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Anaplastic Large Cell Lymphoma and Breast Implants: Results From a Structured Expert Consultation Process

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Abstract:

Background: There are increasing concerns about a possible association between anaplastic large cell lymphoma (ALCL) and breast implants. We conducted a structured expert consultation process to evaluate the evidence for the association, its clinical significance, and a potential biological model based on their interpretation of the published evidence.

Methods: A multidisciplinary panel of 10 experts was selected based on nominations from national specialty societies, academic department heads, and recognized researchers in the U.S.

Results: Panelists agreed that (1) there is a positive association between breast implants and ALCL development but likely under-recognition of the true number of cases; (2) a recurrent, clinically evident seroma occurring ≥ 6 months after breast implantation should be aspirated and sent for cytologic analysis; (3) anaplastic lymphoma kinase (ALK)-negative ALCL that develops around breast implants is a clinically indolent disease with a favorable prognosis that is distinct from systemic ALK-negative ALCL; (4) management should consist of removal of the involved implant and capsule, which is likely to prevent recurrence, and evaluation for other sites of disease; and (5) adjuvant radiation or chemotherapy should not be offered to women with capsule-confined disease. Little agreement, however, was found regarding etiologic risk factors for implant-associated ALCL.

Conclusions: Our assessment yielded consistent results on a number of key issues regarding ALCL in women with breast implants, but substantial further research is needed to improve our understanding of the epidemiology, clinical aspects, and biology of this disease.

Introduction:

Since Duvic et al. published a case series in 1995 of 3 women with breast implants who developed cutaneous T-cell lymphoma,[1] there have been growing concerns that implants are associated with the development of primary non-Hodgkin's lymphoma (NHL) of the breast, most notably an uncommon NHL subtype called anaplastic large cell lymphoma (ALCL). Based on these concerns, the Food and Drug Administration (FDA) has recently issued an alert on January 26th, 2011.[2] Brody et al. have presented but not yet published a series of 34 ALCL cases occurring in women with implants.[3] ALCL is a rare disease, comprising only 2% of all newly-diagnosed NHLs worldwide.[4] Because lymphomas occurring in the breast are even rarer, comprising only 0.04-0.5% of all breast cancers and approximately 1-2% of all extranodal lymphomas,[5-7] multiple reports of ALCL occurring in the breast in women with implants have piqued the attention of plastic surgeons, implant manufacturers, regulatory agencies, and the public.

We recently published a systematic literature review summarizing 29 cases of ALCL involving the breast in women with implants.[8] However, because much of the information in the literature is incomplete and does not address important epidemiologic, clinical, and biologic topics related to ALCL and breast implants, we conducted a structured expert consultation process that combined published evidence with expert assessment to obtain guidance on the following three questions:

1. Is a causative relationship between breast implants and ALCL sufficiently established?
2. What is the clinical behavior of implant-associated ALCL, and how should the disease be managed?
3. What is the current understanding of the biological pathways though which breast implants could lead to developing ALCL?

We also asked the experts for guidance on a research agenda to shed further light on these questions.

Methods:

The expert consultation process is based on the RAND/UCLA Appropriateness Method, which provides a structured and quantifiable way to combine findings from a review of the evidence with input from a multidisciplinary expert panel.[9] It has been demonstrated that guidelines developed using this method are reproducible,[10] are consistent clinically,[11] and are correlated with clinical outcomes.[12] Surgical applications using this method have included organ transplantation[13-15] and carotid endarterectomy.[16] Oncologic applications have included breast cancer,[17] melanoma,[18] colorectal cancer,[19] and hematologic malignancies,[20-22] including lymphoma.[23]

Literature Review & Item Development

We conducted a literature search focused on breast implants and ALCL, which has been previously described.[8] After the data from the literature were abstracted by 2 clinician reviewers trained in health services research (B.K. and C.R.), several authors reviewed the tables (B.K., C.R., V.L.Y., K.C.C., and S.M.) to identify recurring themes and potential gaps in the evidence. Findings from the systematic literature review and input from expert plastic surgeons (V.L.Y. and K.C.C.) were then used to develop 65 statements relating to ALCL and breast implants. The topics addressed by these statements included the epidemiology, clinical presentation and treatment, and biologic mechanism of ALCL diagnosed in patients with breast implants.

