On November 19th 2018, the Dutch National Institute for Public Health and the Environment (RIVM), supported by the Dutch Ministry of Health, Welfare and Sport (VWS) and the Dutch Health and Youth Care Inspectorate (IGJ), brought together in Amsterdam (the Netherlands) an international multidisciplinary group of regulators, public health authorities, medical specialists, epidemiologists, experts on implant registries, and breast implant manufacturers to discuss the problem of a very rare form of lymphoma seen in women with breast implants. This form of lymphoma is called breast implant-associated anaplastic large cell lymphoma (BIA-ALCL).

In the morning, presentations were given by keynote speakers. Enclosed you will find presentations given by:

1. Dr. Wim de Jong - Senior researcher at RIVM, the Netherlands; Member of the Scientific Committee on Health, Environmental and Emerging Risks (SCHEER), DG for Health and Food Safety, European Commission; Chair SCHEER Working Group on PIP silicone breast implants
2. Prof. Flora van Leeuwen - Netherlands Cancer Institute, Amsterdam, the Netherlands
3. Dr. Mark Clemens - Plastic surgeon at MD Anderson Cancer Center, Houston, USA
4. Dr. Hinne Rakhorst - Chair Dutch Breast Implant Registry, Board member International Confederation of Plastic Surgery Societies ICOPLAST, plastic surgeon
5. Prof. Roberto Miranda - Professor in Hematopathology, MD Anderson Cancer Center, Houston, USA
BIA-ALCL
SCHEER advice 2017
The level of evidence

Wim H De Jong,
Demosthenes Panagiotakos,
Theodoros Samaras
Mandate:

“The SCHEER was requested by the European Commission to provide an advice on the state of scientific knowledge regarding a possible association between breast implants (BI) and anaplastic large cell lymphoma (ALCL) and determine whether sufficient scientific information was available for conducting a full risk assessment on a possible association between BI and ALCL”
SCHEER Advice on BIA-ALCL

Scientific Advice on
The state of scientific knowledge regarding a possible connection between breast implants and anaplastic large cell lymphoma.

Published April 2017 for public consultation and revised October 2017.

Prevalence of ALCL

- **Anaplastic Large Cell Lymphoma** (ALCL) is a very rare type of non-Hodgkin lymphoma and one of the subtypes of T-cell lymphoma.
- According to GLOBOCAN 2012 (International Agency for Research on Cancer) the age-standardised annual incidence of non-Hodgkin lymphomas in Europe is estimated to be <6.8 cases per 100,000 individuals, varying from 0.8 to 11.2 cases per 100,000 (Boffetta, 2011);
  - ALCL comprises about 1% of all non-Hodgkin lymphomas and approximately 16% of all T-cell lymphomas (Clemens et al., 2016).
  - However, it should be noted that ALCL in the breast is even rarer (Altekruse et al., 2010).
Breast implants and ALCL

• Since 1960s breast implants (BI) have been used for reconstructive and/or aesthetic reasons.
  
  – Concerns about a possible association of ALCL and BI arose in 1995 based on a case report about women with polyurethane silicone foam-covered, polyurethane-coated silicone and silicone implants (Duvic et al., 1995).
Methodology followed for the SCHEER Opinion

- Information was obtained by two independent methods:
  - (a) literature search and
  - (b) an open call for information.

- All submitted information was considered

  - but conclusions were based exclusively on peer-reviewed scientific papers.
Information retrieved from the literature review

PubMed, Find-ER searches

712 documents

188 scientific papers

7 epidemiologic studies (case-control, historical cohort studies)

No Randomised Clinical Trials

82 case reports / series
18 original research papers
88 reviews, letters, commentaries
Published during Public Consultation

- Doren et al., 2017
  - Evaluated USA cases 1996 – 2015
  - Reported 100 cases with interval implant to diagnosis 10.7 years
  - Calculated incidence rate 203 cases per 100 million person years
  - Only in textured implants
- Loch-Wilkinson et al., 2017
  - Cases in Australia and New Zealand
  - Reported 55 cases between 2007 and 2016
  - Textured implant 7.46 years exposure
- Srinivasa et al., 2017
  - Conducted a review of 40 Government Authority databases

- (De Boer et al., 2018)
  - Clinical study based on pathology database (evaluation of primary non-Hodgkin lymphoma in the breast between 1990 and 2016)
SCHEER Opinion

- The available information suggests that BI may be associated with an increased risk for ALCL.
  - The very low incidence of ALCL and the methodological limitations of the available information/studies (i.e., case reports or case series, retrospective studies) do not currently allow for a robust risk assessment.
  - In addition, similar tumors were also identified near surgical stainless steel plate (Palraj et al., 2010), dental implant (Yoon et al., 2015), dystrofic calcification (Ozkaya et al., 2016), and at location of benign cyst in breast (Mulligan et al., 2014).

- SCHEER recommends a more in-depth evaluation on the possible association of BI with the development of ALCL.
SCHEER Advice

... there is an emerging need for prospective studies in order to be able to perform a more robust evaluation of the possible association between breast implants and ALCL.

- Moreover, the lack of registries, throughout the world, of women with breast implants is a major challenge for providing evidence-based conclusions on the potential association between breast implants and ALCL.
- Such registers, and their systematic evaluations, are urgently needed
Clinical examples of BIA ALCL and using levels of evidence

An association was hypothesized between lymphoma and silicone breast implants based on case reports. **The level of evidence for case reports, depending on the scale used, was 4 or 5.**

Because of these results, several large retrospective cohort studies from the US, Canada, Denmark, Sweden and Finland were conducted. **The level of evidence for a retrospective cohort is 2 or 3 (depending on the scoring system).**

Some of the studies found an elevated risk and others no risk for ALCL.

**Conclusion?**
Grading the level of evidence in medical research

- Evidence Based Medicine: is an approach to medical practice intended to optimize decision-making by giving emphasis to well-conducted research.
- A cornerstone of EBM is the hierarchical system of classifying evidence, i.e., the level of evidence.
- It is widely adopted that hierarchies rank studies according to the probability of bias.
  - Meta-analyses of RCTs or/and large-scale RCTs are given the highest level because they are designed to be unbiased and have less risk of systematic errors.
Pyramid of Clinical Evidence

- Systematic Reviews & Meta-analyses
- RCT
  - Level 1 Evidence
- Cohort Studies
  - Level 2 Evidence
- Case Control Studies
- Case Series
  - Level 3 Evidence
- Case Reports
- Ideas, Editorials, Opinions
- Animal research
- In vitro ('test tube') research
The level of evidence based on study design

- In 1989 the U.S. Preventive Services Task Force (USPSTF) put forth the following
  - **Level I**: Evidence obtained from at least one properly designed Randomized Clinical Trial (RCT)
  - **Level II-1**: Evidence obtained from well-designed controlled trials without randomization.
  - **Level II-2**: Evidence obtained from well-designed cohort or case-control studies.
  - **Level II-3**: Evidence obtained from multiple observational studies, time series or uncontrolled trials.
  - **Level III**: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.
The Grading of Recommendations Assessment, Development and Evaluation (GRADE)

- The GRADE approach is a method of assessing the certainty in evidence (also known as quality of evidence or confidence in effect estimates) and the strength of recommendations in health care.

  - **High** We are very confident that the true effect lies close to that of the estimate of the effect.

  - **Moderate** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

  - **Low** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

  - **Very low** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
Background knowledge

BIA-ALCL cases;

› In 2011 The US-FDA identified a possible association between SBI and ALCL and estimated that there were between 100-250 known cases of ALCL in women with BI out of an estimated number of 5 to 10 million women who have received BI worldwide.

Currently investigated by:

› The Australian Therapeutics Goods Administration (TGA)
› The EU
› The French National Agency for Medicines and Health Products (ANSM)
› The US Food and Drug Administration (FDA)
Recent information


- 272 (65%) of the 414 reports included information on SBI surface
  - 242 (89%) with textured surface and 30 (11%) with smooth surface

- 413 of the 414 reports included information on implant fill types
  - 234 (57%) filled with silicone gel and 179 (43%) filled with saline

- NOTE. Information is related to implant at time of diagnosis but does not give information on patient’s history of breast implants

- Quesada et al 2018, worldwide 561 cases in 29 countries

*retrieved November 16th 2018
Thank you for your attention
Reappraisal of Epidemiological Evidence on Breast Implants and ALCL in the Breast

Flora E. van Leeuwen, PhD
Epidemiology
Netherlands Cancer Institute

No disclosures to report
Breast ALCL: (Inter)National interest

A Shocking Diagnosis: Breast Implants ‘Gave Me Cancer’

Breast Implants Linked to a Rare Cancer: How Big Is the Risk?

