as compared with siltex texture.

Survival analysis showed a significant rise in the cumulative risk of ALCL for patients with Biocell texture after around 8 years of exposure reaching a peak at 12 years post implantation (see figure 2). For Silimed implants, the risk rose significantly after 5 years but further follow up will be required to determine the final cumulative incidence.

An estimation of implant specific risk was calculated by using the sales data for Mentor (Siltex), Allergan (Biocell) and Silimed (polyurethane) implants sold over the 1999-2015 period.

Analysis of implant related risk based on total implant sales and for patients with single texture exposure is shown in table 6. The highest estimated risk as expressed as cases of ALCL per number of implantations was found for Biocell texture at 1 in 3817 (95%CI 2718,5545) as compared with PU at 1 in 7788 (95%CI 3042,28581) and Siltex at 1 in 60631 (95%CI 10882,2397471). The risk for PU is confounded by a shorter duration of exposure in the Australian and New Zealand market as compared with the other two textures and will need further monitoring and updates.

We were unable to calculate risk and surface area for Nagor implants as the company has denied access to sales data and/or implants for the study.

Surface area analysis

Table 7 shows estimate of surface area for implant surfaces for 1x1mm surface block in square milimeters. The findings showed Silimed Polyurethane having the highest surface area by this method of calculation. Figures 3a-f show images of the confocal analysis for polyurethane, Biocell and siltex implant surfaces.

Discussion

This study has provided a detailed clinical and implant history of patients with BIA-ALCL in Australia and New Zealand. To date, this represents the most accurate numerator and denominator for risk calculation of BIA-ALCL in a specific population. The findings with respect to disease presentation and prognosis mirror findings in the literature[1,2].

Two patients with incomplete margins at original surgery had local recurrence and one of these patients died, indicating the importance of an aggressive, oncological clearance and assessment by a multi-disciplinary team when dealing with this disease[6]. By contrast, we and others[13] have confirmed that the **mass type** carries with it a poorer prognosis. There is ongoing debate as to whether the more indolent **seroma type** progresses inevitably to the **mass type** of the disease or whether there are two distinct BIA-ALCL entities[14]. There are similarities of the **seroma type** with primary cutaneous ALCL (PCALCL)[15]. In PCALCL, the presence of chronic inflammation from autoimmune and infectious triggers results in overexpression of CD30, recruitment of T cells and eventual selection of a clone with survival advantages and the establishment of malignancy[15]. This process has a pre-malignant lympoproliferative phase, termed lymphomatoid papulosis (LyP) which can progress into PCALCL and regress into LyP[15,16]. To support this, a recent report by Kadin et al[17] has shown CD30+ clonal expansion in the setting of a late benign seroma. It may be, in time, that **seroma type** BIA-ALCL is eventually reclassified as an *in-situ* malignancy or a mixture of *in-situ* malignancy and lymphoproliferation based on closer analysis of T cell populations in both seroma fluid and in the capsule.

A number of hypotheses have been put forward to explain the genesis of BIA-ALCL. Our findings have shown that Biocell (salt loss) and (Silimed) polyurethane textures carry a significantly higher risk of developing BIA-ALCL as compared with Siltex (imprinted texture). Biomarkers also provide evidence to show that underlying inflammation is the likely initiator of this disease[18]. As to the cause of inflammation, the presence of chronic bacterial biofilm infection is emerging as the likely culprit[19]. It has been shown that textured implants, with their greater surface area, promote higher levels of bacterial biofilm growth[20] and that this higher bacterial load produces

a significant and linear increase in lymphocyte activation[7]. Interestingly, Hu et al[7] found that PU implants were associated with a significantly higher level of both bacterial contamination and lymphocyte activation in human contracture. A recent study has confirmed high levels of bacteria in BIA-ALCL specimens with a detection of a gram negative shift in the microbiome as compared with traditional biofilm species detected in capsular contracture[19]. The presence of higher levels of gram-negative bacteria in BIA-ALCL may explain the pathway to proliferation and transformation that differs from inflammation and fibrosis, which we see in capsular contracture.