Expert Panel Recruitment & Rating Process

We identified a pool of potential panelists with either content or methodology expertise based on nominations from national specialty societies (Table 1), heads of academic departments, and recognized researchers in the United States. The curricula vitae of all nominees were reviewed by 2 research team members (B.K. and S.M.) prior to inviting the experts to participate in this study. Overall, ten panel members were selected to represent a range of relevant academic and clinical specialties (1 medical oncologist, 3 hematopathologists, 2 immunologists, 1 biomaterials expert/pathologist, and 3 cancer epidemiologists) from leading universities across the United States. Each panelist received a draft of the literature review and a document outlining a potential biologic model of implant-associated ALCL. Panelists were instructed to rate each of the 65 statements on a scale from 1 to 9 according to their level of agreement. Low scores (1–3) represented disagreement with the statement, middle scores (4–6) represented uncertainty about the statement, and high scores (7–9) represented agreement with the statement. If the item was outside the panelist's area of expertise, the panelist was allowed to indicate this and not provide a numeric rating.

The first round of ratings was completed prior to the panel meeting. The initial ratings were tabulated, summarized, and presented to the entire expert panel at a subsequent two-day, face-to-face meeting in October 2010. At this meeting, panel members were able to review aggregated ratings, discuss their interpretation of the evidence, and share reasons for their level of agreement or disagreement with each statement. Representatives from plastic surgery specialty societies, implant manufacturers, and regulatory agencies from the United States and Canada were also present to observe the proceedings and provide input. Based on the discussion during the meeting, some statements were revised to improve clarity and incorporate important clinical and biologic nuances before the panelists were asked to conduct a second and final round of ratings. Of note, this modified Delphi method does not strive to achieve consensus but typically leads to a convergence in panelists' ratings after the discussion.

Data Analysis

RAND investigators compiled the final ratings and analyzed panelists' disagreement, uncertainty, or agreement with each item. Results were then summarized and aggregated in tabular form, indicating the number and distribution of the panelists' final ratings, as well as the median and dispersion for each item, which is a statistical measure of the ratings' spread. Median ratings ≥ 7.0 and ≤ 3.0 were interpreted as indicating agreement and disagreement, respectively, with a statement, as long as the average absolute distance from the mean (dispersion) was ≤ 1.00. Ratings between 3.0 and 7.0 as well as those with a dispersion > 1.00 were considered indicative of uncertainty about a statement.

The study was reviewed and considered exempt by the Human Subjects Protection Committee/Institutional Review Board at RAND.

Results:

The 65 final rating results are reported in Table 2. Overall, panelists disagreed with 4 out of the 65 statements (large, bold, red numbers with dispersion ≤ 1.00 in large, bold, black numbers; 6.2%), were uncertain with 44 statements (large, bold, blue numbers or dispersion > 1.00 in small black numbers; 67.7%), and agreed with 17 statements (large, bold, green numbers with dispersion ≤ 1.00 in large, bold, black numbers; 26.2%). Among the 44 items rated "uncertain" were all 10 statements related to behavioral, surgical, and implant-related risk factors for developing ALCL (22.7%). In terms of the variability of panelists' ratings, it ranged from 0.44 to 2.56. There was high concordance—defined as a statement having a dispersion of 1.00 or less—for 22 out of the 65 items (large, bold, black numbers; 33.8%), moderate concordance—dispersion between 1.01 and 1.99—for 38 items (small, black numbers; 58.5%), and low concordance—dispersion of 2.00 or greater—for 5 items (small, italicized, black numbers; 7.7%).

