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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Background: The association between breast implants and breast implant–associated anaplastic large cell lymphoma (ALCL) has been confirmed. Implant-related risk has been difficult to estimate to date due to incomplete datasets.
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 (i.e., Mentor, Allergan, and Silimed) dating back to 1999 were secured to estimate implant-specific risk.
Results: Fifty-five cases of breast implant–associated ALCL were diagnosed in Australia and New Zealand between 2007 and 2016. The mean age of patients was 47.1 years and the mean time of implant exposure was 7.46 years. There were four 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 used (85.3 percent). Biocell salt loss textured (Allergan, Inamed, and McGhan) implants accounted for 58.7 percent of the implants used in this series. Comparative analysis showed the risk of developing breast implant–associated ALCL to be 14.11 times higher with Biocell textured implants and 10.84 higher with polyurethane (Silimed) textured implants compared with Siltex textured implants.
Conclusions: This study has calculated implant-specific risk of breast implant–associated ALCL. Higher-surface-area textured implants have been shown to significantly increase the risk of breast implant–associated ALCL in Australia and New Zealand. The authors present a unifying hypothesis to explain these observations. (*Plast. Reconstr. Surg.* 140: 645, 2017.)





Breast implant–associated anaplastic large cell lymphoma (ALCL) is a CD30$^+$, ALK$^-$, T-cell–derived lymphoma within the non-Hodgkin

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lymphoma group. To date, all patients with breast implant–associated ALCL have had prolonged exposure to textured implants.[1,2]

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

We sought to bring clarity to the implant-related risk in our Australian and New Zealand population. The objectives of this investigation were as follows:

1. Form a joint Australia and New Zealand task force to capture all reported cases of breast implant–associated ALCL cases (numerator).
2. Review and confirm pathologic diagnoses.
3. Lobby industry for release of sales data to calculate the true risk of breast implant–associated ALCL in our population (denominator).
4. Study the association and risk of different textured implant surfaces with breast implant–associated ALCL.

PATIENTS AND METHODS

The task force engaged with members of the plastic surgery, breast oncology, hematology and oncology, and cosmetic surgical societies. A pro forma for reporting cases was distributed electronically and by mail calling for notification of cases in October of 2015. Human ethics approval was obtained from Macquarie University.

Clinical, operative, and implant details were crosschecked with operative and clinical records where available. Pathologic diagnosis was confirmed, where required, by secondary review of the pathology slides by an independent pathologist (Stephen Lade, Peter MacCallum Cancer Center). The tumor, node, metastasis staging system[6] was applied (Table 1).

Patient contact was made to confirm survival status. The task force engaged the three major implant manufacturers in our region [i.e., Mentor Worldwide LLC (Santa Barbara, Calif.); Allergan Sales LLC (Dublin, Ireland); and Silimed, Inc. (Dallas, Texas)] 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 biostatistician [K.J.B. (Macquarie University)] for descriptive, risk, and survival analysis.

Table 1. Tumor, Node, Metastasis Staging for Breast Implant–Associated ALCL*

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

TNM, tumor, node, metastasis.
*From 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;34:160–168.

Surface Area Determination

Surface texture of Silimed polyurethane, Biocell, Siltex, and smooth implants was visualized using a Zeiss LSM 880 inverted Confocal Laser Scanning Microscope (Carl Zeiss, Oberkochen, Germany) and a scanning electron microscope using previously published methods.[7] Three-dimensional reconstruction of confocal images was performed using Imaris version 8.4, ImarisXT (Bitplane, Zurich, Switzerland). The three-dimensional isosurface area was measured by Imaris MeasurementPro (Bitplane).

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 who underwent implantation during or after 1999 within

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Australia or New Zealand and who had been exposed to a single type of texture only. For Silimed, we included only 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 of 2016. Eleven women had multiple-implant exposure, whereas the remaining 44 had single-implant exposure, with a total of 75 implant pairs being deployed in this cohort. The mean age of the patients was 47.1 years (range, 22.4 to 69.6 years). The mean time to develop breast implant–associated ALCL from the time of the last implantation was 7.46 years (range, 0.2 to 27.0 years).