Our surface area analysis has confirmed that Polyurethane (Silimed) and Biocell texture have higher surface area as compared with Siltex texture. There are limitations to the imaging resolution with this method and further work on the analysis of textured implant surface area and their relationship with bacterial growth is ongoing and will be reported in due course. Furthermore, whilst the odds ratio and Kaplan Meier analyses point to higher risk for Biocell implants, the implant specific risk for Silimed polyurethane is impacted by the shorter duration of exposure in the Australian population. Further monitoring of both new cases and sales data will allow better delineation of this risk moving forward.

The finding that 85% of patients in our series have been exposed to higher surface area texture and that these textures carry a higher risk of development of BIA-ALCL strengthens the case for bacteria as the cause of inflammation. We propose the higher surface area acts as a passive conduit for the growth and proliferation of bacteria, which, once they reach a threshold, cause ongoing immune activation and transformation in susceptible hosts over time. Other observations also point to infection including the cluster pattern of incidence with some surgeons having

multiple events, which could represent an infectious cluster from nosocomial contamination.

The implant related risk in this series has given surgeons a clear metric to base their decision-making. There are limitations to the statistical analysis in particular the small number of cases for Siltex and Polyurethane resulting in wide confidence intervals, limited information on deaths by other causes, short duration follow up in some cases, reliance on the accuracy of sales data supplied by manufacturers, cluster patterns of incidence skewing the distribution, and the possibility that there are other unidentified cases of BIA-ALCL through missed clinical and/or pathological diagnosis. The propensity, however, of high surface area texture to generate risks of BIA-ALCL as high as 1 in 4000 implants should be balanced against the clinical advantages of the use of textured implants and the need to combine textured implants with strong and proven strategies to combat bacterial contamination at the time of implant deployment. These strategies, reported as the 14 point plan[21], provide surgeon and patients with a confidence all is being done to reduce the risk of bacterial contamination. Breast implants are unique in that they are placed into a contaminated pocket at the start. The aim of anti-infective strategies is to reduce the bacterial load so that biofilm contamination remains below the threshold for host response. It is the presence of a threshold for host response to biofilm that answers the commonly asked question "if the biofilm theory is true then why don't textured implants cause higher rates of contracture?" If contamination of implants is kept below this threshold, the cycle of biofilm induced inflammation, contracture and potentially transformation of lymphocytes is thus avoided[20]. High surface area implants reduce the margin of error as they provide bacteria with a better growth platform, so that anti-infective measures become even more critical.

We are now in a position to move towards a **unifying hypothesis** to explain the observed phenomena surrounding BIA-ALCL. The contamination of textured implants with higher surface area by bacteria leading to chronic antigen stimulation in genetically susceptible hosts over a prolonged period of time may result in transformation of T cells into BIA-ALCL. We believe that the genesis of BIA-ALCL is thus multifactorial as is the case with most carcinogenesis. Recent findings of mutations in the JAK/STAT3 pathway in patients with BIA-ALCL have suggested that a deficiency in response to chronic inflammation may also play a role in malignant transformation[22]. Until such time as a credible alternative theory is proposed based on accumulation of clinical, epidemiological and scientific data, we should focus our efforts on both disease prevention through modification of implant choice and combatting contamination of breast implants. A recent paper by Adams et al[23] has shown that application of anti-infective strategies in 42,000 macrotextured implants resulted in no recorded cases of BIA-ALCL. Our findings are consistent with the importance of mitigating the risk of implant contamination as a key strategy to reduce the risk of subsequent BIA-ALCL.

Finally, this study raises the possibility of an increasing incidence of BIA-ALCL in Australia and New Zealand Zealand. Projections of implant sales show a significant increase in the utilization of high surface area textured devices in the last 5 years. As the mean time for development of this disease is around 8 years, it is of some concern that we are in store for a rise in BIA-ALCL in our population. As a response, we have engaged with government and regulatory authorities and plan to mature the Australian Breast Device Registry to monitor and respond to this eventuality.