Epidemiology

Panelists believed in a positive association between breast implants and developing ALCL (rating: 8, dispersion: 1.00) but were uncertain about whether it has been proven that implants are causal (6, 2.56). However, they firmly disagreed with the statement that the incidence of NHLs as a whole was higher in women with implants than in those without implants (1, 1.00). When ALCL is diagnosed in a woman who has received a breast implant, the panelists were inclined to view that such cases should be attributed to the implant. In addition, they disagreed, albeit with high dispersion, with statements that affected women would have developed ALCL in the breast even in the absence of having implants (2, 1.33) or if they had undergone a different, non-implant breast surgery, such as transverse rectus abdominus muscle (TRAM) flap reconstruction (2.5, 1.75). In other words, the panelists believed that the breast implant was a necessary factor in cases of ALCL that developed in the seroma fluid surrounding the implant and/or in the breast implant capsule.

Panelists were uncertain about whether certain HLA-DR subtypes (7, 1.67) or other genetic factors (6, 1.11) predisposed women to developing ALCL after receiving breast implants. Substantial uncertainty existed regarding modifiable risk factors, as no agreement was found whether obesity (4, 1.67), smoking (5, 1.67), more involved surgeries (5, 1.56), repeated procedures (5, 1.56), damaged implants (5, 1.33), or subglandular versus submuscular placement (5, 1.78) would increase risk. Similarly, panelists expressed uncertainty regarding implant-related risk factors for ALCL development, such as a silicone- versus polyurethane-coated shell (6, 1.00), silicone gel- versus saline-filled implants (5, 1.33), larger- versus smaller-volume implants (5, 1.89), or textured versus smooth shell implants (6, 1.89).

In terms of timing of developing ALCL after breast implant placement, many panelists believed ALCL does not develop early after implantation (8, 1.22) but were uncertain as to when it usually manifests (4, 2.00). Overall, the panelists gave the opinion, but with substantial dispersion, that cases of ALCL occurring around breast implants are most likely under-identified

and underreported (8, 0.67). This is, in part, due to ALCL's recent classification as a distinct disease in 1994 (7, 1.11) and the fact that, historically, fluid aspirated from some women with unexplained or recurrent seromas was not sent for cytologic examination but instead discarded.

Clinical Issues

The panelists opined that patients who develop a seroma around a breast implant should undergo thorough diagnostic evaluation. Aspiration and cytologic examination of a seroma around the breast implant occurring 6 or more months after implantation should be performed at both the first occurrence (8, 1.89 for aspiration and 8, 1.44 for cytologic evaluation) and especially in recurrent cases (9, 0.56 for aspiration and 9, 0.44 for cytologic evaluation). Once a diagnosis of implant-related ALCL is made, the panelists felt strongly that all affected patients should undergo a full evaluation to rule out systemic disease (9, 0.56). There was agreement that the implant and capsule of the affected breast should always be removed (8, 1.11), but the panelists were uncertain regarding the management of the contralateral breast, specifically, whether the implant and capsule (5, 2.22), only the implant (4, 1.89), or neither (5, 2.44) should be removed as standard practice. They were also uncertain about the risks of disease progression with immediate re-implantation of another implant at the time of implant and capsule removal (5, 1.56).

In terms of management of the patient after removal of the capsule and the implant, the panelists did not believe that patients with localized disease required adjuvant radiation (2.5, 1.0) or chemotherapy (1.5, 0.75). This is due, in part, to the notion that implant-associated ALCL is unlikely to recur following removal of the affected implant and capsule (8, 1.39). Although there was uncertainty as to the safety of delayed re-implantation of another implant (5, 1.44), panelists strongly believed that implant-associated ALCL is a clinically indolent disease (8, 0.89) and has a favorable overall prognosis (9, 0.67).

Biologic Mechanism

Panelists believed, albeit with some uncertainty, that implant-related ALCL is biologically different from primary cutaneous anaplastic lymphoma kinase (ALK)-negative ALCL (7, 1.89), systemic ALK-negative ALCL (8, 1.11), and other CD30+ lymphoproliferative disorders (7, 0.89) but disagreed with the statement that it should not be classified as a lymphoma (3, 2.56). Although the panelists thought the evidence on the biologic model of ALCL development after breast implantation was weak, they believed inflammation (7, 0.67), macrophages (7, 0.89), and clonal T-cells (8, 0.67) were key factors in its etiology. Particulates (7, 1.22) and immunologic factors (7, 1.22) were viewed with less certainty.

