Guideline Resource Unit
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Literature Review: BIA-ALCL

Tumour Team: Breast

Cancer Care Alberta

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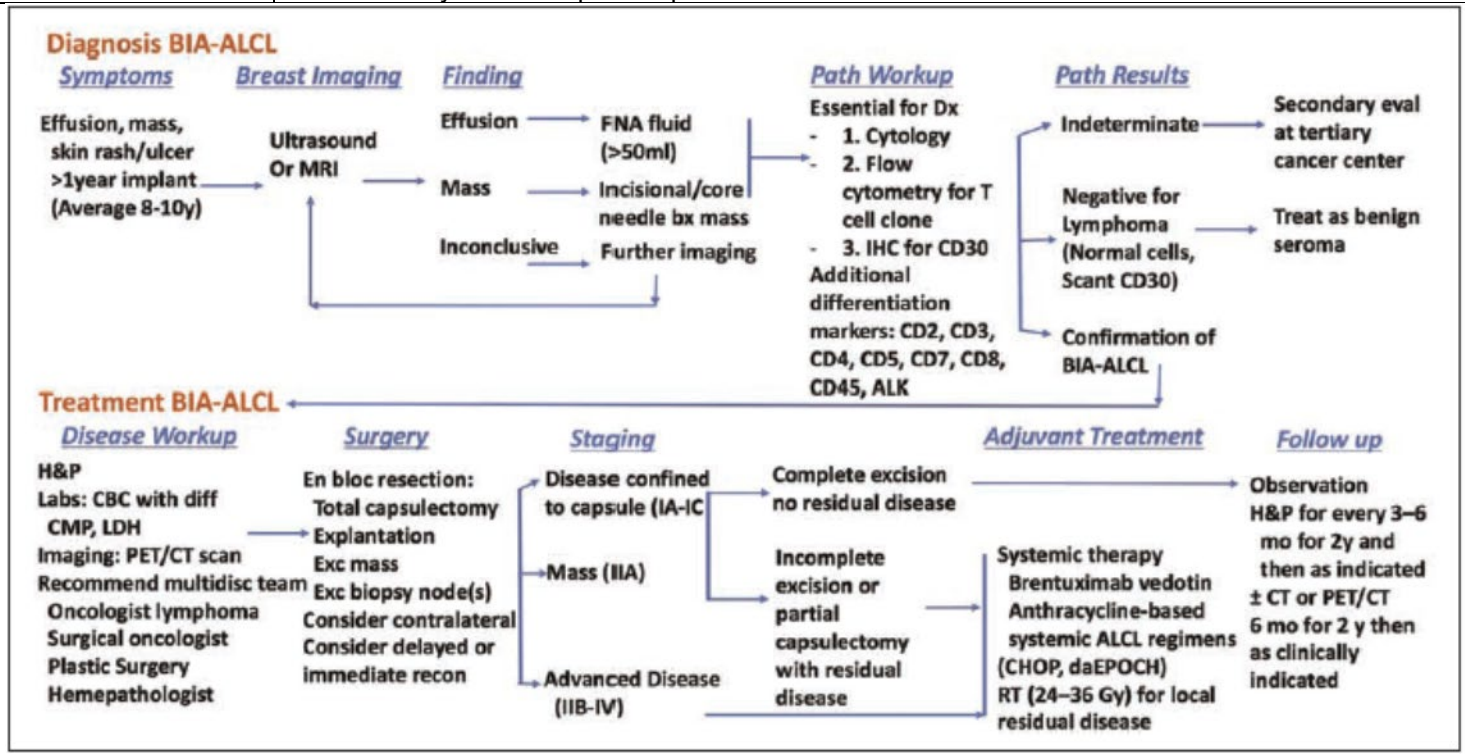
Research Questions:

1. How to manage patients with textured implants and concerns for breast implant-associated anaplastic large cell lymphoma (BIA-ALCL)?
    - Table 1: Summary of Existing Literature for Breast Implant Associated Anaplastic Large Cell Lymphoma
    - Table 2: White Literature results for Textured vs. Non-Textured Implants
    - Table 3: How do we best manage patients with BIA-ALCL and which pathology analysis is required?
    - Table 9: Squamous cell carcinoma and patients with breast implants.
2. How to manage patients with implants concerned with breast implants illness (BII)?
    - Table 4: What literature exists on Breast Implant Illness?
3. How do breast implants alter screening for breast cancer?
    - Table 5: What is the role of routine screening for implant integrity?
    - Table 6: What is the Canadian take on routine screening guidelines for patients with implants?
    - Table 7: Mammography view for implants
4. What are the sequelae associated with radiating an implanted breast?
    - Table 8: What are the effects of radiation on an implant?

Inclusion criteria: Any quality, any time, English, humans, full text (see appendix 1 for search details)

Table 1: Summary of existing literature for Breast Implant Associated Anaplastic Large Cell Lymphoma

Author, Date	Study Type *(level of evidence)*	Patient Characteristics (n)	Outcomes/Recommendations
Up-to-date (Sept, 2019)	Summary	BIA-ALCL	• Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) is an uncommon CD30-positive peripheral T cell lymphoma arising around textured-surface breast implants placed for either reconstructive or cosmetic indications. Among women with breast implants, the absolute risk of developing BIA-ALCL is low, and screening or prophylactic implant removal is not recommended. ●Most cases present approximately one decade after implant placement with either a seroma or, less commonly, a discrete breast mass adjacent to the implant. While most cases are unilateral, bilateral breast involvement has been reported in a minority of patients with bilateral breast implants. ●The tumor involves the luminal surface of the fibrous capsule surrounding the implant and may show varying degrees of infiltration of the capsule, the surrounding soft tissue, or the breast parenchyma. The CD30-positive tumor cells morphologically resemble those of systemic ALCL. Unlike systemic ALCL, BIA-ALCL lacks expression of anaplastic lymphoma kinase (ALK) and does not have gene rearrangements involving the ALK gene on chromosome 2p23. ●The evaluation of suspected cases includes a bilateral breast examination, ultrasound of the involved breast, aspiration of the effusion (seroma), and biopsy of the capsule. The seroma fluid is sent for culture and specific pathology tests such as CD30 immunohistochemistry. ●BIA-ALCL is a clinicopathologic diagnosis based upon characteristic morphologic features and immunohistochemical patterns found on biopsy specimens in conjunction with the clinical features found on presentation. It must be differentiated from primary breast lymphoma, primary cutaneous ALCL, nodal ALCL with breast involvement, primary or recurrent breast cancer, nonmalignant complications of breast implants, and breast infection. ●Disease stage can usually be determined based on the pathologic findings at the time of complete surgical resection in conjunction with findings on imaging (ie, positron emission tomography/computed tomography [PET/CT] scan). Disseminated disease suggested on imaging should be confirmed pathologically. ●Data regarding the treatment of BIA-ALCL come from case series and case reports. Our approach is generally consistent with expert consensus recommendations. •For all patients with BIA-ALCL, we recommend complete surgical resection of the implant, the capsule, and any associated mass (Grade 1B). This recommendation is in accordance with National Comprehensive Cancer Network (NCCN) BIA-ALCL guidelines. •For patients with localized disease (presenting as malignant effusion or mass) that can be completely excised by surgical removal of the breast implant and capsule (Ann Arbor stage IE, MD Anderson TNM Stage 1A to 2A), we suggest no adjunctive therapy (chemotherapy, radiotherapy) (Grade 2C). •For patients with pathologically confirmed disseminated disease or patients who fail surgical therapy alone, we follow NCCN guidelines with either an anthracycline-based regimen (ie. CHOP) or brentuximab vedotin for first-line therapy ●Following the completion of therapy, patients are seen at periodic intervals to monitor for treatment complications and assess for possible relapse. BIA-ALCL generally appears to be a biologically

			indolent disease with a good prognosis with complete surgical resection provided there is no extension beyond the implant capsule.
NCCN	Guideline	
FDA	Report	BIA-ALCL	●Although BIA-ALCL is uncommon, women with breast implants have a small but increased risk of developing BIA-ALCL in the capsule adjacent to a textured-surface breast implant. ●When BIA-ALCL occurs, it is most frequently identified in patients undergoing implant revision operations for late onset, persistent seroma. However, in some cases, patients present with capsular contracture or masses adjacent to the breast implant. ●Women with breast implants should perform regular self-breast exams and contact their health care provider promptly if they notice any changes. ●Screening or prophylactic implant removal is NOT recommended for women with breast implants who are asymptomatic, even for those with a familial susceptibility to cancer.
The Aesthetic Society BIA-ALCL Task Force	Guideline	BIA-ALCL patients	The Revised Takeaway: While about 80% of new BIA-ALCL patients may present with the classic late seroma, the lack of a seroma does not rule out the disease. There have been a small percentage of cases of BIA-ALCL that initially present with capture contracture as described above. Surgeons should be particularly aware of this possibility when seeing a patient with a late capsular contracture – especially in a patient with textured breast implants, associated fluid collection or any gross capsular abnormalities. The point of these case reviews is to remind surgeons to carefully evaluate these patients as BIA-ALCL, although very rarely, may be associated with the capsular contracture. If a