Conclusion

Our joint task force has captured 55 cases of BIA-ALCL in Australia and New Zealand diagnosed since 2007. The availability of an accurate numerator (number of cases/implant type) and denominator (sales data) has shown higher risk for high surface area textured implants . A unifying hypothesis where texture surface area, bacterial contamination and patient genetic susceptibility interact over time to produce T cell transformation may provide an explanation to these observations.

Acknowledgements

The authors wish to acknowledge the cooperation of Mentor, Allergan and Silimed in providing sales data for the analysis. The authors would like to acknowledge Dr. Stephen Lade for assistance with pathological examination. The authors would like to acknowledge Helen Hu and Durdana Chowdhury for assistance with surface area analysis. The authors wish to acknowledge the collaboration with the Therapeutic Goods Administration. A/Prof Karen Vickery is a recipient of the Macquarie University DVC innovation fellowship.

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Legend to Figures and Tables

Table 1: TNM staging for BIA-ALCL[6]

Table 2: Frequency of implant types associated with BIA-ALCL in this cohort of patients (n=56 implants in 46 patients due to reoperation)

Table 3: Number of implants prior to development of BIA-ALCL

Figure 1a: Clinical presentation of patient from our cohort. F 39 presenting with unilateral seroma following cosmetic augmentation 8 years previously. Following diagnosis, she had bilateral completion capsulectomy showing disease in the capsule but with no infiltration. She was given postoperative adjuvant radiotherapy and remains disease free at last follow up.

Figure 1b: Appearance on magnetic resonance imaging showing large seroma and intact implant shell

Figure 1c: Cytology positive for BIA-ALCL

Figure 1d: Histology of implant capsule showing infiltration by BIA-ALCL

Video Graphic 1. See Video, which shows the appearance of BIA-ALCL intraoperatively on patient, available in the "Related Videos" section of the Full-Text article on PRSJournal.com or, for Ovid users, available at INSERT LINK.

Figure 2 : Cumulative proportion of patients with BIA-ALCL per 10,000 implants for Allergan/McGhan (Biocell) versus Mentor (Siltex) implants.

Figure 3a-f: 2D and 3D images of polyurethane, Biocell and Siltex implants used for analysis of surface area.

3a Siltex at 75x magnification 3b 3D image of Siltex texture

3c Biocell at 75x magnification 3d 3D image of Biocell texture

3e Polyurethane (Silimed) at 75x magnification 3f 3D image of Polyurethane (Silimed) texture

Table 4: Presentation of BIA-ALCL (n=46)

Table 5: TNM staging of patients in our cohort

Table 6: Calculated implant specific risk of BIA-ALCL per implants, rate per 10,000 implants and rates per 10,000 implant years (95% Confidence intervals in brackets) for both single implant vs multiple implant analysis.

Biocell (Allergan/Inamed/McGhan)

Siltex (Mentor)

Polyurethane (Silimed)

Table 7: Topographical surface area analysis for Siltex, Biocell, polyurethane (Silimed) textured implants vs smooth implants

Table 1: TNM staging for BIA-ALCL[6]

TNM or Stage Designation	Description
T : tumor extent	
T1	Confined to effusion or a layer on luminal side of capsule
T2	Early capsule infiltration
T3	Cell aggregates or sheets infiltrating the capsule
T4	Lymphoma infiltrates beyond the capsule
N: Lymph node	
N0	No lymph node involvement
N1	One regional lymph node (+)
N2	Multiple regional lymph nodes (++)
M : Metastasis	
M0	No distant spread
M1	Spread to other organs/distant sites
Stage	
IA	T1N0M0
IB	T2N0M0
IC	T3N0M0
IIA	T4N0M0
IIB	T1-3N1M0
III	T4N1-2M0
IV	TanyNanyM1

Table 2: Frequency of implant types associated with BIA-ALCL in this cohort of patients (n=75 implants in 55 patients due to reoperation)