Borstimplantaat zorgt voor groter risico op lymfeklierkanker

BREAST IMPLANTS INCREASE CANCER RISK, LARGE LYMPHOMA STUDY SHOWS
How to use epidemiological methods to assess a possible association between:

- an infrequent exposure (breast implants) and
- a very rare disease (anaplastic large cell lymphoma)?
Observational epidemiological study designs

COHORT STUDY

Study Population
Disease-free (at risk) Population

Cohort 1
(Exposed group)
- Disease
- No Disease

Cohort 2
(Unexposed group)
- Disease
- No Disease

1. Identify exposed and unexposed cohort groups.

2a. PROSPECTIVE STUDY
- During follow-up period, identify diseased subjects (incident cases).

2b. RETROSPECTIVE STUDY
- Identify diseased subjects by interview or written records.

3. Analyze differences (i.e., incidence or relative risk) among those exposed (cohort 1) and those unexposed (cohort 2).

Observational epidemiological study designs

CASE-CONTROL STUDY

1. Identify cases.
2. Select controls, which may be matched to cases.
3. Measure exposure or risk factors of interest.
4. Compare the presence or absence of exposure in cases and controls.

General epidemiological principles

What to choose: cohort or case-control study?

• Rare exposure: cohort study of exposed individuals → search for ‘registry’ and for ‘unexposed reference group’

• Rare disease: case-control study → compare breast ALCL cases and non-cases regarding implant prevalence

What in case of rare exposure and rare disease?
Factors determining the potential to unravel a true association between exposure and disease in epidemiological research

- Prevalence of exposure
- Incidence of disease
- Strength of the association
- Potential for misclassification of exposure
- Potential for misclassification of disease
- Interval between exposure and disease (induction period)
- Confounding factors
## Easy and difficult associations to unravel in cancer epidemiology study designs

<table>
<thead>
<tr>
<th>Difficulty</th>
<th>Exposure</th>
<th>Disease</th>
<th>Association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Easy</td>
<td>Smoking and lung cancer</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Bit difficult</td>
<td>Smoking and colorectal cancer</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Bit difficult</td>
<td>Smoking and laryngeal cancer</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Difficult</td>
<td>Passive smoking and lung cancer</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Very difficult</td>
<td>Passive smoking and laryngeal cancer</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Difficult</td>
<td>In utero DES and vaginal cancer</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Bit difficult</td>
<td>In utero DES and infertility</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Difficult</td>
<td>Breast implants and ALCL</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Very difficult</td>
<td>Breast implants and autoimmune disease</td>
<td>+</td>
<td>++</td>
</tr>
</tbody>
</table>
Available „studies” on breast implants and ALCL in the breast

• Case reports or case series (important role in alerting to possible associations, but population at risk unclear → not a study design)

• Several studies:
  – Upgraded case series „epidemiologicalized”: case series with externally added data on implant sales
    • Incomplete ALCL case ascertainment
    • Sales data ≠ number of women with implants
  – No estimation possible of relative and absolute risk
    • No comparison group without implants
    • No ALCL cases without implants
Examples of large BIA-ALCL case series

Brody et al, 2015, PRS

- 173 cases worldwide (79 cases from literature review, 94 unreported cases)

Miranda et al. JCO 2014, (USA)

- Literature review from 1997-2012
- 60 cases reported worldwide with follow up ranging 1-14 years
Examples of large BIA-ALCL case series

Loch-Wilkinson et al. PRS 2017; 140(4), (New Zealand/Australia)

- 55 ALCL cases 2007-2016
- Interval 7.5 yrs
- 39 /1 million implant-years, 95% CI 27-55/million (Biocell (Allergan))
- 31/million implant-years, 95% CI 8-79/ million (Polyurethane)

Doren et al. PRS 2017, (USA)

- 100 ALCL cases 1996-2015
- Interval 10.7 yrs
- 2.0 / 1 million textured implant – years
- Cumulative risk 33 / 1 million women
Available epidemiological studies on breast implants and ALCL in the breast: Problems

• Very few retrospective (historical) breast implant registries
• Very few countries can identify all breast ALCL cases
  – Self-report by clinicians
  – No request for reporting of cases without implants
• What is background breast ALCL risk (without implants)?
  Very specific diagnosis
Potential study designs for assessing associations between breast implants and breast ALCL

• Cohort study of women with breast implants
  – No large historical registries
  – Breast ALCL is rare – statistical power

• Case-control study of ALCL in the breast
  – How to identify cases?
  – What type of control group?
## Cohort studies of women with breast implants

<table>
<thead>
<tr>
<th>Study</th>
<th>Cohort of women* with breast implants</th>
<th>Comparison group</th>
<th>Mean follow-up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Friis, 2006, Denmark</td>
<td>2763</td>
<td>1736</td>
<td>~ 15 yrs</td>
<td>0 ALCL</td>
</tr>
<tr>
<td>Lipworth, 2009, Sweden &amp; Denmark</td>
<td>6222</td>
<td>General population</td>
<td>16.6 yrs</td>
<td>0 ALCL</td>
</tr>
<tr>
<td>Vase, 2013, Denmark</td>
<td>19,885</td>
<td>General population</td>
<td>9 yrs</td>
<td>0 ALCL</td>
</tr>
<tr>
<td>McLaughlin, 2006, Sweden</td>
<td>3486</td>
<td>General population</td>
<td>18 yrs</td>
<td>0 ALCL</td>
</tr>
<tr>
<td>Wang, 2016, USA†</td>
<td>2990</td>
<td>120,402</td>
<td>20 yrs</td>
<td>2 ALCL HR=10.9</td>
</tr>
</tbody>
</table>

* Identified through hospital registries †California Teachers Cohort
Anaplastic Large-Cell Lymphoma in Women With Breast Implants

Daphne de Jong, MD, PhD
Wies L. E. Vasmel, MD, PhD
Jan Paul de Boer, MD, PhD
Gideon Verhave, MD
Ellis Barbé, MD
Mariel K. Casparie, MD, PhD
Flora E. van Leeuwen, PhD

Context  Recently, we identified 2 patients with anaplastic large T-cell lymphoma (ALCL) negative for tyrosine kinase anaplastic lymphoma kinase (ALK-negative) in the fibrous capsule of silicone breast prostheses, placed for cosmetic reasons. Similar cases have been reported in the literature. Although an increased risk of ALCL in patients with breast prostheses has been speculated, no studies have been conducted so far.

Objective  To determine whether ALCL risk is associated with breast prostheses.

Design  A search for all patients with lymphoma in the breast diagnosed in the Netherlands between 1990 and 2006 was performed through the population-based nationwide pathology database. Subsequently, we performed an individually matched case-control study. Conditional logistic regression analysis was performed to estimate the relative risk of ALCL associated with breast prostheses.

Setting and Patients  Eleven patients with breast ALCL were identified in the registry. For each case patient with ALCL in the breast, we selected 1 to 5 controls with other lymphomas in the breast, matched on age and year of diagnosis. For all cases,

Since the late 1970s, silicone breast implants have been under constant challenge for suspected association with systemic diseases, such as connective tissue disease and breast cancer. The association with connective tissue disease has been well recognized. Connective tissue disease has been associated with connective tissue disease, but it is not known whether this association is causal for breast cancer. The association with ALCL in breast prostheses is a recent development. In this study, we examined the association of breast ALCL with breast prostheses.
Dutch case-control study of breast implants and risk of ALCL in the breast

De Boer et al. JAMA Oncol. 2018;4(3):335-341
Dutch case-control study of breast implants and risk of ALCL in the breast

**Cases:** all women with primary breast ALCL in the Netherlands, diagnosed 1990-2016 (n=43). Identified through the nationwide Dutch Pathology Registry

**Controls:** women with other types of primary breast lymphoma, also identified through the Dutch Pathology Registry (n=146)
Dutch case-control study of breast implants and risk of ALCL in the breast

Assessment of breast implant exposure and clinical ALCL characteristics

• Questionnaires to treating physicians of all cases and controls

• 100% response for cases, 92% for controls
Prevalence of breast implants in the Netherlands

• 3000 chest X-rays performed in 2015, women 20-70 yrs old
• Prior validity study for assessing breast implants from chest X-rays
• Estimation of breast implant prevalence prior to 2015 based on changes in implant sales (nationwide data available) → annual number of women with breast implants
• Calculation of cumulative risk of breast ALCL in women with/without implants
Characteristics of breast lymphomas