			surgeon's index of suspicion preoperatively that the capsular contracture may represent something more than a typical capsular contracture, a PET scan may be indicated; however, the advisability for PET scanning routine capsular contractures is not indicated.
White Literature			
Lazzeri 2011	Retrospective→ This is a summary of cases already reported in the literature (*Level IV)*	n=67, n=40 cases of prosthesis-associated breast lymphomas, and n=27 with a diagnosis of ALCL without implants.	The histologic and clinical similarities of the majority of implant-related ALK-1(-) ALCLs suggest a common mechanism, especially when compared with the counterpart of patients without implants in which very few and highly heterogeneous cases of the same malignancy were detected. Amongst those with implants: - mean age was 50 (range: 28-87) -had either silicone gel-filled (n=18), saline-filled (n=15), polyurethane-coated silcone gel-filled (n=4), or unknown (n=3) -n=23 were cosmetic augmentation vs n=13 developed after breast reconstruction -implant-related lymphomas presented 3 months to 25 years (mean 9.5±7.6 years) after augmentation mammoplasty or 3 years to 17 years (mean 8.9 ±4.5 years) subsequent to breast reconstructive surgery. -a diagnosis of ALCL was made in 32 patients
de Jong 2008	Population-based case-control study (*Level IV*)	n=35, n=11 patients with breast ALCL were identified via registry and 1-5 controls with other lymphomas in the breast were matched based on age and year of diagnosis	ALCL cohort -median age 40 (range 24-68) -n=5 had bilateral silicone breast prostheses, placed 1-23 years before diagnosis of ALCL -All received prostheses for cosmetic reasons -The odds ratio for ALCL associated with breast prostheses was 18.2 (95% confidence interval, 2.1-156.8)
Vase 2013	Retrospective *(Level IV)*	n=19,885, Danish women who underwent breast implant surgery during 1973-2010	-observed 31 cases of lymphoma among the cohort -no cases of ALCL -Standardized incidence ratios for ALCL and lymphoma were 0 (95%CI: 0-10.3) and 1.20 (95%CI: 0.82-1.70), respectively -Conclusion: these results do not support an associated between breast implants and ALCL
Largent 2012	Retrospective (SEER) *(Level IV)*	n=89,382, women with or without prior cancer, stratified by implant type (smooth/textured)	-there were 28 observed cases of lymphoma among 89 382 patients and 204 682 person-years of follow-up compared with 43 expected cases [SIR: 28/43=0.65 (95% CI: 0.43-0.94), P=0.02] -SIRs were calculated stratifying by baseline cancer history: women without prior cancer [SIR: 17/24=0.70 (95% CI: 0.41-1.13), P=0.17] and women with prior cancer [SIR: 11/14=0.79 (95% CI: 0.39-1.41), P=0.52]. SIRs were calculated by implant shell type: textured shell implants [SIR: 16/23=0.70 (95% CI: 0.40-1.13), P=0.16] and smooth shell implants [SIR: 12/19=0.63 (95% CI: 0.33-1.10), P=0.12]. -Results reported 12 cases of primary breast ALCL in women between 1996 and 2007 without a history of cancer, for an average annual incidence of 4.28 (95% CI: 3.51-5.05)/100 million women in the US - these women may or may not have breast implants

			-In clinical studies, three ALCL cases were reported in women with breast implants and a history of breast cancer, yielding a crude incidence rate of 1.46 (95% CI: 0.30-4.3)/100 000 person-years.
Lipworth 2009	Retrospective *(Level IV)*	n=43,000, reviewed patients from 5 long-term follow-up for women with cosmetic breast implants (followed for up to 37 years)	-Overall, there were 48 observed incident cases of non-Hodgkin's lymphoma compared with 53.9 cases expected, yielding a summary standardized incidence ratio of 0.89 (95% CI, 0.67 to 1.18). -None of the epidemiologic cohort studies reported a primary lymphoma originating in the breast.
de Boer 2018	Retrospective *(Level IV)*	n=237 (n=43 ALCL cases, n=146 control- women with other primary breast lymphomas), identified all histo/cyto proven NHL of the breast in the Netherlands from 1990-2016	-Among 43 patients with breast-ALCL (median age, 59 years), 32 had ipsilateral breast implants, compared with 1 among 146 women with other primary breast lymphomas (OR, 421.8; 95% CI, 52.6-3385.2). -Implants among breast-ALCL cases were more often macrotextured (23 macrotextured of 28 total implants of known type, 82%) than expected based on sales data ($p < 0.001$). -The estimated prevalence of breast implants in women aged 20 to 70 years was 3.3%. -Cumulative risks of breast-ALCL in women with implants were 29 per million at 50 years and 82 per million at 70 years. -The number of women with implants needed to cause 1 breast-ALCL case before age 75 years was 6920.
Doren 2017	Retrospective *(Level IV)*	n=100, BIA-ALCL in the US from 1996-2015	-Mean age at diagnosis was 53.2±12.3 years. -Mean interval from implant placement to diagnosis was 10.7±4.6 years. -Forty-nine patients had breast implants placed for cosmetic reasons, 44 for mastectomy reconstruction, and seven for unknown reasons. Assuming that breast implant-associated ALCL occurs only in textured breast implants, the incidence rate is 2.03 per 1 million person-years (203 per 100 million person-years), which is 67.6 times higher than that of primary ALCL of the breast in the general population (three per 100 million per year; $p<0.001$). -Lifetime prevalence was 33 per 1 million persons with textured breast implants.
Brody 2015	Retrospective *(Level IV)*	n=173, grouped known cases (n=79) with previously unreported cases (n=94)	-ALCL lesions first presented as late peri-implant seromas, a mass attached to the capsule, tumor erosion through the skin, in a regional node, or discovered during revision surgery. -The clinical course varied widely from a single positive cytology result followed by apparent spontaneous resolution, to disseminated treatment-resistant tumor and death. -There was no preference for saline or silicone fill or for cosmetic or reconstructive indications. -Where implant history was known, the patient had received at least one textured-surface device. -Extracapsular dissemination occurred in 18 cases; nine of those were fatal. -Histochemical markers were primarily CD-30 and Alk-1. Other markers occurred at a lower frequency. -Risk estimates ranged from one in 500,000 to one in 3 million women with implants.

ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; BIA-ALCL, breast implant-associated anaplastic large cell lymphoma; CBC, complete blood count; CD, cluster of differentiation; CHOP, cyclophosphamide hydroxydaunorubicin oncovin prednisone; CI, confidence interval; CMP, comprehensive metabolic panel; CT, computed tomography; daEPOCH, etoposide phosphate prednisone vincristine sulfate (oncovin) cyclophosphamide, doxorubicin hydrochloride (hydroxydaunorubicin) and rituximab; FNA, fine needle aspiration; H&P, history and physical exam; LDH, lactate dehydrogenase; MRI, Magnetic

resonance imaging; *NCCN, national comprehensive cancer network; OR, odds ratio; PET, positron emission tomography; PET-CT, PET- computerized tomography; RT, radiation therapy; SIR, standardized incidence ratios.*

Table 2: White Literature results for textured vs. non-textured Implants

Author ,Date	Study Type (level of evidence)	Patient Characteristics (n)	Outcomes/Recommendations
Brody 2015	Retrospective *(Level IV)*	n=173, grouped known cases (n=79) with previously unreported cases (n=94)	-All patients who were diagnosed with BIA-ALCL had a history of textured implant
FDA	Report	All adverse events of implants and ALCL reported to the FDA as of Feb. 2019 (non-peer reviewed)	-where surface characteristics were known, 93% of cases occurred with textured devices
FDA	Report	Update to ref above, updated July 2019	-as of July 2019 the FDA was aware of 573 unique pathologically confirmed ALCL cases worldwide, including 33 deaths -of the 573 cases, 481 were attributable to Allergan BIOCELL textured implants -12 of the 13 deaths where type of implant was known were attributed to the Allergan BIOCELL implant -FDA requested a voluntary recall of the Allergan BIOCELL implants, which ultimately led to a worldwide recall
Doren 2017	Retrospective *(Level IV)*	n=100, BIA-ALCL in the US from 1996-2015	-risk of BIA-ALCL with Allergan BIOCELL approximately 6 times higher than with Siltex textured implants
McGuire 2017	Prospective multicenter 10-year study *(Level III)*	n=17,656, women who received Natrelle 410 implants for augmentation (n=5059), revision -augmentation (n=2632), reconstruction (n=7502) or revision-reconstruction (n=2463)	-Median follow-up was 4.1, 2.6, 2.1, and 2.3 years in the augmentation, revision-augmentation, reconstruction, and revision-reconstruction cohorts, respectively. -Incidence of capsular contracture across cohorts ranged from 2.3 to 4.1 percent; malposition, 1.5 to 2.7 percent; and late seroma, 0.1 to 0.2 percent. -Significant risk factors for capsular contracture were subglandular implant placement, periareolar incision site, and older device age in the augmentation cohort ($p<0.0001$), older subject age in the revision-augmentation cohort ($p<0.0001$), and higher body mass index ($p = 0.0026$) and no povidone-iodine pocket irrigation ($p = 0.0006$) in the reconstruction cohort. -Significant risk factors for malposition were longer incision size in the augmentation cohort ($p = 0.0003$), capsulectomy at the time of implantation in the reconstruction cohort ($p = 0.0028$), and implantations performed in physicians' offices versus hospitals or standalone surgical facilities in both revision cohorts ($p<0.0001$). -The incidence of late seroma was too low to perform risk factor analysis.

ALCL, anaplastic large cell lymphoma; BIA-ALCL, breast implant-associated anaplastic large cell lymphoma; FDA, Food and Drug Administration.

Table 3: How do we best manage patients with BIA-ALCL and which pathology analysis is required?

Author, year	Study Type *(level of evidence)*	Patient Characteristics (n)	Outcomes/ Recommendations
Turton, P. 2021 (UK guidelines)	Guideline	BIA-ALCL	Primary treatment (except locally advanced or distant mets): Total *en-bloc* capsulectomy -Total *En-bloc* Capsulectomy and Explantation • un-breached capsule and any associated mess; the implant and associated effusion are fully retained • capsule must be formally orientated by placing external sutures • no role for sentinel node biopsy • histological confirmation with excision of enlarged nodes at the time of surgery should be sought -Processing the Specimen post-explant • Contained peri-implant effusion should be drained form the specimen by making a 2 mm cut into the capsule on the inferior pole and the fluid sent for cytology • capsule should be opened as a full inferior capsulotomy that extends form the 9 O'C to 6 O'C to 3O'C position (clam shell capsulotomy) • capsule should be inspected to identify areas of concern to highlight to pathologist • if double capsule, the inner layer should be peeled off the implant and sent separately • primary analysis of capsule is morphological and done by breast pathology team • hematopathology for secondary molecular assessment as described above -Staging • TNM staging system for solid tumours should be used -Systematic Treatment • vast majority of patients who present with effusion-only BIA-ALCL will not require systemic or adjuvant therapy -Indications for Chemotherapy, Monoclonal Antibody and/or Autologous Stem Cell Transplant • Mass-forming disease, lymph node involvement or distant disease may require systemic treatment, and this is advocated for stage 2-4 disease • At present, CHOP chemotherapy is most frequently used for the upfront treatment of ALCL based on experience with this regimen from high grade B cell lymphoma, despite poorer outcomes in the T cell lymphoma setting • There is conflicting evidence as to whether the addition of etoposide leads to improved outcomes • Recently BV-CHP (BV: anti-CD30 antibody drug conjugate given in place of vincristine) was found to have improved median PFS compared to CHOP • OS benefit seen in favor of A-CHP (most significant in the ALCL subgroup) • BV is licensed and funded in the UK for relapsed/ refractory ALCL • Autologous stem cell transplantation in first remission of advanced stage (3 or 4) ALCL is controversial with poor quality and conflicting evidence -Radiation therapy