Manufacturer	Texture type	Number	Percentage
Allergan/Inamed/McGhan	Biocell (salt loss)	44	58.7
Silimed	Polyurethane	14	18.7
Nagor	Salt loss	5	6.7
Surgitek	Polyurethane	1	1.3
Mentor	Siltex	5	6.7
PIP	PIP	2	2.7
Mentor	Smooth	2	2.7
Unknown	Smooth	2	2.7

Table 3: Number of implants prior to development of BIA-ALCL

No. of implants	Patients	Percentage
1	44	80.0
2	6	10.9
3	3	5.5
5	2	3.6

Table 4: Presentation of BIA-ALCL (n=55)

Presentation	**Number**	**Percentage**
Seroma only	42	76.4
Mass only	5	9.1
Seroma and mass	3	5.5
Seroma and capsular contracture (contralateral)	2	3.6
Mass and capsular contracture (concurrent)	1	1.8
Mass with metastatic disease (axilla)	1	1.8
Incidental finding	1	1.8

Table 5: TNM staging of patients in series

Pathology	TNM	Stage	Number	Percentage	Mortality
BIA-ALCL positive in fluid but negative on capsule	T1N0M0	IA	32	58.2	Nil
BIA-ALCL in fluid and luminal side of capsule	T1N0M0	IA	10	18.2	Nil
BIA-ALCL infiltrating capsule	T3N0M0	IC	6	10.9	Nil
Mass extending beyond capsule	T4N0M0	IIA	5	9.1	2
Mass with Metastatic disease to one lymph node in axilla	T4N1M0	III	1	1.8	1
Mass with Metastatic disease to multiple lymph nodes	T4N2M0	III	1	1.8	1

Table 6: Calculated implant specific risk of BIA-ALCL per number of implants and rates per 10,000 implant years (95% Confidence intervals in brackets) for patients exposed to single implant texture type (excluding exposure to smooth implants)
Biocell (Allergan/Inamed/McGhan) n = 31
Siltex (Mentor) n = 1
Polyurethane (Silimed) n = 6

	Implant numbers per single case of BIA-ALCL	Rate per 10,000 implant-years
Biocell	3817 (2718,5545)	0.39 (0.27,0.55)
Polyurethane (Silimed)	7788 (3042,28581)	0.31 (0.08,0.79)
Siltex	60631 (10882,2397471)	0.028 (0.001,0.156)

Table 7 : Topographical surface area analysis for Siltex, Biocell, polyurethane (Silimed) textured implants vs smooth implants

	Surface area (mm^2) for 1mmx1mm implant surface
Polyurethane (Silimed)	146.7
Biocell	27.9
Siltex	12.4
Smooth(Mentor)	1.0