Median age at ALCL diagnosis: 59 yrs

De Boer et al. JAMA Oncol. 2018;4(3):335-341
Dutch case-control study of breast implants and risk of ALCL in the breast

Results

<table>
<thead>
<tr>
<th>Breast implant</th>
<th>Cases (n=43)</th>
<th>Controls (n=146)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>32</td>
<td>1</td>
</tr>
<tr>
<td>No</td>
<td>11</td>
<td>145</td>
</tr>
</tbody>
</table>

Odds Ratio (OR) = 422 (95% CI: 53 – 3385)
Characteristics of implants in ALCL cases

Indications:
- 65% cosmetic
- 31% reconstruction
- 4% prophylactic mastectomy

Median interval: 13 yrs

82% macrotextured
18% microtextured

De Boer et al. JAMA Oncol. 2018;4(3):335-341
Prevalence of breast implants in the Netherlands

3.3% of all Dutch women had implants (4.2% in women 41-50 years old)
Cumulative risk of breast ALCL

De Boer et al. JAMA Oncol. 2018;4(3):335-341
Conclusions Dutch study on breast implants and risk of breast ALCL

• Strong relative risk increase of breast ALCL after implants

• Absolute risk small:
  1 / 35,000 at age 50
  1 / 7,000 at age 75
Breast ALCL in women with breast implants

Questions to be answered in future epidemiologic studies:

• More precise risk estimation
• Which implant types increase risk?
  – Textured, surface area
• Duration-response relationship
• Do implant revisions increase risk?
• Age at first implant
• Host susceptibility: genetic factors, immuno-compromised individuals
Incidences of breast ALCL is rising

Dutch breast ALCL cohort (1990-2017)

SEER data (2000-2013)
Causes and pathogenesis: why is breast ALCL incidence increasing

Epidemiological considerations
1. Awareness
2. Increasing number of women with implants
3. Increasing number of 'risk-associated' implants
4. Increasing number of 'risk-associated' surgeries

Pathogenesis
1. Toxic products from breast implants
2. Texturing of breast implants
3. Adherent biofilm
4. Foreign body and immune responses
5. Genetic and molecular aspects
Dutch Breast-ALCL consortium

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René van der Hulst, MUMC+ Maastricht
Hinne Rakhorst, Ziekenhuisgroep Twente

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Data-coordination
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Erik van Dijk, Vumc, Amsterdam

Statistics
Michael Hauptmann, NKI-AVL, Amsterdam

PALGA, NVPC

PALGA, NVPC
Breast Implant Associated – ALCL
US Experience on an Emerging Malignancy

International Expert
Meeting on BIA-ALCL
Amsterdam

Mark W. Clemens, MD, FACS
Associate Professor
MD Anderson Cancer Center
Financial disclosures/conflicts of interest

Investigator Motiva US Safety and Effectiveness Clinical Trial (Uncompensated)
Investigator Mentor Athena Trial (Uncompensated)
Chair BIA-ALCL Taskforce for ASPS
ASPS Liaison to FDA
Coauthor Lymphoma NCCN Guidelines
2011, 2016, 2017, 2018 FDA safety communication

- Agrees with World Health Organization BIA-ALCL is a “uncommon” T-cell lymphoma around breast implants
- Support NCCN Guidelines for diagnosis and management
- Support PROFILE Registry reporting
- 414 adverse event reports, nine deaths
- Textured surface cases predominate

1. All government authorities and oncology organizations classify BIA-ALCL as a lymphoma.

2. To date, only noted to occur with textured implants.

3. Report confirmed cases to ASPS/FDA PROFILE Registry.

4. FDA, ASPS, ASAPS support NCCN Guidelines for Diagnosis and Treatment.

5. For clinical situations where use of a smooth vs. textured device is equivocal, should consider a smooth device.
PROFILE US Data Collection Update

- Case Collection
  - 255 suspected/confirmed US cases reported
  - Complete data received for 99 cases

- Report Forthcoming 2019:
  - First African American case
  - First Tissue Expander case
  - First incidental finding case
  - 2 bilateral cases
PROFILE Data

<table>
<thead>
<tr>
<th>Implant Surface***</th>
<th>All PROFILE Data (as of 11/9/2018) (n=100)</th>
<th>All MDR Reports (as of 9/30/2017) (n=414)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Textured</td>
<td>76</td>
<td>76</td>
</tr>
<tr>
<td>Smooth</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Polyurethane</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Not specified</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Silicone</td>
<td>54</td>
<td>54</td>
</tr>
<tr>
<td>Saline</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Saline/Silicone</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Not specified</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Reconstruction</td>
<td>49</td>
<td>49</td>
</tr>
<tr>
<td>Aesthetic</td>
<td>49</td>
<td>49</td>
</tr>
<tr>
<td>Not specified</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

* Please note that all reported smooth cases have either a mixed clinical history of textured/smooth or no clinical history available for review. To date, there are no reported pure smooth implant BIA-ALCL cases.
Online reporting of data
FDA data exchange

Patient Registry and Outcomes for Breast Implants and Anaplastic Large Cell Lymphoma Etiology and Epidemiology (PROFILE): Initial Report of Findings 2012 – 2018

Colleen M. McCarthy MD1, Erin Mullen2, Ali A. Qureshi MD3, Gayle Gordillo MD4, Andrea L. Pusic MD1, and Mark W. Clemens MD5

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5. Chief, Division of Plastic Surgery, Brigham and Women’s Hospital, Boston, MA.
6. Associate Professor, Department of Surgery, University of Texas MD Anderson Cancer Center, Houston, TX.

Forthcoming manuscript 2019
Risk Assessment

- US: 1:11,765 (255 cases, 2018)
- Netherlands 1:6920 (40 cases)
- Australia, 81 cases,\(^1,2\)
  17 polyurethane cases
  - Risk 1:1000-1:10,000\(^1\) for textured implants
  - Allergan Biocell (1:3345)
  - Silimed polyurethane (1:2832)
  - Mentor Siltex (1:86029)

1. Therapeutic Goods Administration update, 20 December 2016;
Polyurethane Risk

- Australia, New Zealand\textsuperscript{1,2}
  - 17 PU cases
    - Silimed polyurethane (1:2832)
- 1\textsuperscript{st} MD Anderson case – Silimed implanted in Bogota, Colombia

CD30+ Effusion
CA/CARE Style 410
FDA Prospective Trials

- McGuire et al. 2017
  - 17,656 patients, 31,985 implants\(^1\)
- 8 BIA-ALCL: 1:2207 (95%CI:1120,5112)
- 9-13% of delayed seromas may be BIA-ALCL

---

No Confirmed Pure Smooth Cases To Date

Out of 414 adverse event reports, 30 reports of “smooth implants” cases. Smooth implant reports had either no clinical history or mixed texture/smooth history.

70 to 80 percent of implants sold in North America are smooth. No cases of ALCL were found in patients with documented smooth devices only.3


58-year-old woman who had undergone bilateral cosmetic breast augmentation with a smooth silicone gel breast implants 19 years previously. In 2006, her device had already been replaced for the same complication.2

BIA-ALCL Global Network Roundtable

30 Countries
Consistent messaging on diagnosis and treatment across international societies
Global prospective registry with standardised data
Cross-country data exchange
Network for disbursement of disease updates
Localised access to medical care
Centralised tissue repositories

- Australia: Anand Deva, MD
- Belgium: Moustapha Hamdi, MD
- Brazil: Alexandre Passos, MD
- Canada: Peter Lennox, MD FRCSC
- Finland: Catarina Svarvar, MD
- France: Michael Atlan, MD
- Japan: Toshiharu Minabe, MD
- Ireland: Catriona Lawlor, MD
- Israel: Eran Bar Meir, MD
- Italy: Riccardo Carnino
- Mexico: Guillermo Ramos Gallardo, MD
- Netherlands: Hinne Rakhorst, MD
- New Zealand: Julian Lofts, MD
- South Africa: Chris Snijman, MD
- South Korea: Roe, Tae Suk MD
- Spain: Antonio Diaz Gutierrez, MD
- Sweden: Per Heden, MD
- Taiwan: Nai-Chen Cheng, MD
- United Kingdom: Joe O’Donoghue, MD
- China: Jie Luan, MD
- Russia: Alex Bessonov, MD
- Switzerland: Ali Modarressi, MD
- Argentina: Martin Colombo, MD
BIA-ALCL Global Network Roundtable