			• Adjuvant chest wall radiotherapy is not routinely recommended after total capsulectomy for histologically confirmed completely excised T1 and T2 tumours • Should be considered when complete excision has not been possible, if surgical margins are positive despite total capsulectomy or where there is chest wall invasion • Unknown what optimal dose should be, but doses similar to that given to patients with other high-grade lymphomas (24-36Gy) have been proposed by the NCCN guideline
Clemens, M.W. 2019 (NCCN)	Guideline	BIA-ALCL	**Pathology Workup** 1) Cytology 2) Flow cytometry for T cell clone 3) IHC for CD30 -Additional differentiation markers:CD2, CD3, CD4, CD5, CD7, CD8, CD45, ALK **Treatment** -En bloc resection: Total capsulectomy, Explantation, Exc Mass, Exc biopsy node(s) -Consider contralateral -Consider delayed or immediate recon -Incomplete excision or partial capsulectomy with residual disease: Systematic therapy • Brentuximab vedotin • Anthracycline-based systemic ALCL regimens (CHOP, daEPOCH) • RT (24-36 Gy) for local residual disease
Jones, J.L. 2019	Guideline	BIA-ALCL	-All patients with implants presenting with late persistent unexplained seroma or peri-implant mass should undergo appropriate imaging (mammogram or ultrasound) - Where fluid is present, the *entire volume* should be aspirated and submitted for cytological examination • Sample should be placed in liquid preservative to facilitate cell-block preparation and adjunct immunocytochemistry studies • Include full clinical details on the pathology request form and a clear indication of suspicion of BIA-ALCL **In laboratory:** • Preparations of May-Grunwald-Giemsa (MGG), Papanicolaou (PAP) or hematoxylin and eosin (H&E)-stained smears should be made from liquid cytoblocks samples, and additional material made into cytoblocks • Primary analysis will be morphological • Strongly recommend that cytopathologists or breast pathologists who may initially receive such specimens work closely with hematopathology colleagues • Samples that are acellular or are composed entirely of inflammatory cells (neutrophils and 'bland' macrophages) → negative without further immunohistochemistry • Samples containing 'atypical' macrophages and/or large atypical lymphoid blasts should have CD30 and CD68/CD163 assessment undertaken • If CD30-positive and CD68-negative→ Supports BIA-ALCL, full IHC panel • If CD30 is negative and CD68/CD163 are positive→'atypical' macrophages (no ALCL panel is required)

			• Diagnostic panel should always include B cell markers (CD20, CD79, PAX5) and EBV to exclude other large cell lymphomas (diffuse B cell lymphoma and classical Hodgkin lymphoma) • Pan-cytokeratin to exclude poorly differentiated carcinoma and S100 and Melan-A to exclude melanoma, are also essential **Management:** • Complete surgical excision, implant removal, complete en bloc capsulectomy (where possible) and removal of any mass with confirmation of negative margins • No routine sentinel lymph node removal but if individual nodes are suspected of involvement, they should be removed. • Capsule should be marked with ink intraoperative and later on the bench with orientation sutures • When complete excision cannot be achieved of there is chest wall invasion→ radiotherapy should be considered. If stage II and above→ systemic chemotherapy (anthracycline-based regimen)
Johnson, L. 2017 (UK)	Guideline	BIA-ALCL	**If effusion:** fine needle aspiration cytology of total effusion volume **If mass:** needle core biopsy ±abnormal axillary lymph nodes **Diagnostic requirements:** • Specimen review by histopathologist experienced with hematological malignancies • CD30 positive cells • ALK negative **Management:** • Multidisciplinary team review • Localized disease (Stage I): explantation and complete capsulectomy • Advanced Disease (stage II+): excision of mass + explantation + complete capsulectomy ± excision of suspicious nodes; consider (neo-)adjuvant chemotherapy-brentuximab vedotin in addition to CHOP, radiotherapy as per local MDT discussion
White Literature-2020			
Ashar, B.S. 2020	Review *(Level V)*	BIA-ALCL	**Pathology:** • fine-needle aspiration of fluid with cytology, including anaplastic lymphoma kinase and CD30 biomarkers • pathology of mass associated with the breast implant **Treatment:** • removal of implant and the surrounding scar capsule
Gardani, M. 2020	Case Report *(Level V)*	BIA-ALCL	**Case:** - Left modified mastectomy with axillary lymphadenectomy and retromuscular reconstruction with silicone implant 17 years ago **Pathology:** • Histological examination performed by microbiopsy of the nodular formation→presence of an ALK negative large cell anaplastic lymphoma

			• IHC demonstrated that the atypical cells were positive for CD2, CD3, CD4, CD30, but were negative for ALK, CD20, CD79a and EMA with 80% of KI-67 • Initial blood analysis, including blood count, chemistry, C-reactive protein, lactate dehydrogenase (LDH), CEA, CA 15-3 were all normal **Treatment:** Underwent surgery with the complete excision of the skin affected by erythema, subcutaneous tissue, pectoral muscle, prosthetic pocket, and prosthesis as a whole
Marra, A. 2020	Review *(Level V)*	BIA-ALCL	**Treatment:** -Prothesis explantation and complete excision of any residual mass -Surgery alone for stages IA to IIA -Lymph node dissection not usually recommended (in absence of lymph node involvement) - Sentinel lymph node biopsy not done (ALCL is not a disease related to the breast parenchyma) -unresctable masses and local residual disease after surgery • may benefit from complementary therapeutic strategies • limited data available • all patients should be discussed with MDT board • some authors suggest radiotherapy as therapeutic control -Locally advanced and disseminated disease • systemic chemotherapy • using treatment protocols adopted for systemic ALCLs (CHOP, CHOEP etc) • anti-CD30 antibody-drug conjugate (ADC) brentuximab vedotin has demonstrated promising activity in some sporadic case reports -Some cases of BIA-ALCL display genetic altercation in JAK/STAT genes • novel clinical trial testing JAK/STAT inhibitors (no reference to clinical trials) -Presence of an upregulated PD1/PDL1 axis should investigate anti-PD-1/PD-L1 immunotherapy agents in patients with advanced disease
Moellhoff, N. 2020 (original article in german)	Case Report *(Level V)*	BIA-ALCL	**Case:** - Bilateral breast reconstruction following mastectomy for breast cancer→Textured silicone gel breast implants inserted **Treatment:** - Removal of right breast implant and total capsulectomy **Pathology:** • ultrasound guided aspiration revealed 650 ml of cloudy yellow fluid; cultures negative • Histological studies of the removed capsules: BIA-ALCL that involved the capsule but not extending to the surrounding breast tissues • no other info provided
Ohishi, Y. 2020	Case Report *(Level V)*	BIA-ALCL (silicone breast implant)	**Treatment:** • Implant removed with as much as surrounding tissue (capsule) as possible • Adjuvant CHOP chemotherapy every 21 days for 6 cycles **Pathology:**

			• Cytological examination of intraoperative fluid: small cluster of atypical cells with large, pleomorphic, hyperchromatic, and severely irregular nuclei→Class IIIb
			• Moderate nuclear atypia was recognized in large lymphoid cells with degeneration of the capsule and tissues surrounding implant
			• Fragmented capsules showed scattered chronic inflammatory cells in the necrotic area near the capsule
			• Atypical and hyperchromatic macrophages were seen
			• Results of immunohistochemistry (IHC) staining revealed CD68 (+), vimentin (+), and CK7 (−), and cells were determined to be histiocytes→ CD30 and ALK not performed
			• Bacterial cultures from fluid collection were negative
			• Postoperative diagnosis was sterile inflammation, but the possibility of BIA-ALCL could not be denied
			• 3 months later: contralateral axillary lymphadenopathy began to grow larger, and core needle biopsy was performed
			  • showed non-neoplastic changes
			  • atypical CD30-positive cells were observed
			  • Blood tests showed WBC 6500/μl (neutrophil 51.4%, eosinophil 8.3%, and basophil 1.3%), CEA 0.8 ng/ ml, CA15-3 9.2 U/ml, NCC-ST-439
			• 5 months post-surgery:
			  • Contralateral axillary lymph node had enlarged more
			  • Fine needle aspiration cytology resulted in a Class IIIb diagnosis
			  • Excisional biopsy was then performed on the contralateral axillary lymph node
			  • Pathological findings showed proliferation of large atypical lymphoid cells with pleomorphic nuclei
			  • Result of IHC staining revealed CD30 (+), ALK (−), CD4 (weakly positive), CD8 (−), CD3 (−), CD20 (−), CD56 (−), GranzymeB (+), AE1/3(−), EMA (−), and CK5/6 (−)
			-Patients diagnosed with BIA-ALCL due to CD30 (+) and ALK (-): stage IV

2019			
Ali, N. 2019	Case report *(Level V)*	BIA-ALCL	**Pathology Workup** 1) Cytology 2) Flow cytometry for T cell clone 3) IHC for CD30 -Additional differentiation markers:CD2, CD3, CD4, CD5, CD7, CD8, CD45, ALK **Treatment** -En bloc resection: Total capsulectomy, Explantation, Exc Mass, Exc biopsy node(s) -Consider contralateral -Consider delayed or immediate recon -Incomplete excision or partial capsulectomy with residual disease: Systematic therapy • Brentuximab vedotin • Anthracycline-based systemic ALCL regimens (CHOP, daEPOCH)

			RT (24-36 Gy) for local residual disease

Broggi, G. 2019	Case report and Review
	
	(Level V)
		BIA-ALCL	**Pathology:**
			• Cytological examination of periprosthetic effusion, revealing sheets of CD30+ and CD4+ large-sized atypical cells with multiple mitosis, was consistent with the diagnosis of BIA-ALCL
			Treatment:
			• Bilateral capsulectomy and prosthetic excision
			• PET exam excluded systemic disease
			1 year later→ left axillary lymphadenopathy
			• Pathology of largest lymph node
			  • Focal presence of clusters of large-sized and pleomorphic cells with abundant cytoplasm, vesicular or hyperchromatic nuclei containing prominent nucleoli
			  • Neoplastic cells were diffusely positive for CD30, epithelial membrane antigen and CD15, and focally positive for leukocyte common antigen and CD4. No staining was obtained with CD3, CD43, CD5, CD20, CD79a, PAX-5 and ALK-1
			• Diagnosis of 'lymph node localization of ALK-negative BIA-ALCL
			• Treatment: systemic chemotherapy (CHOEP-RT): cyclophosphamide 750 mg/mq ev, adriblastin 50 mg/mq ev, vincristine 1.4 mg/mq, etoposide 100mg/mq ev, prednisone 100mg os). Patient underwent 3 cycles of chemotherapy followed by 15 cycles of locoregional RT