All implant histories were obtained, and the frequencies of different implant types associated with the breast implant–associated ALCL–positive breasts in these 55 patients are listed in Table 2. All patients were exposed to textured implants at some point in their implant history. On four occasions, smooth implants were used early in these patients' implant histories (implanted before 1999), reflecting a change to use of textured implants in the Australia and New Zealand market.

In 38 patients (69.1 percent), the indication for breast implants was cosmetic augmentation. In the remaining 17 patients, the indication for implants was postmastectomy reconstruction for both cancer and prophylaxis.

Table 2. Frequency of Implant Types Associated with Breast Implant–Associated ALCL in This Cohort of Patients*

Manufacturer	Texture Type	No. (%)
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)

PIP, Poly Implant Prothèse.
*n = 75 implants in 55 patients because of reoperation.

Table 3. Number of Implants before Development of Breast Implant–Associated ALCL

No. of Implants	No. of Patients (%)
1	44 (80.0)
2	6 (10.9)
3	3 (5.5)
5	2 (3.6)

Eleven patients had multiple implants for revision for rupture, infection, or capsular contracture (Table 3). Of the reconstructive patients, 10 had textured tissue expanders used before insertion of the definitive implant.

Breast Implant–Associated ALCL Diagnosis, Presentation, and Pathology

Table 4 summarizes the clinical presentation of breast implant–associated ALCL. Forty-two patients (76.4 percent) presented with unilateral breast swelling caused by seroma (Fig. 1). (**See Video, Supplemental Digital Content 1**, which shows the appearance of breast implant–associated ALCL intraoperatively in a patient, available in the "Related Videos" section of the full-text article on PRSJournal.com or, for Ovid users, available at ***http://links.lww.com/PRS/C360***.) In two patients, the seroma was associated with contralateral capsular contracture. A total of 10 patients (18.2 percent) presented with a mass. One patient presented with concurrent metastatic axillary disease. Three patients presented with concurrent seroma and mass (5.5 percent).

Geographic Location of Implant Insertion

Of the total of 75 implants placed into patients that developed breast implant–associated ALCL, 65 implants were placed in Australia and eight implants were placed in New Zealand. In two patients, implants were placed outside of Australia and New Zealand (one in Mexico and one in Thailand).

Table 4. Presentation of Breast Implant–Associated ALCL (n = 55)

Presentation	No. (%)
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)

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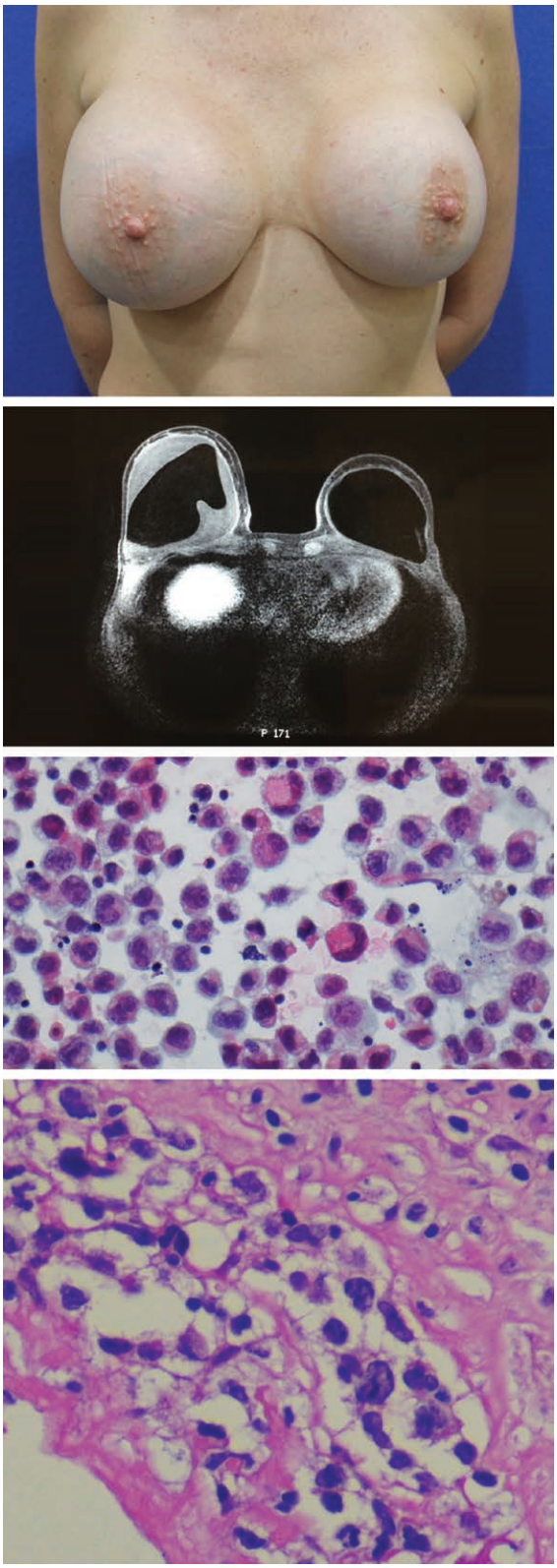