Discussion:

Reports of individual cases and small case series have triggered concerns about a potential association between breast implants and ALCL.[1, 24-45] A retrospective study in the Netherlands by de Jong et al. suggested an elevated risk of developing ALCL in women with breast implants,[36] but prior large epidemiologic studies yielded no evidence for an increased risk of NHL as a whole in women with breast implants.[46-51] This is likely because of ALCL's recent classification as a distinct disease in 1994,[52] infrequent incidence as a subtype of NHL, and pathologic variation and shared histologic features with other, more common diseases. The inconclusive evidence creates difficult questions for patients and doctors. On the one hand, the absolute risk of developing ALCL after breast implantation is extremely small, estimated by de Jong et al. to have an incidence of 0.1-0.3 per 100,000 women with implants per year;[36] however, even this small risk may be concerning to the general public. Providing conclusive answers is difficult given the rarity of the disease, as large numbers of patients must be followed over a long period of time to establish an association and substantial laboratory research is needed to identify a plausible biologic model. Until more scientific data are available, a structured expert consultation process can be useful in providing guidance to patients,

clinicians, implant manufacturers, regulators, and the public who seek information to make evidence-based decisions at the present time.

Our prior literature review suggested that implant-associated ALCL bears similar clinical characteristics with primary cutaneous ALCL in that it too is almost always ALK-negative and has a relatively favorable prognosis.[8] But we also found that the handful of population-based studies, clinical cases, and laboratory-based reports available in the literature lacked information on many key variables (e.g., processing differences between various textured breast implants), which raised questions regarding the epidemiology, clinical management, and pathophysiology of implant-associated ALCL. On January 26th, 2011, the FDA released a notice about a possible association between breast implants and ALCL.[2] Within 1 week, over 800 news articles, editorials, interviews, and blog posts related to breast implants and ALCL have been published on the Internet.[53] Because no additional scientific findings or practice guidelines have followed, women and physicians have largely been left to interpret on their own what they read or hear from media sources.

For the expert consultation process, on which we report here, we convened a multidisciplinary group of clinicians and scientists to assess the systematic literature review data and respond to statements that were relevant to diverse stakeholders, including implant manufacturers and federal regulatory representatives present at the meeting. This process produced valuable insights. First, the panelists agreed that there exists a small but positive association between breast implants and the development of ALCL, but not NHL overall, whereas they perceived that the causality of breast implants is not sufficiently established. Second, they provided important guidance on clinical management of the disease. They agreed that a clinically evident seroma occurring 6 or more months after breast implantation should be aspirated and sent for cytologic analysis (instead of discarded). This is an important step in diagnosing implant-associated ALCL and initiating an appropriate treatment course for the patient. The panelists also affirmed that ALK-negative ALCL developing around breast implants

is a clinically indolent disease with a favorable prognosis that is distinct and different from systemic ALK-negative ALCL. Although there was discordance on whether or not this disease should be called a lymphoma because of its clinical behavior, we believe this is an issue best left up to bodies that determine nomenclature for hematologic malignancies, such as the World Health Organization. In addition, they asserted that management of implant-associated ALCL should consist of removal of both the involved implant and capsule, which is likely to prevent recurrence, and evaluation for other sites of disease but not adjuvant radiation or chemotherapy for women with localized disease confined to the capsule. Although many women received radiation and/or chemotherapy after implant removal and capsulectomy for breast-confined ALCL, more recent reports suggest survival may be equivalent with only implant and implant capsule removal; however, this treatment question will need to be addressed with clinical registries and/or trials. Panelists were largely uncertain about the risk factors and biologic mechanism by which implant-associated ALCL develops but provided guidance for future epidemiologic and laboratory research.