626 World Cases, Unique and pathology confirmed
17 Deaths Worldwide

- **33 countries**
  - Argentina: 6 cases
  - Australia: 81 Cases, 3 deaths
  - Belgium: 9 Cases
  - Brazil: 3 Cases, 1 death
  - Canada: 23 Cases
  - Chile: 2 Cases
  - Colombia: 6 Cases
  - Denmark: 7 Cases
  - Egypt: 1 case
  - Finland: 7 Case
  - France: 50 Cases, 3 deaths
  - Germany: 7 cases
  - Ireland: 1 case
  - Israel: 5 Cases
  - Italy: 28 Cases
  - Japan: 0
  
- Mexico: 4 Cases
  - Netherlands: 40 Cases, 1 Death
  - New Zealand: 13 Cases, 1 death
  - Norway: 3 cases
  - Russia: 2 cases
  - South Africa: 1 Case
  - South Korea: 0
  - Spain: 27 Cases
  - Sweden: 6 Cases, 2 death
  - Switzerland: 4 cases
  - Taiwan: 0
  - Thailand: 1 Case
  - Venezuela: 2 cases
  - United Kingdom: 35 Cases, 1 death
  - United States: 255 Cases, 5 deaths
Emerging Disease

- One Year Increase
  - Worldwide 44%
  - US 45%

All unique cases from 28 countries. US data from PROFILE Registry, www.thepsf.org/PROFILE
Protocol PA14-0321 Biomarker Analysis

H&E stain: pathology analysis

IHC assay

Multiplex IF Analysis (up to 10 markers, 3 Vectra panels): Panel 6#CD11b, CD14, CD33, CD66b, CD68, CD163, DAPI; Panel #7:PD-L1, PD-1, CD137, CD68, CD3, CD30, DAPI; Panel#8, CD33, Arg-1, CD14, CD68, Cd11b, CD30, DAPI.

Optional: RNA Analysis: Nanostring Signature

Tumor Tissue:
- Flow Cytometry

Fresh
- Whole Exome Sequencing (WES)
- RNA sequencing

Blood:
- Flow cytometry
- Liquid Biopsy – cfDNA Guardant Health Panel
- Cytokines- MSD
- Germline DNA

Seromas
- Supernatant and cell pellet- Cytokines MSD
Mechanism of Allergic Inflammation

- IL-13 is the signature cytokine of allergic inflammation
- Th2 Lymphocytes and ALCL both express GATA3 (Th2 transcription factor) and both secrete IL-13
- Creates Feedback loop

Antigen - Multifactorial

Chronic inflammation of capsules with fibrosis, plasma cells, lymphocytes

Th2 Lymphocytes and ALCL express GATA3 and secrete IL-13

IL-13 Ig induces class switch of B cells to produce IgE

Plasma cells expressing IgE in capsule and lymph nodes

mast cells produce prostaglandin D₂ (PGD₂)

Receptor for PGD₂ on ALCL cells

8-10 Years

IL-13 Release

IgE Release

PGD₂ Release
Genetic Predisposition
BIA-ALCL

• JAK1/STAT3 Mutations implicated
  • Blombery 2016
  • Di Napoli 2016

• Feldman 2018
• 36 cases BIA-ALCL
• All cases triple negative
  • Significant homogeneity
• 100% STAT3 Expression
• STAT3 is mediated by JAK1/STAT3 mutations

Genetic subtyping of breast implant-associated anaplastic large cell lymphomas

CD30 ELISA for Rapid Screening

- CD30 ELISA may be used as an inexpensive, office based, rapid (2 hour) screening test
- All BIA-ALCL demonstrated CD30 ELISA detection at full and all serial concentrations
- Control specimens were negative at all concentrations.
HLA Predisposition to Lymphoma

- Familial aggregation and ethnic variation suggest genetic susceptibility
- Hodgkin lymphoma (HL) was the first disease to be associated with HLA variation
- Epstein-Barr virus (EBV)-positive and -negative HL are strongly associated with specific HLA polymorphisms
  - HLA class I alleles: EBV-positive HL
  - Polymorphism HLA class II: strongest predictor of risk of EBV-negative HL
- Follicular lymphoma strongly associated with two distinct haplotypes in HLA class II
HLA Distribution in BIA-ALCL

• HLA data may signify genetic susceptibility factors in patients with BIA-ALCL
• Need to further elucidate if these alleles confer susceptibility or resistance to the disease in women with implants
Gram Negative LPS Antigen\textsuperscript{1}

- 2016 *Ralstonia pickettii*
- 2018 Gram-Negative Bacteria

Intraoperative Techniques in BIA-ALCL Patients

- 29 Consecutive BIA-ALCL patients

- Betadine Irrigant: 12 patients (No full strength, 6 50% Strength, 4 25% Strength, 2 “tea colored”)
- Antibiotic Irrigant: 16 patients (7 Baci/Cef/Gent, 9 Polymyx/Baci)
Pathogenesis - Established

1. Textured Implant
2. Time (8-10 years)
3. Chronic Inflammation (Allergic)
4. TH1/TH2/TH17 Precursor
5. JAK1/STAT3 Mutation

Normal lymphocytes
Inflammation

Lymphoma
Pathogenesis - Theoretical

Normal lymphocytes
Inflammation

1. Macrophage digestion of particulate
   1. Receptor independent
   2. Innate Immunity
2. Chronic gram-negative biofilm
   1. Toll receptor dependent
   2. Adaptive Immunity

Lymphoma

1. 
2. Secondary tumour-promoting epigenetic events?
NCCN Guidelines\textsuperscript{1}

- Internationally recognised algorithms for the diagnosis and treatment of cancer
- Utilized by the majority of oncologists
- Adopted by international societies

\textsuperscript{1} Clemens MW, Horwitz SM. Aesthet Surg J 2017;37:285–89.
Diagnosis BIA-ALCL

**Symptoms**
Effusion, mass, skin rash/ulcer >1 year implant (Average 8-10y)

**Breast Imaging**
Ultrasound or MRI

**Finding**
- Effusion
- Mass
- Inconclusive

**Path Workup**
Essential for Dx
- 1. Cytology
- 2. Flow cytometry for T cell clone
- 3. IHC for CD30
  Additional differentiation markers: CD2, CD3, CD4, CD5, CD7, CD8, CD45, ALK

**Path Results**
Indeterminate
- Secondary eval at tertiary cancer center
- Negative for Lymphoma (Normal cells, Scant CD30)
- Treat as benign seroma

**Symptoms**
Breast Imaging
Finding
Path Workup
Path Results

En bloc resection: Total capsulectomy
Explantation
Exc mass
Exc biopsy node(s)
Consider contralateral
Consider delayed or immediate recon

Disease confined to capsule (IA-IC)

Complete excision no residual disease
Incomplete excision or partial capsulectomy with residual disease

RT (24–36 Gy) local residual disease
Systemic therapy
Brentuximab vedotin
Anthracycline based systemic ALCL regimens

Observation H&P for every 3–6 mo for 2 y and then as indicated ± CT or PET/CT 6 mo for 2 y then as clinically indicated

**Abbreviations:** MRI Magnetic Resonance Imaging, FNA Fine needle aspiration, CBC Complete blood count, PET/CT Positron emission tomography–computed tomography, CMP Complete metabolic profile, LDH Lactate dehydrogenase, RT Radiation therapy
Surgery essential for cure

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<thead>
<tr>
<th>Treatment after diagnosis</th>
<th>Number</th>
<th>%</th>
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<tr>
<td>Limited surgery</td>
<td>43</td>
<td>52.9</td>
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<tr>
<td>Complete surgery</td>
<td>74</td>
<td>85.1</td>
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<tr>
<td>Radiation</td>
<td>39</td>
<td>44.8</td>
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<tr>
<td>Chemotherapy</td>
<td>51</td>
<td>58.6</td>
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<tr>
<td>ASCT</td>
<td>6</td>
<td>6.9</td>
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<tr>
<td>Immunotherapy</td>
<td>2</td>
<td>2.3</td>
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</table>

Patients can progress or up-stage if untreated

<table>
<thead>
<tr>
<th>Treatment</th>
<th>1 year (%)</th>
<th>3 years (%)</th>
<th>5 years (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>35</td>
<td>50.8</td>
<td>50.8</td>
</tr>
<tr>
<td>Limited surgery</td>
<td>60</td>
<td>89</td>
<td>89</td>
</tr>
<tr>
<td>Complete surgery</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Radiation</td>
<td>18</td>
<td>28</td>
<td>28</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>24</td>
<td>32</td>
<td>32</td>
</tr>
</tbody>
</table>

Immediate/Delayed Reconstruction BIA-ALCL

• Reconstructive options require thorough discussion to ensure shared decision-making

• Stage IA-IC: Consider immediate or delayed reconstruction based on patient desire

• Stage IIA-IV: Relative contraindication for immediate reconstruction
  • Consider delaying 6-12 months following clear PET/CT scans
BIA-ALCL originally thought to be two distinct diseases?