Fig. 1. (*Above*) Clinical presentation of a patient from our cohort, a 39-year-old woman presenting with unilateral seroma following cosmetic augmentation 8 years previously. After diagnosis, she had bilateral completion capsulectomy showing disease in the capsule but with no infiltration. She was given postoperative adjuvant radiotherapy and remains disease free at last follow-up. (*Second row*) Appearance on magnetic resonance imaging showing large seroma and intact implant shell. (*Third row*) Cytologic image positive for breast implant–associated ALCL. (*Below*) Histologic image of implant capsule showing infiltration by breast implant–associated ALCL.

Pathology, Staging, Treatment, and Survival

All patients underwent total capsulectomy and removal of implants on both the diseased and the nondiseased sides. All samples were $CD30^+$ and ALK^-.

Thirty-two patients (58.2 percent) had no evidence breast implant–associated ALCL on histopathologic examination of the capsule, indicating that the disease was confined to the peri-implant malignant effusion. In three of these patients, there was an intense associated (benign) lymphocytic hyperplasia in the capsule. In a further 10 patients (18.2 percent), tumor cells were seen to populate the inner lining but did not invade into the capsule. These patients represent early-stage disease, and six of them were treated with adjuvant postoperative chemotherapy early in the series. The remainder were treated with surgery only.

Twelve patients (21.8 percent) had evidence of tumor infiltrating the capsule, with associated mass lesions present in five 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 tumor, node, metastasis staging[6] of patients in this series.

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

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

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

Mortality

There were four patient deaths in this series. One patient presented with a clinical seroma

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Video. Supplemental Digital Content 1 shows the appearance of breast implant–associated ALCL intraoperatively in a patient, available in the "Related Videos" section of the full-text article on PRSJournal.com or, for Ovid users, available at ***http://links.lww.com/PRS/C360***.

and three others presented with mass and/or metastatic disease. Two cases followed cosmetic augmentation and two followed cancer reconstruction. The mean age was 49.7 years (range, 44.5 to 58.0 years); three patients had single Allergan Biocell implants and one had multiple implants (smooth then Allergan Biocell two times). The mean time to developing this disease was 7.35 years. All patients had mass disease extending beyond the capsule on histologic staging. In two of these patients, disease had spread to lymph nodes (ipsilateral axilla/axilla and mediastinum) at the time of presentation. Two patients had recurrence (one had incomplete resection on histology) after treatment (surgery/adjuvant therapy), with subsequent spread to mediastinum and distant metastases. They died as a result of obstructive respiratory failure. Two other patient deaths were related to complications of adjuvant therapy (sepsis after chemotherapy/bone marrow transplantation). A multicenter analysis of poor outcomes following breast implant–associated ALCL presentation and treatment is currently in progress and will report these cases in more detail.