Limitations

There are a few limitations of our study. First, because evidence directly addressing many of the statements did not exist, panelists might have largely relied upon their own preconceptions or input from other experts to determine their ratings. It is unclear, however, how this could have influenced the direction and magnitude of the aggregate results. Second, we only asked panelists to rate their level of agreement with each statement and not the level of evidence supporting each item's validity. Rating the level of evidence for validity was not an aim of our process, because we were not attempting to develop clinical guidelines, but this would be an important question to ask in future studies as the evidence base strengthens. Third, because of the lack of a strong scientific base to support a biologic model of implant-associated ALCL development, some hypotheses may not have been represented by the statements

adequately or at all. Finally, although we asked all non-panelists to provide objective data to the panel only when called upon, clinical experience and information presented by plastic surgeons and implant manufacturers' representatives present at the meeting may have potentially influenced the panelists' final ratings.

Implications

Our study integrates the available evidence and the assessment of a multidisciplinary expert panel to provide initial clinical guidance to women, surgeons, pathologists, and oncologists on the issue of ALCL in women with breast implants. The results suggest a need for increased vigilance to detect this rare disease but also provide a certain level of reassurance, because this disease seems to take a clinically indolent course and because chemotherapy and radiation do not seem to be required in patients with localized disease.

However, substantial research efforts, such as *in vitro* experiments using immortalized implant-associated ALCL cell lines, collection of detailed clinical information in breast implant registries, and well-designed epidemiologic studies will be necessary to support our initial findings. Short-term goals could include improving the case definition of implant-associated ALCL, collection of patient samples, and centralized collection of date from all existing cases. Long-term goals could include developing a detailed patient survey to collect epidemiologic data in a systematic fashion, performing a prospective, case-control study, and pooling of clinical trial populations. Already, the FDA is planning to collaborate with the American Society of Plastic Surgeons to develop a prospective registry to gather detailed information on women with implant-associated ALCL to help provide answers about this vexing disease.[2] Such future research efforts will enhance our understanding of the epidemiology, clinical aspects, and biology of this disease.

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Table 1. National Specialty Societies Contacted for Panel Nominations

Specialty Society	Field of Expertise
Content	
American Society of Clinical Oncology	Cancer
American Society of Hematology	Cancer
American Association of Cancer Research	Cancer
Leukemia & Lymphoma Society	Cancer
Lymphoma Research Foundation	Cancer
Society of Surgical Oncology	Surgery, Cancer
American Society of Clinical Pathology	Pathology
College of American Pathologists	Pathology
Clinical Immunology Society	Immunology
American Association of Immunologists	Immunology
Society for Biomaterials	Biomaterials
Methodology	
American College of Epidemiology	Epidemiology
Society for Epidemiological Research	Epidemiology
American Public Health Association	Public Health
American Statistical Association	Statistics

Table 2. Final Ratings of Breast Implants and ALCL Statements

	Median									Dispersion
	Disagree			Uncertain			Agree			
EPIDEMIOLOGY										
Association Between Breast Implants and ALCL										
There is a positive association between breast implants and the development of ALCL.	1	2	3	4	5	6	7	**8**	9	**1.00**
Current evidence is sufficient to support a causative relationship between breast implants and ALCL development	1	2	3	4	5	**6**	7	8	9	*2.56*
The overall incidence of NHL is increased in patients with breast implants.	**1**	2	3	4	5	6	7	8	9	**1.00**
Attribution of Implants										
Women who develop ALCL after receiving breast implants would likely have developed ALCL in the breast even in the absence of implants.	1	**2**	3	4	5	6	7	8	9	1.33
Women who develop ALCL after receiving breast implants would likely have developed ALCL in the breast even if they had undergone TRAM reconstruction.	1	**2.5**		4	5	6	7	8	9	1.75
Predisposition to ALCL after Implants										
The finding of certain HLA-DR subtypes among patients with ALCL around breast implants suggests a possible underlying genetic predisposition to developing the disease.	1	2	3	4	5	6	**7**	8	9	1.67
Multiple cases of women within geographic areas or families diagnosed with ALCL around breast implants suggest a possible underlying genetic predisposition to developing the disease.	1	2	3	4	5	**6**	7	8	9	1.11
ALCL Behavioral Risk Factors										
Overweight or obese women are more likely to develop ALCL around breast implants than women who are normo- or underweight.	1	2	3	**4**	5	6	7	8	9	1.67
Women who smoke are more likely to develop ALCL around breast implants than women who do not smoke.	1	2	3	4	**5**	6	7	8	9	1.67
ALCL Surgical Risk Factors										
More involved breast surgeries, such as complex reconstructions, are associated with higher risks of developing ALCL than less involved surgeries, such as simple augmentations.	1	2	3	4	**5**	6	7	8	9	1.56
Repeated surgical procedures on breasts increase the risk of developing ALCL.	1	2	3	4	**5**	6	7	8	9	1.56
Non-obvious perioperative damage to implants increases the risk of ALCL development.	1	2	3	4	**5**	6	7	8	9	1.33