Ebner, P.J. 2019	Systematic Review (85 case reports) *(Level V)*	BIA-ALCL	**Pathology:** • CD30+ IHC, large anaplastic cells on cytology, and clonal expansion on flow cytometry • Fine needle aspiration should then be combined with flow cytometry **Treatment:** • Complete surgical excision of the implant and capsule • Additional chemotherapy if the disease found to have spread outside the capsule

Kalyon, H. 2019	Case Report
	
	(Level V)
		BIA-ALCL
		Macro-textured silicone gel implants
			Case:
			-Diagnosed with left-sided invasive ductal carcinoma
			• Treated with neoadjuvant chemotherapy + mastectomy and axillary lymph node dissection of the left side and nipple sparing mastectomy of the right side
			• Macro-textured silicone gel implants and fat grafting
			• Adjuvant chemotherapy
			-5 years later Ultrasound and MRI revealed effusion in the fibrous capsule surrounding the breast implant
			• Initial evaluation of the effusion was benign
			• The implant was replaced by another one after partial capsulectomy
			• Seroma recurred
			  • Third sampling: IHC analysis revealed typically large and pleomorphic CD30-positive hallmark cells
			  • Diagnosed BIA-ALCL (Ann Arbor stage 1E, TNM stage 1A)
			  • Complete excision of the breast implant and capsule

			no capsule invasion reported by pathology
Ben Naftali, Y. 2019	Case series *(Level V)*	BIA-ALCL	- 4 cases with textured implants for 7-14 years **Pathology:** • Initial workup included ultrasound and cytology evaluation for the fluid collection • All CD30 positive, ALK-1 negative, histological examination presented abnormal morphology with large anaplastic cells **Treatment:** • Bilateral breast implant removal and capsulectomy • No further adjuvant chemotherapy or radiotherapy was needed
Yim, N. 2019	Case report *(Level V)*	BIA-ALCL	**Case:** - Bilateral breast reconstruction following mastectomy for breast cancer→Textured silicone gel breast implants inserted **Treatment:** - Removal of right breast implant and total capsulectomy **Pathology:** • ultrasound guided aspiration revealed 650 ml of cloudy yellow fluid; cultures negative • Histological studies of the removed capsules: BIA-ALCL that involved the capsule but not extending to the surrounding breast tissues no other info provided
2018			
Clemens, M.W. 2018	Continuing Education Module *(Level V)*	BIA-ALCL	**Pathology:** • Morphologic evaluation by a pathologist and determination of clonal expansion on flow cytometry are critical to diagnosis -Monoclonal T-cell expansion of large anaplastic (Reed Sternberg-like) cells that express CD30 within a periprosthetic effusion or mass aggregate
Collins, M.S. 2018	Retrospective study *(Level IV)*	Early stage (n=65) vs advanced BIA-ALCL (n=39)	**Advanced disease:** Bilateral disease (n=7), Lymph node and organ metastasis-stage IIB-IV (n=24), Disease-related death (n=8) **Treatment type for advanced disease:** complete surgery (n=16, 55.2%), limited surgery (n=19, 65.5%), chemotherapy (n=26, 89.7%), salvage chemotherapy (n=11, 37.9%), radiation (n=15, 51.7%), autologous stem cell transplant (n=6, 20.7%) **Complete remission:** bilateral (4/7, 57%, p<0.001), lymphadenopathy (16/24, 67%, p=0.128) **Definitive surgery:** early-stage (88%) vs advanced (59%); p=0.001 **Mean time to definitive surgery:** early stage (8 months) vs advantaged (21 months); p=0.028 **Rate of complete surgery:** Advanced (59%) vs early stage (88%), p=0.004
Mehta-Shah, N. 2018	Review *(Level V)*	BIA-ALCL	**Pathology:** • Cytological examination of the fine needle aspiration specimen • large volume of fluid (at least 10mL but ideally >50mL • Communicate with pathology the concern for BIA-ALCL • Include smears or cytospin preparations to assess cytology of cells in effusion, paraffin-embedded cell block for morphology and IHC and a cell suspension (where possible) for flow cytometric immunophenotyping

			• neoplastic cells of BIA-ALCL: large, pleomorphic cells with irregular cell membranes, abundant, vacuolated cytoplasm, and large polymorphic, frequently multilobate nuclei and prominent nucleoli • cytological features overlap other malignant conditions (high-grade breast cancer) • need immunophenotyping (IHC) and flow cytometry • neoplastic cells strongly and uniformly express CD30 with a membranous and Golgi pattern, frequently CD4, but often lack expression of other T-cell-specific markers (CD3, CD5) and lack ALK • If BIA-ALCL spreads beyond the implant capsule into adjacent tissues or regional lymph nodes, it cannot be distinguished from systemic ALK-negative ALCL by morphology, immunophenotype, or genetic features alone. **Management:** • Localized Disease: therapy: surgical removal of the implant, total capsulectomy, and complete removal of any disease or mass with negative margins • Advanced Disease (stage II-IV): surgery (mass, lymph nodes), systemic therapy per NCCN guidelines (CHOP or CHOEP or brentuximab vedotin). • RT for unresectable disease (24-36 Gy) • Advanced BIA-ALCL with a history of prior chemotherapy (significant anthracycline exposure): modified CHOP-based regimen like CEOP (cyclophosphamide, etoposide, vincristine, prednisone) can be considered • Advanced relapsed disease who have been treated with systemic therapy: treated similarly to those with recurrent ALK^- ALCL • patients who experience systemic relapse after localized therapy can be treated similar to those with newly diagnosed systemic ALCL
Pastorello, R.G. 2018	Case report *(Level V)*	BIA-ALCL in Li-Fraumeni patient	**-**Paget disease of the nipple→ underwent modified radical mastectomy followed by prophylactic contralateral mastectomy and bilateral reconstruction with silicone implant • microinvasive carcinoma in the background of high grade ductal carcinoma in situ -7 years later: right sided recurrent breast swelling, ultrasound imaging showed fluid collection adjacent to implant, fine needle aspiration showed no signs of malignancy • sent for MRI: 6 cm heterogenous mass with contrast peripheral enhancement, adjacent to the implant fibrous capsule in right breast, large lymph nodes of the ipsilateral axillary and internal mammary chains • biopsy taken, pathology: • 10% buffered neutral formalin fixed and paraffin embedded • routine staining with H&E and additional sections were submitted to immunohistochemical phenotyping • antibody panel included: (AE1/AE3), epithelial membrane antigen (EMA, E-29), CD45/CLA (RP2/18), CD20 (L26), PAX5 (SP34) CD2 (MRQ-11), CD3(2GV6), CD4(SP35), CD5 (SP19), CD7 (CBC37), CD8 (SP57), CD30 (Ber-H2), CD68 (KP-1), ALK (ALK01), TIA1 (C-20) and Ki-67 (30–9) • results:

			• H&E showed infiltration of the capsule's fibrous tissue by a dense population of granulocytes (especially eosinophils) interspersed with large atypical lymphoid cells (moderate pleomorphism, high nuclear to cytoplasmic ratio and easily found mitotic figures; some exhibited eccentric kidney-shaped nuclei, with homogeneous eosinophilic cytoplasm) • atypical cells showed strong and diffuse expression of CD30 on immunohistochemistry • CD2, CD3, CD4, CD5 were at least focally positive in malignant cells • CD7 more extensively deleted • CD8 negative • P53 extensively expressed by atypical cells • Ki-67 proliferation index was high (80%) • no expression of AE1/AE3, CD20, PAX5, CD68, ALK and TIA-1 • treatment: right modified radical mastectomy with breast implant excision and axillary region dissection followed by systemic therapy (no details given)
Patzelt, M. 2018	Case report *(Level V)*	BIA-ALCL	-Transgender male to female underwent bilateral breast augmentation with textured silicone gel filled implant - 7 years later • 5 cm tumorous mass in her left breast • MRI revealed ruptured implant and a tumorous mass penetrating into the capsule and infiltrating the pectoral muscle • Treatment: • implant, silicone gel and capsule were removed; mass resected together with part of the pectoral muscle • standard chemotherapy for systemic ALCL (6 cycles of CHOP-21) • Pathology: • smears taken during operation: negative for aerobic and anaerobic cultivations, tuberculosis and actinomycosis • H&E staining: tumor cells with vesicular nuclei and prominent nucleoli, which are disco hectically organized • excised capsule revealed infiltration with malignant lymphocytes highly positive for CD30 and CD4 and also diffuse expression of cytotoxic markers perforin and granzyme B; negative for B-cell markers CD20 and PAX5 and also lacked expression of CD45RO, CD3, CD8 and ALK1
Quesada, A.E. 2018	Review *(Level V)*	BIA-ALCL	**Pathology:** • In Wright–Giemsa or May–Grünwald–Giemsa stained slides shows highly cellular specimens composed of a homogeneous population of non-cohesive large cells with irregularly lobated nuclei, prominent nucleoli and abundant cytoplasm • Cells are typically four to five times larger than a small mature lymphocyte