Implant-Related Risk

The odds ratio for developing breast implant–associated ALCL for Biocell implants compared to Siltex implants was 14.11 (95 percent CI, 1.20 to 561.46; $p = 0.0005$). The odds ratio for developing breast implant–associated ALCL for polyurethane (Silimed) implants compared to Siltex implants was 10.84 (95 percent CI, 1.00 to 566.34; $p = 0.05$). This shows that the risk of developing breast implant–associated 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 approximately 8 years of exposure, reaching a peak at 12 years after implantation (Fig. 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 to 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 one in 3817 (95 percent CI, 2718 to 5545) as compared with polyurethane at one in 7788 (95 percent CI, 3042 to 28,581) and Siltex at one in 60,631 (95 percent CI, 10,882 to 2,397,471). The risk for polyurethane is confounded by a shorter duration of exposure in the Australian and New Zealand market 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 an estimate of surface area for implant surfaces for 1 × 1-mm surface block in

Table 5. Tumor, Node, Metastasis Staging of Patients in This Series

Pathologic Findings	TNM	Stage	No. (%)	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

TNM, tumor, node, metastasis; BIA, breast implant–associated.

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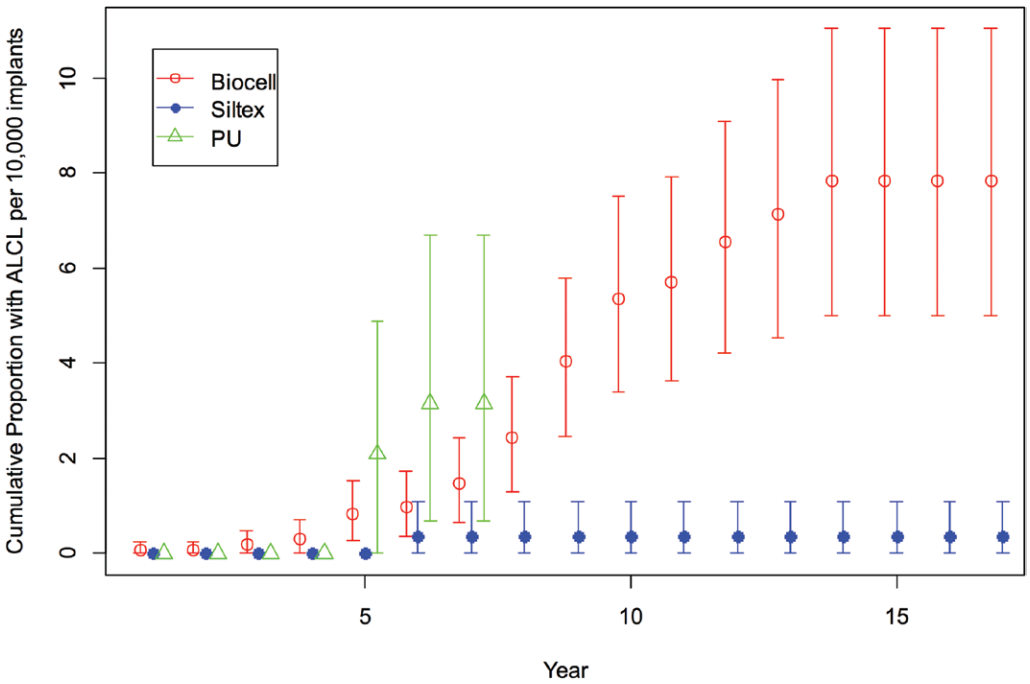


Fig. 2. Cumulative proportion of patients with breast implant–associated ALCL per 10,000 implants for Allergan/McGhan (Biocell) versus Mentor (Siltex) implants. *PU*, polyurethane.

Table 6. Calculated Implant-Specific Risk of Breast Implant–Associated ALCL per Number of Implants and Rates per 10,000 Implant Years for Patients Exposed to Single Implant Texture Type*

Implant	No.	No. of Implants per Single Case of BIA-ALCL	Rate per 10,000 Implant-Years
Biocell (Allergan/Inamed/McGhan)	31		
Mean		3817	0.39
95% CI		2718–5545	0.27–0.55
Polyurethane (Silimed)	6		
Mean		7788	0.31
95% CI		3042–28,581	0.08–0.79
Siltex (Mentor)	1		
Mean		60,631	0.028
95% CI		10,882–2,397,471	0.001–0.156

BIA, breast implant–associated.
*Excluding exposure to smooth implants.