- Laurent 2016
- Effusion-limited (in situ) versus massively infiltrative
- Based on pathology review 19 BIA-ALCL patients to Lymphopath

Breast implant-associated anaplastic large cell lymphoma: two distinct clinicopathological variants with different outcomes

C. Laurent¹,²*, A. Delas¹, P. Gaulard³,⁴, C. Haioun⁴,⁵, A. Moreau⁶, L. Xerri⁷, A. Traverse-Glehen⁸, T. Rousset⁹, I. Quintin-Roue¹⁰, T. Petrella¹¹, J. F. Emile¹², N. Amara¹, P. Rochaix¹, M. P. Chenard-Neu¹³, A. M. Tasei¹⁴, E. Menet¹⁵, H. Chomarat¹⁶, V. Costes⁹, L. Andrac-Meyer¹⁷, J. F. Michiels¹⁸, C. Chassagne-Clement¹⁹, L. de Leval²⁰, P. Brousset¹,², G. Delsoi¹,² & L. Lamant¹,²
MDACC BIA-ALCL staging

- TNM classification
- Clinical–pathological staging system

### BIA-ALCL TNM staging

<table>
<thead>
<tr>
<th>Tumour size</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>T4</th>
</tr>
</thead>
<tbody>
<tr>
<td>T</td>
<td>Confined to effusion</td>
<td>Early capsule invasion</td>
<td>Mass aggregate, confined to capsule</td>
<td>Tumour locally invasive out of capsule</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lymph nodes</th>
<th>N0</th>
<th>N1</th>
<th>N2</th>
</tr>
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<tbody>
<tr>
<td>N</td>
<td>No lymph node involvement</td>
<td>One regional lymph node</td>
<td>Multiple regional lymph nodes</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Metastasis</th>
<th>M0</th>
<th>M1</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>No distant spread</td>
<td>Other organs/distant sites</td>
</tr>
</tbody>
</table>


# Reported Disease Staging Worldwide

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Ann Arbor</th>
<th>MDA Solid Tumor TNM Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>IE</td>
<td>IIE</td>
</tr>
<tr>
<td>Brody 2015 (n=173)</td>
<td>USA</td>
<td>89.6</td>
<td>10.4</td>
</tr>
<tr>
<td>Clemens 2016 (n=87)</td>
<td>USA</td>
<td>86.2</td>
<td>13.8</td>
</tr>
<tr>
<td>Loch-Wilkinson 2017 (n=55)</td>
<td>Australia</td>
<td>96.4</td>
<td>3.6</td>
</tr>
<tr>
<td>De Boer 2017 (n=32)</td>
<td>Netherlands</td>
<td>81.3</td>
<td>18.8</td>
</tr>
<tr>
<td>Campanale 2017 (n=22)</td>
<td>Italy</td>
<td>81.8</td>
<td>18.2</td>
</tr>
</tbody>
</table>

**Note:**
- **IE** = Invasion Extent
- **IIE** = Invasion Extent II
- **IA** = Invasion Area
- **IB** = Invasion Boundary
- **IC** = Invasion Center
- **IIA** = Invasion Interface A
- **IIB** = Invasion Interface B
- **III** = Invasion Interface III
- **IV** = Invasion Interface IV

**Legend:**
- **Effusion Only**
- **Infiltrative**
Patterns of Lymph Node Involvement

- 13-20% of BIA-ALCL Cases
- 85% Axillary, 10% Supraclav, 5% internal mammary
- Mass, LNI portend Worse Prognosis

Deaths rare, Good prognosis if treated

- **17 attributable deaths**\(^1,2\)
- No spontaneous resolution to date
- Delay in treatment or under-treatment
- **45-month mean follow up**\(^1\)
- 13 years median overall survival\(^1\)
  - 93% at 3 years
  - 89% at 5 years

### Table

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age</th>
<th>Tumour size (cm)</th>
<th>Treatments</th>
<th>Cause of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unpublished 1</td>
<td>52</td>
<td>7</td>
<td>Limited surgery, chemo, RT</td>
<td>ALCL, mediastinal mass with progressive bronchial compression</td>
</tr>
<tr>
<td>Aladily et al.(^1)</td>
<td>47</td>
<td>2.5</td>
<td>Chemo, RT</td>
<td>ALCL, mediastinal mass with progressive bronchial compression, pleural effusion, pneumonia</td>
</tr>
<tr>
<td>Carty et al.(^1)</td>
<td>57</td>
<td>‘large’</td>
<td>Limited surgery, chemo, RT</td>
<td>ALCL, chest wall invasion, pleural infiltration, respiratory failure</td>
</tr>
<tr>
<td>Miranda et al.(^1)</td>
<td>63</td>
<td>1.2</td>
<td>Limited surgery, chemo</td>
<td>DLBCL, follicular lymphoma, disseminated disease. Free of ALCL for 120 months and at death</td>
</tr>
<tr>
<td>Ivaldi et al.(^1)</td>
<td>53</td>
<td>‘Voluminou’</td>
<td>Limited surgery</td>
<td>ALCL, axillary and internal mammary lymph nodes, tracheal narrowing, pleural effusion, respiratory failure</td>
</tr>
<tr>
<td>Lechner et al.(^1)</td>
<td>43</td>
<td>NA</td>
<td>Limited surgery, chemo, RT</td>
<td>ALCL, mediastinal mass with progressive bronchial compression, pleural effusions</td>
</tr>
<tr>
<td>Unpublished.(^3)</td>
<td>52</td>
<td>NA</td>
<td>Limited surgery, chemo</td>
<td>ALCL, chest wall invasion, respiratory failure</td>
</tr>
<tr>
<td>Unpublished.(^3)</td>
<td>42</td>
<td>8</td>
<td>Complete surgery, chemo, SCT</td>
<td>Sepsis, multiorgan dysfunction during SCT</td>
</tr>
<tr>
<td>Unpublished.(^3)</td>
<td>56</td>
<td>6</td>
<td>Limited surgery, chemo</td>
<td>ALCL, axillary lymph nodes, tracheal narrowing, mediastinal mass, respiratory failure</td>
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<td>X</td>
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<td>Limited surgery, chemo, SCT</td>
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<td>X</td>
<td>Limited surgery, chemo</td>
<td>Mediastinal invasion</td>
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<tr>
<td>Unpublished – TGA(^3)</td>
<td>X</td>
<td>X</td>
<td>Limited surgery, chemo</td>
<td>Mediastinal invasion</td>
</tr>
</tbody>
</table>

CD30-targeted therapy

- Adjunct chemotherapy: anthracycline based
- 100% CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone
- 8% ICE: ifosfamide, carboplatin, etoposide
- 4% CVAD: cyclophosphamide, vincristine, doxorubicin, dexamethasone
- BIA-ALCL: 32% recurrence rate at 3 years
- Salvage radiation therapy for unresectable disease

- Anti-CD30-targeted therapy
  - Brentuximab vedotin for refractory sALCL: objective response rate – 86%

References:
Case study: Brentuximab

- 47-year-old female
- 2009: augmentation mammaplasty, SL implants

- 2015: implant contracture, lymphadenopathy, chest wall mass
- June 2015: implant exchange
  - Dx BIA-ALCL
- July 2015: total capsulectomy
- Six rounds of CHOEP
- Two rounds of GDP
- Four rounds of brentuximab vedotin
- Complete remission BIA-ALCL
Prosthesis-associated?