Figure 1

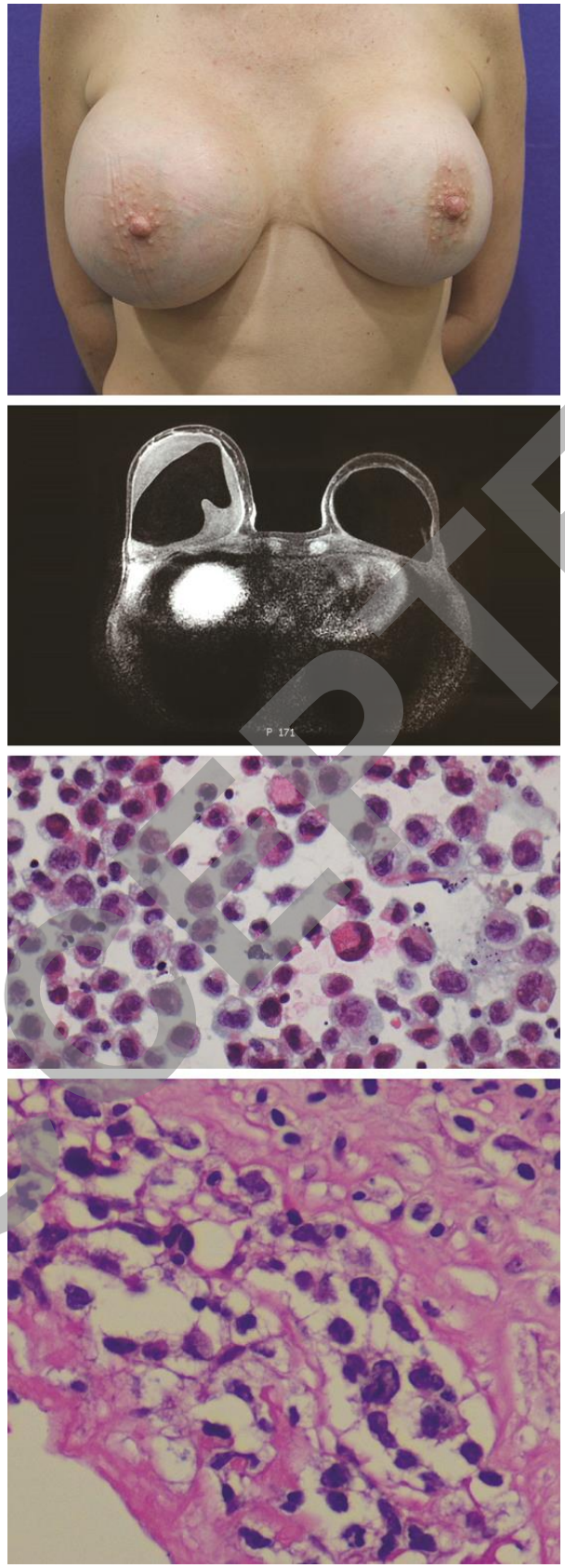


Figure 2

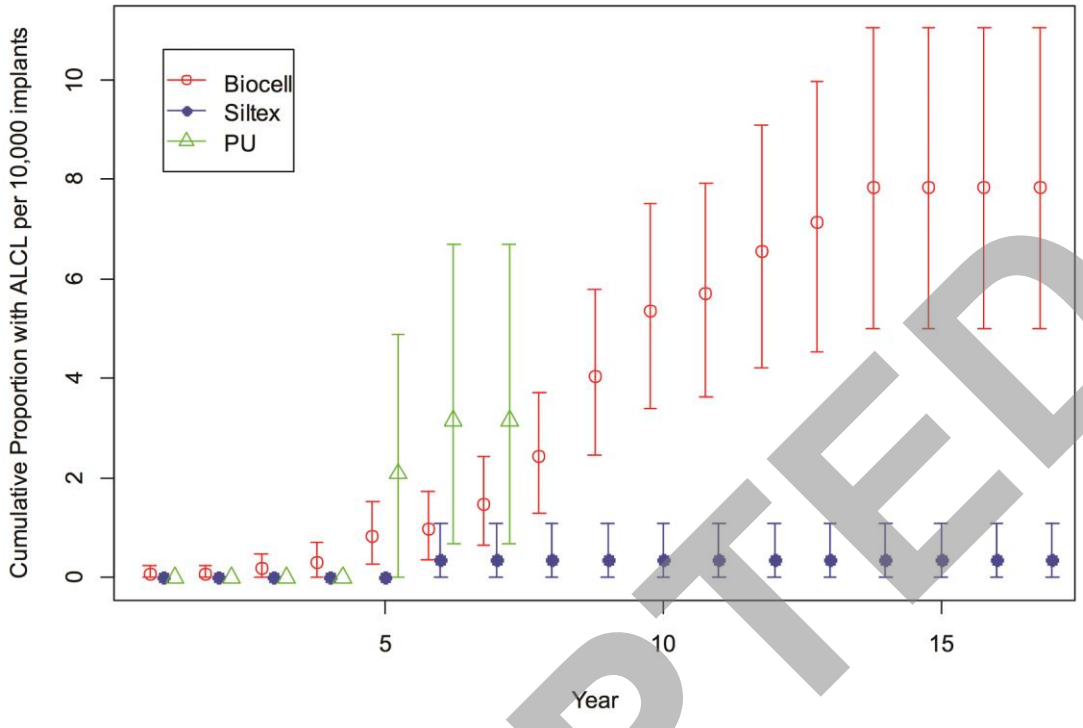