Subglandular implant placements carry higher risks of ALCL development than submuscular placements.	1	2	3	4	**5**	6	7	8	9	1.78
ALCL Implant-Related Risk Factors										
Silicone-coated implants increase the risk of ALCL development more than polyurethane-coated implants	1	2	3	4	5	**6**	7	8	9	**1.00**
Silicone gel breast implants carry higher risks of ALCL development than saline implants.	1	2	3	4	**5**	6	7	8	9	1.33
Larger implants are associated with higher ALCL development risk than smaller implants.	1	2	3	4	**5**	6	7	8	9	1.89
ALCL development around breast implants is exclusively found in patients with textured implants.	1	2	3	4	5	**6**	7	8	9	1.89
ALCL Development and Temporal Relationship										
ALCL does not develop within the first 6 months of breast implantation but rather oftentimes occurs many years later.	1	2	3	4	5	6	7	**8**	9	1.22
There is evidence for a positive association between length of time with a breast implant and risk of developing ALCL.	1	2	3	**4**	5	6	7	8	9	*2.00*
ALCL Cases Under-identified and Underreported										
The lack of reported T-cell lymphoma cases around breast implants before 1994 is most likely due to pathologists' limited ability to characterize ALCL and other T-cell lymphomas prior to that time.	1	2	3	4	5	6	**7**	8	9	1.11
The lack of reported T-cell lymphoma cases occurring before 1994 suggests that a more recent change in the manufacturing of breast implants rendered them more carcinogenic.	1	2	3	4	5	**6**	7	8	9	1.44
There is under-recognition of the true number of patients who develop ALCL around breast implants, which may include patients with unexplained or recurrent seromas.	1	2	3	4	5	6	7	**8**	9	**0.67**
CLINICAL ISSUES										
Diagnostic Evaluation of Seromas										
Patients with a clinically evident seroma occurring more than 6 months after breast implantation should undergo aspiration of the seroma the first time it occurs.	1	2	3	4	5	6	7	**8**	9	1.89
If a clinically evident seroma occurring more than 6 months after breast implantation is aspirated the first time it occurs, it should be sent for cytologic analysis.	1	2	3	4	5	6	7	**8**	9	1.44
Patients with a clinically evident seroma occurring more than 6 months after breast implantation should undergo aspiration of the seroma if it is recurrent.	1	2	3	4	5	6	7	8	**9**	**0.56**