- Tibial Implant
- Dental implant ALCL\(^2\)
- Chest port ALCL\(^3\)
- Shoulder repair ALCL
- Lap Band ALCL
- Gluteal Implants x 2

Bariatric Implant–Associated Anaplastic Large-Cell Lymphoma

Multidisciplinary Messaging

- Pathology
- Oncology
- Surgical Oncology
- Radiology
- Plastic Surgery
Conclusions

- BIA-ALCL is a lymphoma based on pathology and clinical course
- NCCN guidelines are the standard for the diagnosis and management of BIA-ALCL
- Continues to be an emerging disease, therefore awareness and reporting are critical

Thank you

Mark Clemens, MD  mwclemens@mdanderson.org  @clemensmd
Wei Yang, MD  Breast Diagnostic Radiology
Roberto Miranda, MD  Hematopathology
Kelly Hunt, MD  Breast Surgical Oncology
Swaminathan Iyer, MD  Lymphoma Oncology
Mark Clemens, MD  Plastic Surgery
Gregg Staerkel, MD  Cytopathology

mwclemsens@mdanderson.org  @clemsmd
BIA-ALCL: monitoring incidence and finding answers; The power of registry data and (inter) national collaboration

Mintsje De Boer, Babette Becherer, Pauline Spronk, Marc Mureau, Juliette Hommes, Xavier Keuter, Manuel Harmsen, Annette Gijsbers, Jean Paul de Boer, Michael Hauptmann, Lucy Overbeek, Marc Lobbes, Nathalie Hijnmering, Arthur Sernee, Bauke Ylstra, Phylicia Stathi, Margaretha Roemer, Erik van Dijk, Rene van der Hulst, Floor van Leeuwen, Daphne de Jong

All pathologists in the Netherlands
All plastic surgeons in the Netherlands
BIA-ALCL: monitoring incidence and finding answers; The power of registry data and (inter) national collaboration

Hinne Rakhorst, believer in (inter)national collaboration to improve patient care

Thanks to;
All pathologists in the Netherlands
All plastic surgeons in the Netherlands
Thank you
Disclosures

None other than voluntary board work
No disclosures,
especially not to breast implant industry
1:30 adult Dutch women has one or two
3.3%

Approximately the same as hip athroplasties
Breast implants are safe implants, class III
70% vs 30%

Esthetic vs Reconstructive
Many types from few variables

Texture; Smooth vs macrotextured vs microtexture vs nanotexture
Shape; Round vs Anatomical
Fill; Saline fill vs silicone vs methylcelullose vs air
Coating; Silicone vs polyurethane coating
Duration; Temporary (tissue expander) vs Permanent

Large international variation in preferred types
Texture;

• Smooth
• Macrotextured
• Microtexture
• Nanotexture
• ‘We have another, different one’.
Breast implants have adverse events
Breast implants often need revision surgery

AESTHETIC

- Primair (n=12,513)
- Gemiddelde leeftijd: 49,7
- Revisie (n=768)
- Gemiddelde leeftijd: 52,6

RECONSTRUCTIVE

- Primair (n=4,934)
- Gemiddelde leeftijd: 49,7
- Revisie (n=824)
- Gemiddelde leeftijd: 52,6

*Replacement of TE for implant is excluded
Breast implants have serious adverse events
A Shocking Diagnosis: Breast Implants ‘Gave Me Cancer’
Breast implants and Anaplastic Large Cell Lymphoma

Scientific Committee on Health Environmental and Emerging Risks
SCHEER

Scientific Advice on
The state of scientific knowledge regarding a possible connection between breast implants and anaplastic large cell lymphoma

The SCHEER adopted this advice by written procedure on 5 April 2017

Breast implants

Update - additional confirmed cases of anaplastic large cell lymphoma

Hi May 2017
Consumers and health professionals are advised that since the statement below was published, the TGA has confirmed more cases of anaplastic large cell lymphoma (ALCL) in Australian patients, with a total of 33 cases reported to date.

The US Food and Drug Administration also published an update regarding this issue on 23 March 2017.

The Plastic and Reconstructive Surgery Journal has recently accepted for publication an epidemiological study of patients in Australia and New Zealand and this should appear in an upcoming edition.

Expert advisory panel advice on association with anaplastic large cell lymphoma

Related information

- Information for women with breast implants
- Information for men and women who have had breast implants
- Information for health professionals
- Medical Devices
- Breast Implants
- FDA Medical Devices Regulation
- Breast Implant Surveillance
- Breast Implant Cancer
- Breast Implant-Related Anaplastic Large Cell Lymphoma

Medical Devices

Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL)

In 2011, the FDA identified a possible association between breast implants and the development of anaplastic large cell lymphoma (ALCL), a rare type of non Hodgkin's lymphoma.

At that time, the FDA knew of 15 cases of this disease that it was not possible to determine what factors increased the risk. In a report summarizing the Agency's findings, we emphasize the need to gather additional information to better characterize ALCL in women with breast implants.

Our breast implant device database contains data on 51.6 million breast implants. The most common complications are capsular contracture, implant rupture, or deflation. Since 2011, we have strengthened our understanding of the condition and will continue to monitor the World Health Organization's designation of breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) as a rare T-cell lymphoma that can develop following breast implants. The exact number of cases remains difficult to determine due to significant limitations in medical reporting and lack of global implant sales data. At this time, most data suggest that BIA-ALCL occurs more frequently following implantation of breast implants with textured surfaces rather than those with smooth surfaces.

We continue to collect and evaluate information about ALCL in women with breast implants. On an ongoing basis, we:

- Review and analyze scientific literature and studies.
Breast implants have serious adverse events

so what can do we tell
patients/ clients/ citizens / salespersons
We only know the problem
We need to find the solution;

Prevent
Identify; implant / patient / surgical factors
What is the risk?
Risk;\[\frac{\text{Numerator}}{\text{Denominator}}\]
Number of cases

Total number of women that have implants
Challenge

Rough estimate number of cases

Rough estimate number of women that have implants
Challenge

Rough estimate number of cases

Rough estimate number of women with types of implants
Solution; know about; numbers AND types
But what if something happens extremely rarely
Need to register data
Need Big data
Dutch Breast Implant Registry
Start 2015

National
All patients
All procedures
Opt out for surgeons, hospitals and patients
Dataset

- Originated from Australia
- Hospital/surgeon
- Patient
- Device
- Surgery
- complication
## Data

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<thead>
<tr>
<th>Patient;</th>
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<tbody>
<tr>
<td>name</td>
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<tr>
<td>Age</td>
</tr>
<tr>
<td>History?</td>
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<tr>
<td>other diseases</td>
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<table>
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<td>New or exchange</td>
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<tr>
<td>Complications;</td>
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<tr>
<td>BIA-ALCL</td>
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<table>
<thead>
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<th>Implant</th>
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<tbody>
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<td>Shape</td>
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<td>Texture</td>
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<td>Fill</td>
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### Adverse and serious adverse events

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<td>Yes</td>
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<td>Yes</td>
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<table>
<thead>
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<tr>
<td>Intra capsular</td>
<td></td>
</tr>
<tr>
<td>Extra capsular</td>
<td></td>
</tr>
<tr>
<td>Distant</td>
<td></td>
</tr>
</tbody>
</table>
DUTCH BREAST IMPLANT REGISTRY (DBIR)
ANNUAL REPORT 2015 – 2017

DBIR
DUTCH BREAST IMPLANT REGISTRY
Is this registry valid?

• Independent
• Funded without industry
• Payed by clients and health insurance

• Board without disclosures
• Young registry
• growing
Registrations


Total number of
- Patients ± 18,000
- Operations ± 20,000
- Implants ± 38,000
Completeness DBIR; centers

Figure 1. Coverage of DBIR in the Netherlands (2016)

- Hospitals: 95% (n=73)
- Private clinics: 78% (n=28)
- TOTAL: 89% (n=101)

*IGJ: Dutch Health and Youth Care Inspectorate.*
Figure 2. Data completeness (2015 - 2017)

- Patient characteristics
- Surgery characteristics
- Surgery techniques
- Antiseptic precautions
- Indication for revision
- Device characteristics (inserted)
- Device characteristics (explanted)

Completeness (with minimum and maximum range)
Figure 8. Indications for replacement or explantation after reconstructive surgery, per breast (2015 – 2017)

A. Surgery-related

- Indication for surgery
- Found incidentally

B. Patient-related

- Capsule contracture
- Newly diagnosed breast cancer
- BRAF-V600E
- ASIA syndrome
- Breast pain
- Asymmetry
- Disconnected with volume

C. Device-related

- Device rupture
- Device deflation
- Device malposition
- Silicone extravasation
So is it effective for detection?