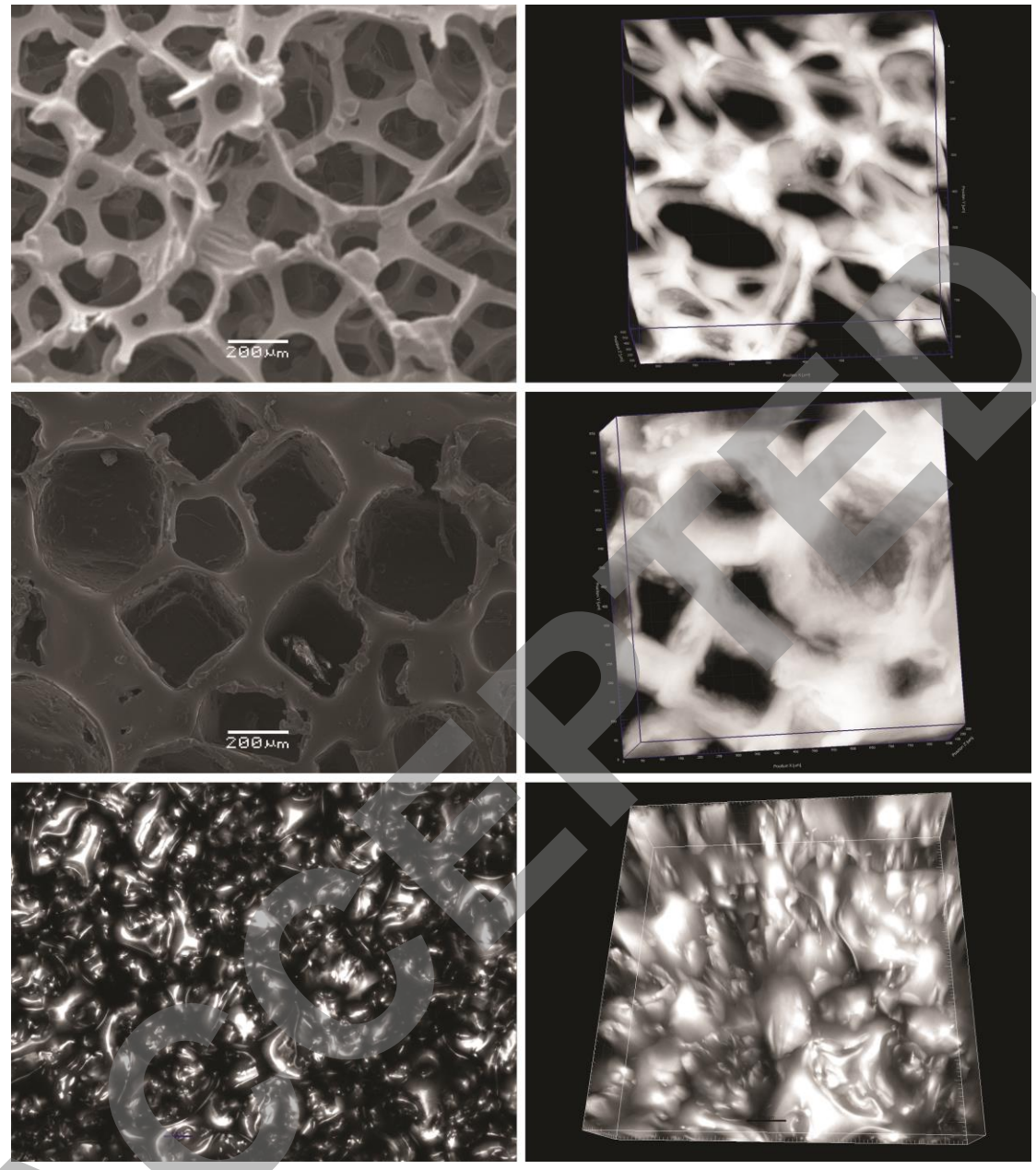


Figure 3



Video Graphic 1