If a recurrent, clinically evident seroma occurring more than 6 months after breast implantation is aspirated, it should be sent for cytologic analysis.	1	2	3	4	5	6	7	8	**9**	**0.44**
Full Evaluation for Systemic Disease										
Patients with ALCL that develops around a breast implant should be investigated for evidence of systemic disease.	1	2	3	4	5	6	7	8	**9**	**0.56**
Surgical Removal of Implant and Capsule										
The implant and capsule from the ALCL-affected breast should always be surgically removed.	1	2	3	4	5	6	7	**8**	9	**0.78**
If the capsule from the ALCL-affected breast does not visually appear to be abnormal, only the implant needs to be surgically removed.	1	**2**	3	4	5	6	7	8	9	**0.67**
Surgical Management of Contralateral Breast										
The implant and capsule from the breast NOT affected with ALCL should always be surgically removed.	1	2	3	4	**5**	6	7	8	9	*2.22*
If the capsule from the breast NOT affected with ALCL does not visually appear to be abnormal, only the implant needs to be surgically removed.	1	2	3	**4**	5	6	7	8	9	1.89
Neither the implant nor capsule from the breast NOT affected with ALCL should be surgically removed.	1	2	3	4	**5**	6	7	8	9	*2.44*
Immediate Re-implantation Risks										
There is low risk of disease progression associated with immediate re-implantation of a new breast implant in patients who have a history of ALCL around a breast implant and have had only the implant from the affected breast removed.	1	2	**3**	4	5	6	7	8	9	1.33
There is low risk of disease progression associated with immediate re-implantation of a new breast implant in patients who have a history of ALCL around a breast implant and have had both the implant and capsule from the affected breast removed.	1	2	3	4	**5**	6	7	8	9	1.56
Post-Surgical Radiation or Chemotherapy in Localized Disease										
After removal of the implant and capsule from the ALCL-affected breast, patients do not require further treatment but should be followed clinically.	1	2	3	4	5	6	**7**	8	9	1.22
After removal of the implant and capsule from the ALCL-affected breast, breast irradiation should be offered to patients with localized disease confined by the breast capsule.	1	**2.5**		4	5	6	7	8	9	**1.00**
After removal of the implant and capsule from the ALCL-affected breast, chemotherapy should be offered to patients with localized disease confined by the breast capsule.	**1.5**		3	4	5	6	7	8	9	**0.75**
Chemotherapy should only be offered to patients with ALCL around a breast implant that has spread beyond the capsule.	1	2	3	4	5	6	**7**	8	9	1.56

Recurrence after Capsule and Implant Removal										
Once the implant and capsule are removed from the ALCL-affected breast, patients with localized ALCL confined by the breast capsule are cured of their disease.	1	2	3	4	5	**6**	7	8	9	1.33
Once the implant is removed from the ALCL-affected breast, patients with localized ALCL confined by the breast capsule are cured of their disease (i.e., capsule does not need to be removed).	1	2	**3**	4	5	6	7	8	9	1.33
Once the implant and capsule are removed from the ALCL-affected breast, patients with localized ALCL confined by the breast capsule are unlikely to have recurrence of their disease.	1	2	3	4	5	6	7	**8**	9	1.89
Once the implant is removed from the ALCL-affected breast, patients with localized ALCL confined by the breast capsule are unlikely to have recurrence of their disease (i.e., capsule does not need to be removed).	1	2	3	**4**	5	6	7	8	9	1.44
Delayed Re-implantation Risks										
There is low risk of recurrence associated with delayed re-implantation of a new breast implant in patients who have a history of ALCL around a breast implant and have had both the implant and capsule from only the affected breast removed.	1	2	3	4	**5**	6	7	8	9	1.44
There is low risk of recurrence associated with delayed re-implantation of new bilateral breast implants in patients who have a history of ALCL around a breast implant and have had implants and capsules from both breasts removed.	1	2	3	4	**5**	6	7	8	9	1.44
Implant-associated ALCL Prognosis										
As opposed to systemic ALK (-) ALCL, which involves organs outside the breast, ALK (-) ALCL that develops around breast implants is, in general, a clinically indolent disease.	1	2	3	4	5	6	7	**8**	9	**0.89**
As opposed to systemic ALK (-) ALCL, which involves organs outside the breast, ALK (-) ALCL that develops around breast implants has, in general, a good prognosis.	1	2	3	4	5	6	7	8	**9**	**0.67**
BIOLOGIC MECHANISM										
Biological Difference of ALCL and CD30+ Disorders										
Patients who have a history of ALCL prior to developing ALCL around breast implants have a distinct disease from those who develop ALCL around breast implants de novo.	1	2	3	4	5	6	7	8	**9**	**0.89**
ALK (-) ALCL that develops around breast implants is a distinct entity from primary cutaneous ALK (-) ALCL.	1	2	3	4	5	6	**7**	8	9	1.89
ALK (-) ALCL that develops around breast implants is a distinct entity from other CD30+	1	2	3	4	5	6	**7**	8	9	**0.89**