			• Cytoplasm is clear or light blue, usually containing scattered small vacuoles, and the cellular outlines demonstrate cytoplasmic fragmentation (Less frequently, the cytoplasmic vacuoles are abundant and confluent giving the neoplastic cells a signet ring appearance) • Background is granular or fibrinoid, sometimes with karyorrhectic debris • Lymphoglandular bodies are not typically seen • Inflammatory cells in the background are variable, and can range from few to abundant small lymphocytes, neutrophils, histiocytes or eosinophils • The Papanicolaou stain demonstrates similar features to Wright–Giemsa • nuclei appear more hyperchromatic and nuclear lobation can be more apparent • prominent nucleoli are common • cytoplasm appears opaque, basophilic, or cyanophilic • Immunophenotype • determined by IHC • CD30 is expressed in all cases • Other markers frequently expressed in breast implant ALCL are CD43 (~80%), CD4 (~80%), TIA-1 (~69%), granzyme B (~68%), epithelial membrane antigen (~60%), CD3 (~33%), and CD8 (~10%) • ALK negative • Negative for CD1a, TdT, and cyclin D1 **Management:** • complete capsulectomy with removal of implants and all evidence of disease • Chemotherapy for non-resectable cases • Cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP and CHOP-like)
Rastogi, P. 2018	Review *(Level V)*	BIA-ALCL	**Pathology:** • Histopathologic assessment must involve cytological examination of seroma fluid and tissue histology • Diagnosis requires a minimum of a suitable flow cytometry panel and tissue immunohistochemistry • Diagnosis confirmed b presence of large anaplastic cells with uniform expression of CD30 and the absence of ALK protein expression • BIA-ALCL may appear as individual cells, cell clusters or as coherent sheets **Management:** -T1-T3 disease is considered curable with surgery alone • Total capsulectomy and excision of any associated capsular mass with negative surgical margins • strict oncologic technique (specimen orientation sutures, change of instruments if performing contralateral explantation • complete posterior capsulectomy may be technically challenging with subpectoral or dual-plane implants • Explantation of the breast implant

			• consider removal of the contralateral implant (~4.5% of cases have demonstrated incidental ALCL in the contralateral breast) • Excisional biopsy of suspicious lymph nodes • fine needle aspiration may yield false negative results (given focal localization of lymphoma in most cases with lymph node involvement) -Adjuvant • Extended disease with lymph node involvement warrants adjuvant chemotherapy • NCCN supports using an anthracycline-based regimen (CHOP or alternatively using brentuximab vedotin • NCCN suggests radiation therapy to the chest wall may be used for local residual or unresectable disease in the salvage setting
Shine, J.J. 2018	Case Report *(Level V)*	BIA-ALCL	-Previously presented with right breast capsular contracture following prior breast augmentation • original saline implant replaced by anatomical textured silicone implants -10 years later • Presents with rapid painful enlargement of the left breast • ultrasound imaging shows seroma • fine needle aspiration fluid sent for bacterial culture, cytology, flow cytometry and cell block analysis • shows diffuse proliferation of CD30-positive cells • diagnosed BIA-ALCL • **Treatment** • bilateral implant removal, total capsulectomy of left breast and immediate bilateral replacement with smooth silicone implants • Capsule housed evident seroma (about 100 cc), 30 cc sent for bacteriology, cytology, and flow cytometry • Capsule and implant sent en bloc for pathology (right implant sent as well) • mitoses were frequent • no tumor infiltration of capsule and peri-prosthetic mammary tissues • expression of CD3, CD5, CD30, EMA, Granzyne-B, bcl2, bcl6, c-myc, MUM1 and Ki-67 • no expression of ALK1, CD20, CD79A, PAX5 and EBER-probe
2017			
de Boer, M. 2017	Case report *(Level V)*	BIA-ALCL	-Transgender woman received bilateral breast augmentation with silicone-filled textured implants -patient subsequently underwent multiple revisional breast surgeries to treat unexplained pain and low-grade fever, severe capsular contracture (Baker grade III-IV), and implant rupture -20 years after first surgery: patient presented with rapid enlargement of the left breast • Treatment: • unilateral explantation (textured, gel filled) and complete capsulectomy • Seroma fluid and capsular tissue sent for analysis

			• Pathology
			  • presence of small collection of atypical lymphoid cells adherent to the inner surface of the fibrous capsule
			  • large atypical lymphoid cells were abundant in the seroma fluid
			  • immunocytologic results on the cytological preparations
			  • positive for CD30, CD2 and CD3
			  • negative for CD4, CD8, TIA1, granzyme B, ALK1, EBER and B-cell markers
			-retrospectively analyzed all available histologic specimens: absence of lymphoma localization at that time

Kaartinen, I. 2017	Review *(Level V)*	BIA-ALCL	**Pathology** -Cytologic analysis is crucial for diagnosis -All cases of late periprosthetic effusion should be screened for BIA-ALCL. -Aspiration is indicated, and pathology examination should first and foremost exclude ALCL by staining for CD30. -Biopsy is not recommended as the first step, but in cases in which implant removal is performed, the gross and histopathologic examination of the capsule for possible ALCL is pertinent for diagnosis and detection of infiltrative growth. -If lymph node enlargement is detected, an excisional biopsy of the enlarged lymph nodes is recommended for further pathologic examination. -Fresh, unfixed abundant cytologic (e.g. whole aspirate) or tissue specimens are recommended for pathology to enable full chromosomal and immunophenotypic analyses -Cytologic diagnosis based on identification of large pleomorphic lymphoid cells with characteristic immunophenotype by flow cytometry and IHC -Histopathology may demonstrate BIA-ALCL as individual cells, cell clusters in aggregates, or coherent sheets lining the capsule surface, or an infiltrative phase. -Neoplastic cells are CD30 positive with frequent co-expression of EMA and incomplete cytotoxic T-cell phenotype (CD4 + 80%–84%, CD43 + 80%–88%, CD3 + 30%–46%, CD45 + 36%, and CD2 + 30%). -Expression of CD5, CD7 or CD8 is rare. -ALK staining is consistently absent. CD15 and PAX-5 may be positive, which can cause differential diagnostic problems to classical Hodgkin lymphoma especially in the infiltrative BIA-ALCL subtype. -T-cell receptors are often rearranged. Nuclear pSTAT3 expression is common, suggesting a constitutive activation of STAT3 **Treatment** -Often curable with surgery alone -Mainstay of treatment: complete removal of prosthesis and the capsule with negative margins -Infiltrative cases (T3-4), the extracapsular mass should also be excised with negative margins -Lymph node involvement: affected lymph nodes should be removed according to current understanding (role of lymph node clearance remains unclear)

			-sentinel node biopsy is not currently recommended -Presence of breast mass or lymphoma that spread beyond capsule may indicate more aggressive clinical course -Among patients with proper surgical excision, the rate of events is 0% for T1-T2 patients and 14.3% for T4 patients; median overall survival is 12-13 years; overall and progression-free survival are similar whether or not patients receive chemotherapy after surgery -implantation of new breast prosthesis is not recommended after BIA-ALCL has been diagnosed -When chemotherapy is used alone, relapse occurs in 54.5% thus alone it is not sufficient -In advanced BIA-ALCL cases, chemotherapy should be considered (most common protocol CHOP regimen, and the addition of etoposide) -RT recommended for the treatment of local residual disease that cannot be surgically resected (30.6 Gy in 17 fractions) -Most commonly used treatment and the only globally approved salvage treatment for relapsed ALK-negative lymphoma: anti-CD30 antibody conjugate brentuximab vedotin -Some BIA-ALCL patients have undergone auto-SCT but long term results have not yet been reported

Leberfinger, A.N. 2017	Systematic Review (115 included articles)
	
	(Level III)
		BIA-ALCL, n=95	-30 review articles, 44 case reports or series, 15 original articles, 26 “other” articles
			-**Assessment/Pathology**
			• fine needle aspiration
			• cytological analysis of peri-implant fluid shows large pleomorphic, epithelioid lymphocytes with abundant cytoplasm and as eccentric, kidney-shaped nucleus with prominent nucleolus
			• IHC used to confirm the diagnosis (CD30 positive, epithelial membrane antigen positive and ALK negative)
			• T cell antigen expression is variable (most frequently expressed markers being CD4, CD3, CD45, CD2
			-**Treatment**
			• Indolent course: complete capsulectomy and removal of implant
			• More advanced disease (tumor mass, lymph node involvement, distant disease)
			  • CHOP chemotherapy with or without radiotherapy or both.
			  • 6 cycles of CHOP are recommended
			  • other preferred regimens include: cyclophosphamide, hydroxydaunorubicin, vincristine, etoposide, and prednisone (CHOEP) and dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and hydroxydaunorubicin(EPOCH).
			  • Brentuximab vedotin, an antibody-drug conjugate directed to CD30, has also gained favor for systemic therapy.

O’Neil, A.C. 2017	Review *(Level V)*	BIA-ALCL	-IHC consistently identifies CD30, variable but commonly includes CD2, CD3, CD4, CD43, CD45 -Surgical management must adhere to strict principles • removal of implant, complete capsulectomy • wide resection of any extracapsular disease to clear margins • sentinel lymph node biopsy of limited value

			- role of chemotherapy and radiation is less well defined, reserved for recurrent or more invasive and metastatic disease
2016			
Clemens, M.W. 2016	Retrospective Study *(Level IV)*	BIA-ALCL, n=87	Follow Up (med): 45 months (range 3-217 months) OS (med): 13 years OS: 3 yrs (93%) and 5 yrs (89%) EFS: both 3 yr and 5 yr 49% -patients with lymphoma confined by capsule had better event-free survival (EFS) and OS than patients with lymphoma that had spread beyond the capsule (p=0.3) -patients who underwent a complete surgical excision that consisted of total capsulectomy with breast implant removal had better OS (p=0.22) and EFS (p=0.14) than did patients who received partial capsulectomy, systemic chemotherapy, or radiation therapy -Conclusion: surgical management with complete surgical excision is essential to achieve optimal EFS in patients with BIA-ALCL
2015			
Clemens, M.W. 2015	Review *(Level V)*	BIA-ALCL	**Pathology:** -individual cells, cell clusters in aggregates or coherent sheets -strong and uniform membranous expression of CD30 immunohistochemistry -T cell antigens are expressed variably: CD4 (80-84%), CD43 (80-88%), CD3 (30-46%), CD45 (36%), CD2 (30%) -Expression of CD5, CD7, CD8, or CD15 is rare **Treatment:** -surgical treatment requires complete tumor ablation (removal of implant, complete removal of any disease mass with negative margins and a total capsulectomy -excisional biopsies should be performed of any suspicious lymph nodes -inadequate local surgical control may subject patient to the need for adjunctive treatments (chemotherapy or radiation therapy) -surgery should be performed with strict oncologic technique, including use of specimen orientation sutures, placement of surgical clips within the tumor bed, and use of new instruments if performing a contralateral explantation -Role of adjunctive treatments, such as chemotherapy, chest wall radiation, anti-CD30 immunotherapy, and stem cell transplant for advanced disease is under investigation.
Estes, C.F. 2015	Case Report *(Level V)*	BIA-ALCL	**Case:** -Gel breast implantation performed 20 years prior to presentation -Later replaced by saline implants, which leaked 1 year before presentation and were replaced with gel implants - Developed a recurrent fluid collection involving her right breast, a drain was placed and yielded minimal output before being removed 1 week later -Cytology of fluid showed atypical appearing lymphocytes -fluid later reaccumulated and right axillary lymphadenopathy was noted on physical exam (largest node 5.1cm on ultrasound) -Core needle biopsy of the node revealed rare, atypical cells