Return on investment
• National pathology report database
• All path labs are connected
• Collecting almost all reports nationally
• Survey this registry for ALCL and Breast
Breast Implants and the Risk of Anaplastic Large-Cell Lymphoma in the Breast

Mintsje de Boer, MD; Flora E. van Leeuwen, PhD; Michael Hauptmann, PhD; Lucy I. H. Overbeek, PhD; Jan Paul de Boer, MD, PhD; Nathalie J. Hijmering, MSc; Arthur Sernee, MSc; Caroline A. H. Klazen, MD, PhD; Marc B. I. Lobbes, MD, PhD; René R. W. J. van der Hulst, MD, PhD; Hinne A. Rakhorst, MD, PhD; Daphne de Jong, MD, PhD
1 = 1?
$1 + 1 = 3?$
## BIA-ALCL; completeness

<table>
<thead>
<tr>
<th>Indication for revision (Breast level)</th>
<th>Complete (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2015</td>
</tr>
<tr>
<td>Total number of records n = 12,016</td>
<td>n = 17,956</td>
</tr>
<tr>
<td>Change TE for implant</td>
<td>83%</td>
</tr>
<tr>
<td>Flap problem</td>
<td>3%</td>
</tr>
<tr>
<td>Skin necrosis</td>
<td>84%</td>
</tr>
<tr>
<td>Skin scarring</td>
<td>84%</td>
</tr>
<tr>
<td>Deep wound infection</td>
<td>84%</td>
</tr>
<tr>
<td>Seroma/Hematoma</td>
<td>83%</td>
</tr>
<tr>
<td>Capsular contracture</td>
<td>93%</td>
</tr>
<tr>
<td>Capsular contracture grade</td>
<td>77%</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>82%</td>
</tr>
<tr>
<td><strong>BIA-ALCL</strong></td>
<td>79%</td>
</tr>
<tr>
<td>ASIA</td>
<td>78%</td>
</tr>
<tr>
<td>Breast pain</td>
<td>81%</td>
</tr>
<tr>
<td>Asymmetry</td>
<td>80%</td>
</tr>
<tr>
<td>Dissatisfaction with volume</td>
<td>2%</td>
</tr>
<tr>
<td>Device rupture/deflation</td>
<td>86%</td>
</tr>
<tr>
<td>Silicone extravasation</td>
<td></td>
</tr>
<tr>
<td>Silicone extravasation type</td>
<td>82%</td>
</tr>
<tr>
<td>Device malposition</td>
<td>84%</td>
</tr>
</tbody>
</table>
### Table 10. Device characteristics in aesthetic procedures, per device (2015 – 2017)

<table>
<thead>
<tr>
<th></th>
<th>INSERTED</th>
<th>EXPLANTED</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total number of records</strong></td>
<td>n = 5,791</td>
<td>n = 9,005</td>
</tr>
<tr>
<td>Permanent implant</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Tissue expander</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Device shape</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Round</td>
<td>66%</td>
<td>68%</td>
</tr>
<tr>
<td>Shaped/Anatomical</td>
<td>32%</td>
<td>30%</td>
</tr>
<tr>
<td>Not stated</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td><strong>Device texture</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Textured</td>
<td>96%</td>
<td>97%</td>
</tr>
<tr>
<td>Smooth</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Not stated</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td><strong>Device coating</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Silicone</td>
<td>97%</td>
<td>97%</td>
</tr>
<tr>
<td>Polyurethane</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Not stated</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td><strong>Device fill</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Silicone</td>
<td>98%</td>
<td>97%</td>
</tr>
<tr>
<td>Saline</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Hydrogel</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Air</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Other</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Not stated</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td><strong>Device volume</strong></td>
<td>Median volume in cc (IQR)</td>
<td></td>
</tr>
<tr>
<td>Permanent implant</td>
<td>350</td>
<td>(300-405)</td>
</tr>
<tr>
<td>Tissue expander</td>
<td>439</td>
<td>(400-690)</td>
</tr>
<tr>
<td>Fill of tissue expander perop</td>
<td>Not stated</td>
<td>Not stated</td>
</tr>
</tbody>
</table>

* Characteristics of explanted devices have been registered since September 2013 (n= 701 in 2017).
* IQR: interquartile range. Perop: per-operatively.
Picking up the cases
*In these patients, BIA-ALCL was not histo- or cytologically proven in PALGA and therefore considered to be reported false positive in DBIR.
International professionals all want the same data
<table>
<thead>
<tr>
<th>Case</th>
<th>Patient*</th>
<th>Surgery</th>
<th>Breast Implant (explanted)*</th>
<th>Pathological Report</th>
</tr>
</thead>
</table>
International Collaboration of Breast Registry Activities

20 countries
• Standardize to compare
  • Dataset
  • Datadefinitions
  • Quality indicators

2019;
- Standize outcome figures
- Pool data
- Privacy laws
- Reason for revision/explantation
  - BIA-ALCL
  - Device rupture
  - Device malposition/rotation
  - Breast pain
  - Postoperative antibiotics
  - Preoperative antibiotics
  - Laterality
  - Indication for surgery – to include subpoints
  - Type of intervention (primary, revision, explant only)
  - Implant position/plane
  - Incision site – to include subpoints
  - Nipple sparing
  - Flap cover

- Fat grafting
- Capsulectomy – to include subpoints
- Rinse of the pocket – to include subpoints
- Drain use
- Glove change before insertion
- Previous radiotherapy
- Date of birth/Age of patient
- Height
- Weight
- Device details – to include subpoints
- Texture
- Fill
- Shape
- Volume of implant
- ADM/Mesh used – to include subpoints
- Date of insertion of removed implants
- Device details of explanted device – incl subpoints
- Marker/Medical record of explanted device if known
Joining registries have a potential for 1,000,000 implants/yr
MINIMUM DATA SET; implant

- UDI; serial number/Lot
- Producer
- Texture
- Fill
- Shape
- Volume of implant
Conclusion

• Registries work
• Shed better, independent, light on real world
• facilitate innovation
• Facilitate finding answers
• International collaboration and pooling is pivotal
Challenges/future

• Funding
• Define texture types
• UDI development

• Privacy laws;
  • uniform internationally
  • international pooling strategy development
  • Use of social security number/BSN/personal number
  • Sharing data between national registries
DUTCH BREAST IMPLANT REGISTRY (DBIR) ANNUAL REPORT 2015 – 2017

DBIR
DUTCH BREAST IMPLANT REGISTRY

Be in touch;
Rakhorst@gmail.com
Breast implant ALCL: Pathologic Diagnosis, Progression of Disease and Pathogenic Mechanisms

Roberto N. Miranda, M.D.
Professor
Department of Hematopathology
MD Anderson Cancer Center
Conflict of Interest:
Scientific Advisory Board Allergan, Inc
(Honorarium for Conference Time)
Outline

• What is ALCL and how is classified?
• Pathologic Diagnosis, Staging and Prognosis
• Brief: Etiologic factors and mechanisms
• Analysis of causality between breast implants and ALCL
ALCL

- T-cell lymphoma
  - CD3, CD4, cytotoxic markers
  - CD30
- Cells are large and anaplastic
- Monoclonal T-cell receptor (TCR) gene rearrangement
- Aberrant karyotype
- Activation of Carcinogenic Pathways
The Spectrum of ALCL

1) **Systemic:** Aggressive; requires chemotherapy, immunotherapy, SCT
   - **ALK+:** ALK rearranged 2p23/ALK: Better
   - **ALK-:** TP63, DUSP22

2) **Localized**
   - Primary Cutaneous ALCL: Indolent
   - Breast implant ALCL
Clinical Presentation
Effusion (CT Scan)

Adrada et al. Breast Cancer Res Treat, 2014; 147: 1
Mass (PET Scan)

Sergio Pina Oviedo, MD (U Arkansas HSC)
Lymphoma Cells Lining Luminal Surface
T1: Early Pathologic Stage
Lymphoma Cells Lining Luminal Surface
Massive necrosis on top

CD30
T2: Lymphoma Cells with Minimal Infiltration
T2: Lymphoma Cells with Minimal Infiltration
Advanced Pathologic Stage T4: Mass Beyond Capsule
T4: Advanced Pathologic Stage

Luminal Side

Capsule

Tumor Infiltration

CD30

T4: Advanced Pathologic Stage
Patients who present with a mass have worse OS and PFS than patients without a mass.
Is Chemotherapy Required to Treat Breast Implant ALCL?
The Effect of Chemotherapy

A subset of patients are cured with surgery alone (removal of the implant and capsulectomy) Do not appear to require chemotherapy or radiation

Miranda et al. J Clin Oncol 2014; 32: 114
Lymph Node Involvement in Breast implant ALCL

OS: Breast Implant ALCL with Lymph Node Involvement

Hypothesis of Tumor Progression

Does Pathologic Stage Predict Outcomes?
Outcomes by Pathologic Stage (n= 87)

<table>
<thead>
<tr>
<th>Stage</th>
<th>n</th>
<th>Event (n)</th>
<th>Event (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>37</td>
<td>10</td>
<td>27%</td>
</tr>
<tr>
<td>T2</td>
<td>12</td>
<td>10</td>
<td>83%</td>
</tr>
<tr>
<td>T3</td>
<td>7</td>
<td>4</td>
<td>57%</td>
</tr>
<tr>
<td>T4</td>
<td>30</td>
<td>21</td>
<td>70%</td>
</tr>
</tbody>
</table>