Table 7. Topographic Surface Area Analysis for Siltex, Biocell, and Polyurethane (Silimed) Textured Implants versus Smooth Implants

Implant	Surface Area (mm^2)*
Polyurethane (Silimed)	146.7
Biocell	27.9
Siltex	12.4
Smooth (Mentor)	1.0

*For 1 × 1-mm implant surface.

square millimeters. The findings showed Silimed polyurethane to have the highest surface area by this method of calculation. Figure 3 shows 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 breast implant–associated ALCL in Australia and New Zealand. To date, this represents the most accurate numerator and denominator for risk calculation of breast implant–associated 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, oncologic clearance and assessment by a multidisciplinary team when dealing with this disease.[6] By contrast, we and others[13] have confirmed

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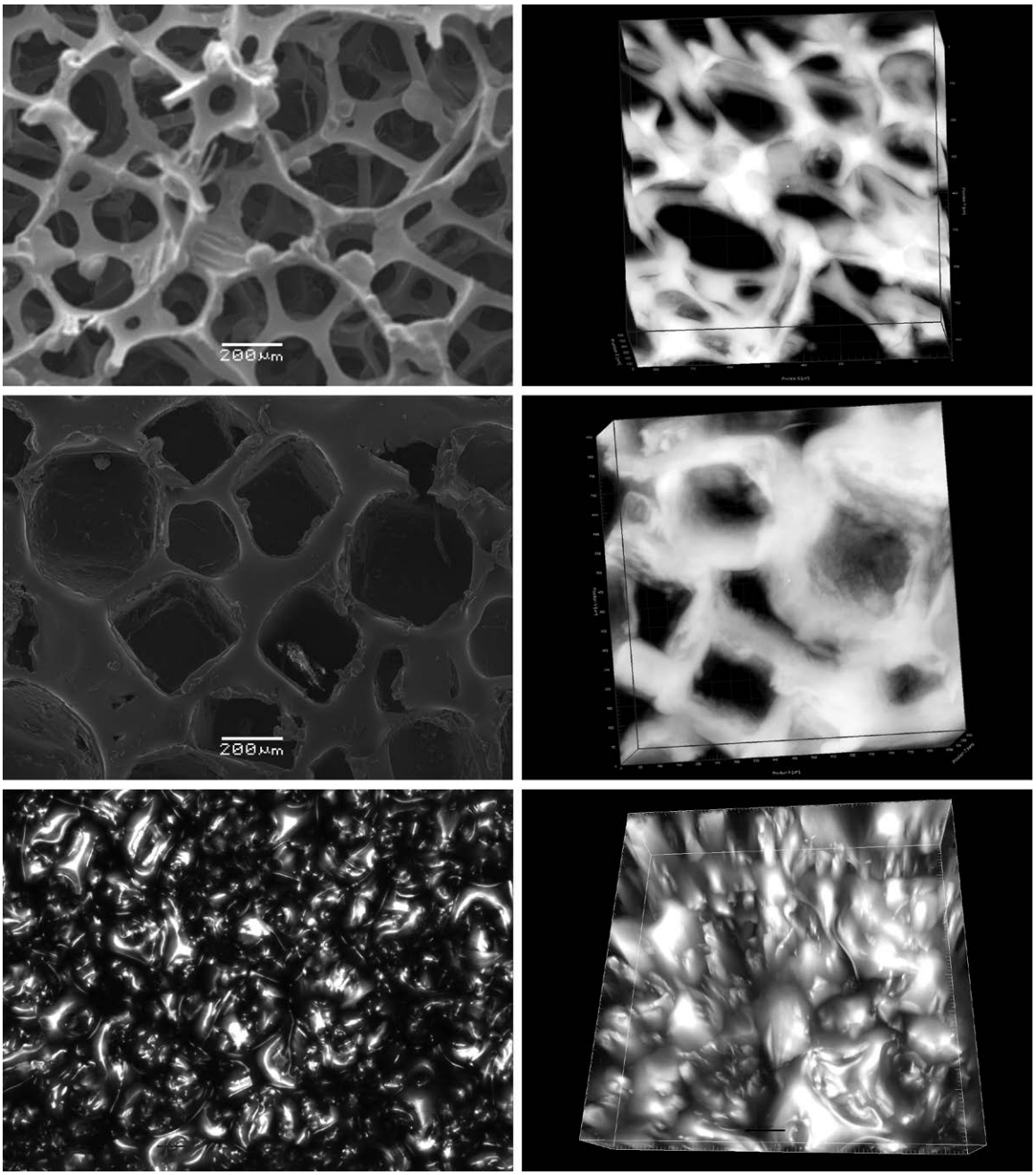