			-After surgery, diagnosed Ann arbor stage IIE (CT and PET showed residual right axillary lymphadenopathy with FDG avidity) **- Pathology:** - ALCL, ALK-negative demonstrated in the fibrous capsule, cystic fluid, axillary lymph -**Treatment:** - capsulectomy and right axillary nodal excisional biopsy with bilateral implant removal - 6 cycles of cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, vincristine 2mg and prednisone (prednisone required a dose reduction from 100 to 75 mg after the first cycle to minimize hyperglycemia secondary to diabetes mellitus type II) - Pegfilgrastim 6 mg injected each cycle for hematopoietic support - Ciprofloxacin 500 mg BID used daily for bacterial infection prophylaxis - After cycle 2 Tetrahydrocannabinol was administered for treatment of nausea and anorexia - adjuvant RT to right breast, axilla and right supraclavicular nodes to 30.6 Gy in 1.80 Gy fractions
Gidengil. C.A. 2015	Systematic review *(Level IV)*	BIA-ALCL (27 articles)	-54 cases of ALCL in patients with breast implants -Detailed clinical info lacking in many cases - most presented with a seroma (76%) -associated with capsule (48%) -most presented as IE (61%) -all but 1 was ALK-negative -Treatment: chemotherapy (57%) or radiotherapy (48%), stem cell transplants (11%) - about 25% recurred -9% died -**Conclusions:** Despite the typically benign course, many of the cases have been treated with radiation therapy and/or chemotherapy. Increasing awareness of this disease entity among clinicians would be helpful, along with standardizing an approach to diagnosis, staging, and treatment
Hwang, M. 2015	Case report *(Level V)*	BIA-ALCL	**Case:** -multiple bilateral breast augmentation (3 different sizes) -8 years later reports 3 month history of spontaneous swelling of left breast associated with generalized discomfort and pain -**Pathology:** • aspiration cytology: degenerate, large atypical cells with prominent mitotic figures • Post-surgery histology confirmed features of ALK-negative ALCL of T-cell phenotype arising from, and confined within, the implant capsule -**Treatment:** • Surgery • well-formed capsule and a stringy proteinaceous seroma • firm plaque of tumour confined to the inner surface of the capsule • implant removed intact but it was partially enveloped in a developing second capsule

			• contralateral right implant removed intact but no capsulectomy was performed on this side
2014			

Hart, A.M. 2014	Case series and lit review
	
	(Level IV)
		BIA-ALCL, n=2	**Case1:**
			-9 years after bilateral submuscular breast augmentation with textured silicone implants
			-Percutaneous fluid aspiration produced 200ml oof clear yellow fluid
			-Pathology:
			• flow cytometric immunophenotyping of the aspirate
			  • phenotypically aberrant population of large cells
			  • expressed CD2, CD5, CD4, CD30
			  • did not express CD3 or CD7
			• immunohistochemical staining with H&E
			  • negative for ALK-1
			• After treatment: implants and capsules sent for flow cytometry and cytogenetic analysis
			  • immunohistochemical staining did not show any unique cell populations
			-Treatment:
			• bilateral total capsulectomy and implant removal without implant replacement
			Case 2:
			-Bilateral breast augmentation with textured silicone implants 16 years before presenting with acute enlargement of the right breast
			-**Treatment:**
			• bilateral capsulectomies and implant removal
			-**Pathology:**
			• Before surgery: Ultrasound-guided aspiration showed CD30 positive, ALK negative ALCL
			  • Cells positive to CD45, CD5, CD4 but didn't express CD34, CD20, CD68 or CD10
			• After surgery: Flow cytometry, cytogenetic analysis and immunohistochemical staining
			  • no unique cell populations
			Lit Review:
			- 63 cases of BIA-ALCL (including our 2 patients) were identified.
			-Forty patients had capsulectomy, 7 of whom underwent implant replacement.
			-Of the 44 patients with known treatment, 33 received chemotherapy and 23 received radiation.
			-**Conclusions:** although most cases have an indolent clinical course, the variety of presentations defined as "seroma" vs "capsular involvement" emphasizes the importance of investigating a definitive method of diagnosis, management, and treatment of this disease.

Miranda, R.N. 2014	Retrospective Study *(Level IV)*	BIA-ALCL, n=60	**Treatment:** • Capsule excised in 56 patients; capsule left in place for 4 patients • Mastectomy in 5 patients • plus axillary lymph node dissection in 5 patients • no surgery in 4 patients

			• Chemotherapy in 39 patients: CHOP (n=30), CHOEP (n=1), CHOP and ICE (n=3), CHOP, ICE and CY (n=1), Hyper-CVAD(n=1); number of cycles 6 (n=22), 5 (n=1), 4 (n=1), 3 (n=4)
			• RT in 31 patients
			• Chemotherapy plus radiation in 26 patients
			• SCT in 8 patients
			Pathologic Findings
			• histologic examination revealed tumour confined within capsule in 42 patients
			  • ALCL cells were present as small clusters within the effusion and/or lining the fibrous capsule, but without growth as a distinct tumor mass
			• in 18 patients, a distinct mass of tumour cells was found within the thickness of the capsule or beyond the capsule
			  • confluent sheets or loose clusters of ALCL cells with a variable amount of necrosis or sclerosis
			• In both subsets the lymphoma cells were large and anaplastic and included cells with horseshoe-shaped nuclei
			• all tumours were uniformly and strongly positive for CD30 and had a T-cell immunophenotype
			• all tumours tested for ALK were negative

2013			

Parthasarathy, M. 2013	Case Report
	
	(Level V)
		BIA-ALCL	-Bilateral breast augmentation with silicone breast implants 8 years before presentation
			-Presented with discomfort and hardening of the left breast
			-Interestingly, had presented to the breast clinic with vague left breast symptoms 3 years previously and had seroma fluid aspirated from the left breast
			-Clinical exam: vague mass measuring 5 cm with palpable axillary lymph nodes, bilateral capsular contracture (left worse than the right)
			-Mammogram: 4 cm mass with enlarged axillary lymph nodes
			-Ultrasound: large irregular hypoechoic mass, adjacent to implant, measuring 4 cm and relatively vascular; multiple enlarges axillary lymph nodes suggestive of metastasis were also seen
			-US-guided biopsy of both breast mass and axillary lymph nodes
			-**Pathology:**
			• core biopsies showed numerous, large, mitotically active pleomorphic cells with abundant cytoplasm
			• majority were mononuclear with occasional bi-nucleate and multinucleate cells
			• IHC: excluded breast carcinoma (negative for cytokeratins CAM 5.2, AE1/3 and CK7) and malignant melanoma (negative for melanocyte markers S100, HMB45 and melan A)
			  • cells negative for leukocyte common antigen and CD45 and did not express CD20
			  • strong staining for CD30 and CD4 and focal staining for CD15 but not CD3
			  • negative for EMA and ALK

			-Diagnosed ALK protein negative-ALCL of the breast
			-CT showed low attenuation lesion in the liver
			-PET-CT scan confirmed macroscopic. metabolically active, FDG-avid 100x60 mm mass in the left breast, and left axillary lymph nodal disease but no malignant liver lesions
			-Treatment:
			• 2 cycles of first-line chemotherapy using cyclophosphamide, doxorubicin, vincristine, and prednisone
			  • repeat PET-CT scan showed a persistent 100x 60 mm mass within the left breast, unchanged from the previous PET-CT
			• second-line chemotherapy (cisplatin and gemcitabine)
			  • repeat PET-CT scan confirmed axillary lymph node resolution but progressive disease in the left breast measuring 120x 80mm
			  • repeat core biopsy of the breast mass confirmed persistent ALK negative ALCL
			• Left mastectomy (including pectoralis major muscle fibers) and removal of the breast implant and an axillary clearance→ clear margins
			Adjuvant treatment completed with radiotherapy to the chest wall, 40 Gy in 15 fractions over 3 weeks
			  • no sign of local recurrence 3 months post surgery.

Thompson, P.A. 2013	Systematic review and mini-meta-analysis
	
	(Level IV)
		BIA-ALCL, n=49 cases	**Pathology:**
			• All 35 cases (those with data) strong membrane expression of CD30
			• 22/26 shower a CD4+ phenotype, with only 2/20 being CD8+ (both of which were aberrantly co-expressed with CD4)
			• frequent loss of expression of mature T cell markers CD2, CD3, CD5 and CD7, with CD7 being expressed in only 1/14 cases)
			• 19/23 were positive for CD43
			• 9/23 having lost CD45 expression
			• CD3 expression was negative in all but three cases, while Pax-5 was universally negative
			• Cytotoxic markers such as TIA-1 and granzyme B were positive in some but not all
			• TCR gene rearrangement studies were monoclonal in 18/19 cases
			• no identifiable immunophenotypic differences between patients presenting with effusion alone compared to those presenting with a mass lesion
			Treatment:
			• 38/42 had immediate surgical removal of the implant, while 4 underwent treatment without initial implant removal
			• 8/41 had no further treatment after surgical removal
			• 33/41 had further treatment after implant removal:
			  • 16 had chemotherapy alone (most commonly CHOP 13/16, remaining 3 not stated)
			  • 3 had RT alone
			  • 14 has combined chemoradiotherapy

			• in 1 patient the combined therapy included an upfront autologous stem cell transplant
			• Clinical response and Follow-up
			  • 32 had follow up data available
			  • 27 achieved CR with initial therapy
			  • lack of initial surgical implant removal was strongly associated with failure to achieve CR (p=0.002 Fisher's exact test)

ALCL, anaplastic large cell lymphoma; A-CHP, adcetris (brentuximab vedotin)- cyclophosphamide hydroxydaunorubicin prednisone; BIA-ALCL, breast implant-associated anaplastic large cell lymphoma; BID, twice a day; BV, brentuximab vedotin; BV-CHP, brentuximab vedotin- cyclophosphamide hydroxydaunorubicin prednisone; CEA, carcinoembryonic antigen; CHOEP, CHOP and etoposide; CHOP, cyclophosphamide hydroxydaunorubicin oncovin prednisone; CR, complete remission; CT, computerized tomography; CVAD, cyclophosphamide vincristine doxorubicin dexamethasone; CY, Cytoxan; daEPOCH, etoposide phosphate prednisone vincristine sulfate (oncovin) cyclophosphamide, doxorubicin hydrochloride (hydroxydaunorubicin) and rituximab; EFS, event-free survival; H&E, hematoxylin and eosin; ICE, ifosfamide carboplatin etoposide; IHC, immunohistochemistry; MDT, multidisciplinary team; MRI, Magnetic resonance imaging; *NCCN, national comprehensive cancer network; O'C, O' clock; OS, overall survival; PET, positron emission tomography; PET-CT, PET- computerized tomography; PFS, progression free survival RT, radiation therapy; SCT, stem-cell transplantation; US, ultrasound.*

Table 4: What literature exists on Breast Implant Illness?