$P = .022$
Events After Various Interventions (n= 87)

<table>
<thead>
<tr>
<th>Intervention</th>
<th>n</th>
<th>Event</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>FNA</td>
<td>36</td>
<td>25</td>
<td>69%</td>
</tr>
<tr>
<td>Limited Surgery</td>
<td>46</td>
<td>39</td>
<td>85%</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>39</td>
<td>10</td>
<td>26%</td>
</tr>
<tr>
<td>Radiation</td>
<td>51</td>
<td>15</td>
<td>29%</td>
</tr>
<tr>
<td>Complete Surgery</td>
<td>74</td>
<td>4</td>
<td>5%</td>
</tr>
</tbody>
</table>

P < .0001

Breast Implant ALCL Staging

- TNM Classification
- Pathology staging system

<table>
<thead>
<tr>
<th></th>
<th>Tumor Size T</th>
<th>Lymph Nodes N</th>
<th>Metastasis M</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MDACC ALCL Staging</strong></td>
<td>T1 Confined to Effusion</td>
<td>NO No lymph node involvement</td>
<td>MO No distant spread</td>
</tr>
<tr>
<td>T2 Early capsule invasion</td>
<td>N1 One regional lymph node</td>
<td>M1 Other organs/ distant sites</td>
<td></td>
</tr>
<tr>
<td>T3 Mass aggregate, confined to capsule</td>
<td>N2 Multiple regional lymph nodes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4 Tumor locally invasive out of capsule</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Stage Ia: T1N0M0
- Stage Ib: T2N0M0
- Stage Ic: T3N0M0
- Stage IIa: T4N0M0
- Stage IIb: T1-3N1M0
- Stage III: TanyN2M0, T4N1M0
- Stage IV: TanyNanyM1

Etiology and Pathogenesis
Not Involved Implant Surrounded by Capsule

Interior of Implant and Attached Capsule
What Events Lead to the Transformation From a Reactive Capsule to a Capsule with Lymphoma?
Etiology and Pathogenesis

1. What is the possible etiology?
   a) Texturing of surface of implants
   b) Bacteria: Biofilm

2. What are the risk factors?
   a) Breast cancer susceptibility: \textit{BRCA1}
   b) Cancer susceptibility: \textit{TP53}
Surface of the Implants

Smooth

Textured
SEM of Textured Implant

Allergan

Mentor
Etiology Theories

• Biofilm
  • “Infectious Hypothesis”
  • Ralstonia sp

• Chronic T-Cell induced immune response
  • To silicone
  • To bacteria

• Mechanisms
  • Direct immunologic response
  • Indirect cytokine mediated damage
  • Toxic damage by silicone products
An Analysis of Causality

Is there a Cause - Effect Relationship Between Breast Implants and ALCL?
The 4 Koch Postulates: Microorganism as Cause of Disease

R Koch and Causality

The microorganism must be found in all cases of the disease.

It must be isolated from the host and grown in pure culture.

It must reproduce the original disease when injected into a susceptible host.

It must be found in the experimental host so infected.
The Bradford Hill Criteria of Causality

A Bradford-Hill and Causality. I

BRITISH MEDICAL JOURNAL
LONDON SATURDAY SEPTEMBER 30 1950

SMOKING AND CARCINOMA OF THE LUNG
PRELIMINARY REPORT

BY

RICHARD DOLL, M.D., M.R.C.P.
Member of the Statistical Research Unit of the Medical Research Council

AND

A. BRADFORD HILL, PH.D., D.Sc.
Professor of Medical Statistics, London School of Hygiene and Tropical Medicine; Honorary Director of the Statistical Research Unit of the Medical Research Council

... I have no wish, nor the skill to embark upon a philosophical discussion of the meaning of 'causation'

The Bradford Hill Criteria

- 1965: Support to assess evidence of causation
- Used as a checklist to assess causality

1. Strength:
2. Consistency: Different observers, different places
3. Specificity: Very specific population, site, disease:
   The more specific the association, the bigger the probability of causality
4. Temporality: Sequence of events
5. Biological Gradient: Higher stage of disease is worst
6. Plausibility: Mechanisms
7. Coherence: Clinical and experimental
8. Experiment: Supports plausibility
9. Analogy: Other diseases similar
Roberto, can you help Sameer with his project?
Breast Lymphomas

• Patients without breast implants
  – B-cell NHL: 90%
  – Other T-cell NHL: 10%
  – ALCL: 2%

• Patients with breast implants
  – ALCL: 90%
  – Other NHL: 10%
## Bradford Hill Criterion of Specificity

<table>
<thead>
<tr>
<th></th>
<th>B-Cell</th>
<th>T-Cell</th>
<th>ALK- ALCL Breast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast Lymphoma (n= 106)</td>
<td>93%</td>
<td>7%</td>
<td>3%</td>
</tr>
<tr>
<td>Breast Lymphoma with Implants (n= 40)</td>
<td>10%</td>
<td>90%</td>
<td>80%</td>
</tr>
<tr>
<td>Systemic ALCL (n= 72)</td>
<td>NA</td>
<td>100%</td>
<td>1.5%</td>
</tr>
</tbody>
</table>

**Lazzeri et al; Clin Breast Cancer 2011; 11: 283**
Bradford Hill Criterion of Specificity

- **Very specific population:** Women with breast implants
- **Site:** Breast
- **Histologic feature:** ALK(-) ALCL
- “The more specific the association, the bigger the probability of causality”
## The Bradford Hill Criteria of Causality

<table>
<thead>
<tr>
<th>#</th>
<th>Criterion</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Strength</td>
<td>Pathologic evidence</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Consistency</td>
<td>&gt; 500 cases worldwide</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Specificity</td>
<td>Rare ALCL in breast without implants</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Temporality</td>
<td>Median, 9 years after implantation</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Biologic gradient</td>
<td>Recurrence, progression</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Plausibility</td>
<td>Go together, textured implants</td>
<td>Rare cases (1) without implant</td>
</tr>
<tr>
<td>7</td>
<td>Coherence</td>
<td>Surgical intervention and removal of implants usually lead to cure</td>
<td>Chemotherapy, Radiation therapy</td>
</tr>
<tr>
<td>8</td>
<td>Experimental evidence</td>
<td>Not yet available</td>
<td>No related research</td>
</tr>
<tr>
<td>9</td>
<td>Analogy</td>
<td>Chronic inflammation and myxoma, DLBCL</td>
<td>Scant evidence</td>
</tr>
</tbody>
</table>
Evidence that Breast Implant ALCL is Underdiagnosed
Evidence that Breast Implant ALCL is Underdiagnosed

– CAP: No policies for microscopic processing
– Adrada et al (n= 48)
  • Imaging: Suboptimal sensitivity
– Clemens: (n= 87)
  • Delayed diagnosis in 30% (1 – 3 y)
– Aladily et al (n= 48)
  • 40% of effusions not analyzed
– Liu et al (in progress): Disease is focal, multifocal and evidence of sampling error
Breast implant-associated anaplastic large cell lymphoma: sensitivity, specificity, and findings of imaging studies in 44 patients

Beatriz E. Adrada · Roberto N. Miranda · Gaiane Margishvili Rauch · Elsa Arribas · Rashmi Kanagal-Shamanna · Mark W. Clemens · Michelle Fanale · Nisreen Haideri · Eid Mustafa · John Larrinaga · Neal R. Reisman · Jesse Jaso · M. James You · Ken H. Young · L. Jeffrey Medeiros · Wei Yang
Mammography

- Sensitivity for effusion: 31%
- Sensitivity for mass: 17%

Ultrasound

- Sensitivity for effusion: 89%
- Sensitivity for mass: 50%

BI ALCL is Underdiagnosed by Pathologists

- ALCL looks like carcinoma
  - Triple negative breast cancer
- ALCL looks like Hodgkin lymphoma
  - Particularly with presentation in LN
- ALCL looks like inflammatory process
  - Abundant necrosis
- Tumor is not grossly identifiable in most cases
- Belief implants do not cause harm/cancer
  - h/o implant not included in clinical notes
What Are The Two Tails of Breast Implant ALCL?

- What is the earliest evidence of disease?
- What is the aggressive end?
Conclusions - I

• Breast Implant ALCL is a distinct disease clinically, pathologically and pathogenetically

• The implants or its components and concurrent infection, inflammation may play a pathogenic role
Conclusions - II

- There is supportive evidence of causality between breast implants and ALCL.

- There is evidence that the disease is still under-recognized by health care professionals.
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