Fig. 3. Two- and three-dimensional images of polyurethane, Biocell, and Siltex implants used for analysis of surface area. (*Above*, *left*) Siltex at 75× magnification. (*Above*, *right*) Three-dimensional image of Siltex texture. (*Center*, *left*) Biocell at 75× magnification. (*Center*, *right*) Three-dimensional image of Biocell texture. (*Below*, *left*) Polyurethane (Silimed) at 75× magnification. (*Below*, *right*) Three-dimensional image of polyurethane (Silimed) texture.

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 breast implant–associated ALCL entities.[14] There are similarities of the seroma type with primary cutaneous ALCL.[15] In primary cutaneous ALCL, 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 premalignant lymphoproliferative phase, termed lymphomatoid papulosis, which can progress into primary cutaneous ALCL and regress into lymphomatoid

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papulosis.[15,16] To support this, a recent report by Kadin and Glicksman[17] has shown $CD30^+$ clonal expansion in the setting of a late benign seroma. It may be, in time, that seroma type breast implant–associated 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 both in seroma fluid and in the capsule.

A number of hypotheses have been put forward to explain the genesis of breast implant–associated ALCL. Our findings have shown that Biocell (salt loss) and (Silimed) polyurethane textures carry a significantly higher risk of developing breast implant–associated ALCL compared with Siltex (imprinted texture). Biomarkers also provide evidence to show that underlying inflammation is the likely initiator of this disease.[18] As for 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 polyurethane 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 breast implant–associated 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 breast implant–associated 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 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 its relationship with bacterial growth is ongoing and will be reported in due course. Furthermore, although 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 percent of patients in our series have been exposed to higher-surface-area textures and that these textures carry a higher risk of development of breast implant–associated ALCL strengthens the case for bacteria as the cause of inflammation. We propose that 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 with which 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 breast implant–associated ALCL through missed clinical and/or pathologic diagnosis. The propensity, however, of high-surface-area texture to generate risks of breast implant–associated ALCL as high as one 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 surgeons and patients with the confidence that 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 that, if the biofilm theory is true, why do textured implants not 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.

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We are now in a position to move toward a unifying hypothesis to explain the observed phenomena surrounding breast implant–associated ALCL. The contamination of textured implants with a higher surface area by bacteria leading to chronic antigen stimulation in genetically susceptible hosts over a prolonged period may result in transformation of T cells into breast implant–associated ALCL. We believe that the genesis of breast implant–associated ALCL is thus multifactorial, as is the case with most carcinogenesis. Recent findings of mutations in the JAK/STAT3 pathway in patients with breast implant–associated 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, epidemiologic, 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 article by Adams et al.[23] has shown that application of anti-infective strategies in 42,000 macrotextured implants resulted in no recorded cases of breast implant–associated 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 breast implant–associated ALCL.

Finally, this study raises the possibility of an increasing incidence of breast implant–associated ALCL in Australia and New Zealand. Projections of implant sales show a significant increase in the use of high-surface-area textured devices in the past 5 years. As the mean time for development of this disease is approximately 8 years, it is of some concern that we are in store for a rise in breast implant–associated 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.

CONCLUSIONS

Our joint task force has captured 55 cases of breast implant–associated 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 a 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 for these observations.

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