Author, year	Study Type *(level of evidence)*	Patient Characteristics (n)	Outcome
Cohen Tervaert,J.W. 2022	Review *(Level V)*	Silicone breast implants	**Two Hypothesis on the development of BII:** (a) 'Adjuvant hypothesis': activation of the immune system by silicones that are leaked (known as silicone 'bleeding') and/ or spread into the body after rupture of the implant. (b) The 'psychosomatic illness hypothesis'. Patients have mental health issues where SBI act as a nociceptive stimulator. -We should be using the term ASIA (autoimmune/autoinflammatory syndrome induced by adjuvants) due to 'silicone incompatibility syndrome' -BII is too nonspecific -Mental health issues in SBI patients are secondary to BII/ASIA -Patients with a history of allergy are at risk of developing BII/ASIA -Patients with established autoimmune disease or a familial predisposition to autoimmune disease are at risk of developing BII/ASIA **Conclusion:** "there is a causal association between SBIs and BII/ASIA. Using data derived from patients with BII/ASIA and from other medically implanted devices, there appears to be clear pathogenic relationship between SBI and BII/ASIA. Breast implants cause characteristic systemic reactions in certain women, leading to symptoms of sufficient severity to warrant device removal. The morbidity suffered is variable. SBI removal resolves the symptoms in most women, and removal is the most effective treatment."
Rohrich 2022	Special Topic Article *(Level V)*	BII or related conditions (11 studies)	**Key points:** -a subset of BII patients respond to implant removal, while others do not. • response varies over time, with some recurring 6-12 months later -BII management trends have evolved over the past 30 years, empirically mirroring that of the unrelated condition BIA-ALCL -Breast augmentation patient report higher nonspecific systemic symptoms at baseline, irrespective of specific diagnosis.
McKernan, C.D. 2021	Review *(Level V)*	Breast Implants	**Connective Tissue illness:** -no association between silicone breast implants and risk of connective tissue diseases **BII:** Poorly understood collection of systemic symptoms that may be linked with breast implants -providers should refer patients to plastic surgery for discussion of the risks and benefits of potential explantation
Adidharma, W. 2020	View Point *(Level V)*	Breast Implant Illness	- exponential increase in search popularity in early 2019 (google) - positive correlation between tweets per week involving #breastimplantillness and google trends • 11 tweets-50 tweets /week #breastimplantillness

			- A thematic analysis found many tweets concomitantly referenced cancer, breast cancer, BIA-ALCL, and/or lymphoma -All but 1 tweet contained non-evidence-based sources - Our data suggest that the online community is also associating breast implant illness with cancer-related terms, particularly after issuance of the U.S. Food and Drug Administration's BIA-ALCL letter. - short comings: • our sources prevent us from ascertaining users' definitions of breast implant illness • sampling bias may result from deidentified google data, tweets with similar topics from the same user, and use of trending hashtags to increase a tweet's popularity -**Conclusion:** our results do show increasing public interest in breast implant illness. It also suggests that influencers and social media are popularizing breast implant illness and perhaps inadvertently perpetuating misconceptions about breast implant illness and breast cancer. Physicians should be aware of these potential misunderstandings to better address patient concerns while delivering appropriate patient-centered care.
Caracvantes-Coretes 2020	Review *(Level V)*	SBIs	-no literature showing the appearance of a specific immunological disease in patients with SBIs -no case-control studies or reports of patients proving that symptoms of auto/inflammatory syndrome induces by adjuvants (ASIA) occurred after placement of silicone implants nor patients having pre-existing symptoms -Several theories about the effects of silicone on the body -a therapy with greater acceptance: adjuvant effect on silicone on the development of auto immune diseases in genetically predisposed patients - variety of symptoms occurring in patients who develop these pathologies leads to doubts about the relationship between the adjuvant effects of a silicone prosthesis may have with a specific autoimmune disease or a mix of these diseases
Latack, K. 2020	View point *(Level V)*	Transwoman who underwent chest feminization	-388 post on Reddit re: Brest implant Illness and BIA-ALCL -317 posted in 2019-2020 - 3 shared on transgender-specific sub-reddits • 1 newspaper article on textured implants and cancer • 2 were questions about risks of breast implants as they related to breast implant illness - Anecdotal evidence from clinical experience: absence of breast implant illness discussion and presentation in transgender patients - Anecdotal evidence from senior author's clinic: • >200 transfemale patients who have undergone breast augmentation in past 5 years, none mentioned symptoms related to Breast Implant Illness - 2nd author's experience:

			• out of 150 breast implant illness patients, 0 were transgender -Results suggest there are relatively few patients experiencing or discussing Breast Implant Illness among transgender community -May be related to improved gender dysphoria after chest feminization, which may mask symptoms of patients who experience breast implant illness
Jewell, M.L. 2019	Letter *(Level V)*	Breast implant illness	- Patient 1: registered nurse • requested enbloc capsulectomy and implant removal 6 months after successful breast augmentation. • convinced unilateral axillary lymphadenopathy and fatigue she was experiencing was caused by silicone gel implants. • had been on many websites and believed that her symptoms fit into what was described as “breast implant-related illness.” • had not gone to see her doctor • convinced by clinical nurse to see her doctor: confirmed a case of mononucleosis from the Epstein Barr virus - Common thread of a google search and time spent on the internet and social media that promote a link between silicone breast implants and systemic illness. - These sites advocate for enbloc capsulectomy to remove the capsule that contains “toxins” in addition to the implants - Sites also have a referral function to plastic surgeons throughout the world who are willing to perform implant removal with enbloc capsulectomy that is not covered by health insurance -“medicine by belief”: where objective evidence and outcome data are discarded and anxiety leads patients to make irrational treatment choices. -the New England Journal of Medicine published an article by Chang and Lee that promotes the concept of “interpersonal medicine”: a disciplined approach to delivering care that responds to patient’s circumstances, capabilities and preferences that is outside of evidence-based medicine - these 2 terms fit together well especially when linking breast implants to vague systemic illness -if there were benefit from enbloc capsulectomy surgery for the treatment of ”breast implant illness”, someone would have published an outcome series of this in an indexed peer-reviewed scientific journal somewhere in the world during the last 25 years • scientific evidence does not exist to prove benefit -There ARE a variety of high -quality, per-reviewed, scientific studies and meta-analysis of the outcome data from breast implant studies that fail to show an association between systemic illness and silicone breast implants • most common adverse events: capsular contracture and rupture -plastic surgeon remains best source of information and clinical judgement for these patients. When a patient calls, this represents an opportunity to address her concerns and provide scientific education and treatment if a problem exists

Khoo, T. 2019	Retrospective study *(Level IV)*	Silicone Implants presenting with autoimmune disease, n=30	**Duration between breast implantation and initial rheumatology clinic presentation was very variable:** mean 16.1 yrs, range 2-38 yrs **Depression:** n=12 **Fibromyalgia:** n=6 **Chronic fatigue syndrome (CFS):** n=3 - Implant rupture not associated with any of the above(p=1) - there was no difference in the incidence of depression (p=1), fibromyalgia (p=0.76) or CFS (p=0.3) between cases and systemic lupus erythematosus controls - significantly more patients with fibromyalgia and/or CFS in the case group (20.0% of cases vs 2.2% of systemic sclerosis controls, p = 0.01) but no difference in depression (p = 0.12). **Conclusion:** Fibromyalgia and CFS are more common in patients with silicone implants than systemic sclerosis (SSc) controls but not systemic lupus erythematosus (SLE) controls.
Rohrich, R.J. 2019	Special Topic/ Review *(Level V)*	Silicone breast implants	-few medical devices have undergone the degree of scrutiny and speculation that silicone breast implants have -overwhelming evidence to support the safety of silicone breast implants -ongoing studies are strongly encouraged in all these areas (cancer detection to auto-immune disease causes) -to the best of our body of scientific knowledge to date, there have not been any concrete or evidence-based studies or peer-reviewed data concerning the formation of a new syndrome: silicone implant illness
Watad, A .2018	Cross-sectional study (*Level IV)*	Silicone breast implants, n=24 651 SBI-free, n=98604	**Adjusted OR between SBI and any autoimmune/rheumatic disorder:** 1.22 (95% CI 1.18-1.26) **OR between SBIs and Sjögren's syndrome:** 1.58, p<0.001 **OR between SBIs and systemic sclerosis:** 1.63, p<0.001 **OR between SBIs and sarcoidosis:** 1.98, p<0.001 **HR for being diagnoses with at least 1 autoimmune/rheumatic disorder for SBIs vs those without**: 1.45 (95% CI 1.21-1.73) **Conclusion:** convincing evidence is found that patients with breast implants have an increased risk of developing autoimmune diseases
Maijers, M.C. 2013	Descriptive cohort study *(Level III)*	Silicone Breast Implants and unexplained systematic symptoms, n=80	**Total exposure time(mean):** 14.5 yrs (range 2-42 yrs) **Pre-existing allergy:** 75% (metals 4%; food 2%; eczema, hay fever, pollen and dust mites allergy 24%; medicines 17%; latex/rubber/plasters 4%; multiple 24%) **Local symptoms:** 79% of patients (breast pain 51%; capsular contraction 50%; Lymphadenopathy 25%; changed size/form/consistence 25%; lost sensibility 11%; infection 6%; local skin disorders 4%; rotation 1%) **Systemic symptoms:** 100% of patients (fatigue 89%; neurasthenia 74%; joint pian 69%; night sweats 63%; dyspnea 45%; cognitive problems 35%; dermatological symptoms 31%; GI symptoms 30%; alopecia 23%; sleep disorders 19%; depression 4%) **Confirmed autoimmune diseases**: 14%