lymphoproliferative disorders.										
Lymphoma Classification										
ALK (-) ALCL that develops around breast implants is a distinct entity from systemic ALK (-) ALCL.	1	2	3	4	5	6	7	**8**	9	1.11
ALCL that develops around breast implants should not be called a "lymphoma."	1	2	**3**	4	5	6	7	8	9	*2.56*
Microbial and Particulate Factors in Implant-related ALCL Etiology										
The implant surgical site is commonly contaminated by bacteria (even if cultures from seromas are negative), which are likely to play a role in ALCL development.	1	2	3	4	5	**6**	7	8	9	1.78
Over time, particles come off of the implant surface via degradation and/or microtrauma.	1	2	3	4	5	6	**7**	8	9	**0.67**
The finding of ALCL in seromas or capsules surrounding implants and not in breast tissue suggests that particles from the implant surface are likely to play a role in ALCL development.	1	2	3	4	5	6	**7**	8	9	1.22
Immunologic Factors in Implant-related ALCL Etiology										
With repeated microtrauma, the fibrous capsule around breast implants is disrupted, causing re-initiation of the immune response and potentially leading to the development of ALCL.	1	2	3	4	5	6	**7**	8	9	1.22
Implant surfaces are immunologically inert.	1	2	**3**	4	5	6	7	8	9	1.88
Inflammatory Factors in Implant-related ALCL Etiology										
ALCL development around breast implants stems from a chronic, inflammatory reaction.	1	2	3	4	5	6	**7**	8	9	**0.67**
When silicone particles come in contact with native tissue, tissue macromolecules such as fibronectin, fibrinogen, and apolipoprotein B can become denatured, evoking an inflammatory response.	1	2	3	4	5	6	**7**	8	9	1.33
Macrophages' Role in Implant-related ALCL Etiology										
Particles from the implant surface are taken up by macrophages, potentially starting the development of ALCL.	1	2	3	4	5	6	**7**	8	9	**0.89**
Denatured "self" tissue macromolecules (e.g., fibronectin, fibrinogen, and apolipoprotein B) are taken up by macrophages, potentially starting the development of ALCL.	1	2	3	4	5	6	**7**	8	9	1.89
T-cells' Role in Implant-related ALCL Etiology										
Chronic T-cell hyperstimulation occurs adjacent to the implant surface where particles and denatured tissue macromolecules are found.	1	2	3	4	5	6	**7**	8	9	**0.78**
The finding of T-cell gene rearrangement in ALCL cells suggest that ALCL develops from an expanded T-cell clone.	1	2	3	4	5	6	7	**8**	9	**0.67**

There is a subsequent "hit" that is required to expand a T-cell clone.	1	2	3	4	5	6	7	**8**	9	**0.75**
Macrophages' Role in Silicone Particles and Regional Lymph Nodes										
If axillary lymph nodes of patients with ALCL around breast implants are biopsied, silicone particles from the implant surface are likely to be found.	1	2	3	4	5	6	**7**	8	9	**0.56**
If found in axillary lymph nodes, silicone particles from the implant surface are likely to have been carried there by macrophages instead of arriving there via lymphatic drainage.	1	2	3	4	5	6	**7**	8	9	1.22

Key & Definitions: ALCL = Anaplastic Large Cell Lymphoma,
NHL = Non-Hodgkin's Lymphoma,
TRAM = Transverse Rectus Abdominus Myocutaneous,
HLA-DR = Human Leukocyte Antigen-DR (class II major histocompatibility complex cell surface receptor found on antigen presenting cells to facilitate their interactions with T-cells),
ALK = Anaplastic Lymphoma Kinase (a cell membrane-associated tyrosine kinase receptor seen in some ALCLs),
CD30 = Cluster of Differentiation molecule 30 (a cell membrane protein of the tumor necrosis factor receptor family and also a tumor marker seen in all ALCLs)