			Median time after implant of diagnosis: 7 yrs (range 3-30yrs) **Symptom free period:** median 4.5 yrs (range 1 month- 30 yrs) -all woman had 2 major ASIA criteria -79% of woman has ≥ 3 typical clinical ASIA manifestations 36/52 woman experienced a significant reduction of symptoms after explanation
Ahern,M. 2002	Letter *(Level V)*	Women with silicone implants, n=179	**Indications for surgery:** cosmetic (82%), cancer (9%), fibrocystic disease (7%), congenital hypoplasia (2%) **Common Symptoms:** burning breast pain (79%), chronic fatigue (79%), arthralgia (75%), sicca symptoms (56%), night sweats (54%), myalgia (51%) **Findings on clinical examination:** chest wall abnormalities (34%), tender trigger points (17%), carpal tunnel syndrome (3%) **Radiological and/or surgical proof of implant leakage or rupture:** 36% **Signs of implant contractures:** 34% -no evidence of increased occurrence of any connective tissue disorder such as rheumatoid arthritis. systemic lupus erythematosus or Sjorgren's syndrome. -These women found to have as much anxiety as psychiatric patients (using the General Health Questionnaire, and Speilberger State-Trait Anxiety Inventory) -Could be that high anxiety causes maybe related to the reasons these women sought breast implants (poor self-esteem, interpersonal and psychological problems) -high anxiety levels are exacerbated by litigation and media attention
Dush, D.M. 2001	Hypothesis *(Level V)*	Breast Implants	**-**review of literature have found no increased risk of specific systemic disease and no treatment recommendations have emerged - a mass somatization model may also help to discern the potential effects of litigation and other social influences **-**no direct tests of the presumed effect or treatment of somatization processes in women with breast implants **-**there are likely to be symptoms that fall outside this model—for example, the specific local complications of breast implants that occur in a proportion of cases **-**Large scale health related fears, accusations, and litigation have substantial psychological aspects **-**Existing methods of treatment for the broader spectrum of somatization and stress related disorders, combined approaches to behavioral and medical rehabilitation, and the development of new interventions tailored to women with implants, warrant serious consideration.
Vasey, F.B. 1997	Comment on the editorial *(Level V)*	Systematic illness in women with silicone breast implants	-To clinicians who see these symptomatic patients, most of them have a fibromyalgia/chronic fatigue, peripheral neuritis, irritable bowel and bladder syndrome that has not been precisely defined -What is convincing about the association of silicone and rheumatic disease to clinicians who see these patients is the beneficial effect of implant removal without replacement

			-Objective measures such as fever, swollen lymph nodes, and swollen joints improve, as do subjective symptoms of pain and fatigue - Hennekens C.H. study proves that breast implants can make one sick (JAMA 275:616-621, 1996) - The angry macrophage and lymphocytic infiltrate described by Hill, Lendavere and Rose coupled with evidence of widespread silicone/silica debris throughout the patient's body (breast capsule, lymph nodes, blood, skin, synovium) would provide sufficient biologic plausibility (Curr Top Microbiol Immunol 210:123-137, 1995). -Author's advice to symptomatic women with silicone breast implants is to consider having them removed -Anecdotal data indicate that symptomatic women who have their gel-filled implants replaced with saline-filled silicone envelope implants do not do as well as those who do not have them replaced
Hennekens, C.H. 1996	Retrospective cohort study *(Level IV)*	Female health professionals who completed mailed questionnaires, n=395543	-10 830 women reported breast implants. -11 805 reported connective-tissue diseases -compared with women who did not report breast implants, the RR of the combined end point of any connective-tissue disease among those who reported breast implants was 1.24 (95% CI, 1.08 to 1.41, p=0.0015) - The findings for the individual diseases of rheumatoid arthritis, Sjogren's syndrome, dermatomyositis or polymyositis, and scleroderma were of borderline statistical significance (0.05<p<0.10). - The finding for systemic lupus erythematosus was not statistically significant(p=0.44) -No clear trends in RR with increasing duration of breast implants **Conclusions:** These self-reported data from female health professionals are compatible with prior reports from other cohort studies that exclude a large hazard, but do suggest small increased risks of connective-tissue diseases among women with breast implants
Logothetis, M.L. 1995	Qualitative study *(Level IV)*	Women with health problems they attributed to their implants, n=55	-Questionnaire with 10 questions: circumstances leading to initial implantation, understanding risks and benefits, health problems and symptoms, physician response, choices made about implant removal, and psychosocial and emotional consequences -Findings included dissatisfaction with implants, similarity of health problems, and recurrent surgical and nonsurgical procedures -Dominant themes included lack of informed consent, physician denial of health problems, and the decision to remove implants
Bridges, A.J. 1993	Case Series *(Level V)*	Women with silicone breast implants and rheumatic disease complaints, n=156 Controls: women with silicone implants and no rheumatic symptoms, n=12; and women with	- 3 subgroups: joint and muscle pain (n=95), joint selling (n=32), connective tissue disease (n=29) - Most women had normal immunologic studies - Patients with joint swelling had mild, asymmetric, rheumatoid-factor-negative synovitis that did not meet American College of Rheumatology criteria for rheumatoid arthritis -14 patients had a scleroderma-like illness and anti-centromere or anti-PM-Sci antibodies by Western blot -10 patients had a positive Western blot for BB' polypeptide, a small nuclear ribonucleoprotein (snRNP), but did not meet criteria for systemic lupus erythematosus.

		fibromyalgia without silicone implants, n=174	-No autoantibodies to known disease-related polypeptides were detected on Western blot on the control groups -Most women with silicone implants and rheumatic complaints had normal results of serologic tests and nonspecific symptoms, suggesting no serious connective tissue disease -A subset of women had clinical signs and serologic tests that were unusual even for referred patients which suggests some women with silicone breast implants may develop atypical immunologic reactions

AEs, adverse events; ASIA, autoimmune syndrome induced by adjuvants; BIA-ALCL; breast implant associated- anaplastic large cell lymphoma; BII, breast implant illness; CI; confidence interval; CFS, chronic fatigue syndrome; HR, hazard ratio; SBI, silicone breast implant; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; RR, relative risk.

Table 5: What is the role of routine screening for implant integrity?

Author, year	Study Type	Patients Characteristics (n)	Outcome
FDA 2020	Guideline- Breast Implants-Certain Labeling Recommendations to Improve Patient Communication	Patients with Silicone Breast Implants	-Asymptomatic patients: first ultrasound or MRI should be performed at 5-6 years postoperatively, then every 2-3 years thereafter. -Symptomatic patients or patients with equivocal ultrasound results for rupture at any time postoperatively: MRI is recommended - Additional imaging may be required depending on your medical history or circumstances (I.E., screening mammography for breast cancer) * Saline-filled breast implants do not have screening recommendations as rupture is detectable without screening
FDA 2019	Advisory Committee Meeting Notes	General and Plastic Surgery Devices	Remove current FDA MRI screening recommendations and to adopt screening recommendations that begin between years 5 and 6 post surgery, and every 2-3 years after that. -Ultrasound was recommended as an acceptable alternative for screening asymptomatic patients -MRI only for symptomatic patients and patients with equivocal ultrasound results
ACR 2018	Appropriateness Criteria	Patients with Breast Implants	1) Evaluation of saline breast implants: asymptomatic patient, any age, initial imaging • Mammography screening: usually not appropriate • Digital breast tomosynthesis screening: usually not appropriate • US breast: usually not appropriate • MRI breast without IV contrast: usually not appropriate • MRI breast without and with IV contrast: usually not appropriate 2) Evaluation of saline breast implants: clinical examination equivocal for implant rupture. age younger than 30 years, initial imaging. • US breast: usually appropriate • Mammography diagnostic: usually not appropriate • Digital breast tomosynthesis diagnostic: usually not appropriate • MRI breast without IV contrast: usually not appropriate • MIR breast without and with IV contrast: usually not appropriate 3) Evaluation of saline breast implants. Clinical examination equivocal for implant rupture. Age 30-39 years. Initial imaging • Mammography: usually appropriate • Digital breast tomosynthesis diagnostic: usually appropriate • US breast: usually appropriate • MRI breast without IV contrast: usually not appropriate • MRI breast without and with IC contrast: usually not appropriate 4) Evaluation of saline breast implants. Clinical examination equivocal for implant rupture. Age 40 years or older. Initial Imaging • Mammography diagnostic: usually appropriate

			• digital breast tomosynthesis diagnostic: usually appropriate • US breast: May be appropriate • MRI breast without IV contrast: usually not appropriate • MRI breast without and with IV contrast: usually not appropriate 5)Evaluation of silicone breast implants. Asymptomatic patient, any age, initial imaging • Mammography screening: usually not appropriate • Digital breast tomosynthesis screening: usually not appropriate • US breast: usually not appropriate • MRI breast without IV contrast: usually not appropriate • MRI breast without and with IV contrast: usually not appropriate 6) Evaluation of silicone breast implants. Suspected implant complication. Age younger than 30 years. Initial imaging. • Mammography screening: usually appropriate • US breast: usually appropriate • Mammography diagnostic: usually not appropriate • Digital breast tomosynthesis screening: usually not appropriate • MRI breast without and with IV contrast: usually not appropriate 7) Evaluation of silicone breast implants. Suspected implant complication. Age 30–39 years. Initial imaging. • MRI breast without IV contrast: usually appropriate • Mammography diagnostic: usually appropriate • Digital breast tomosynthesis diagnostic: usually appropriate • US breast: usually appropriate • MRI breast without and with IV contrast: usually not appropriate 8) Evaluation of silicone breast implants. Suspected implant complication. Age 40 years or older. Initial imaging. • MRI breast without IV contrast: usually appropriate • Digital breast tomosynthesis diagnostic: usually appropriate • Mammography diagnostic: usually appropriate • US breast: may be appropriate (disagreement) • MRI breast without and with IV contrast: Usually not appropriate -Saline implant rupture is usually clinically apparent, with diagnosis made by physical examination -Silicone implant integrity is best assessed with imaging
NHS 2017	Guideline	Patients with Breast Implants	-NHS Breast Screening Programme is a cancer detection service and does not provide an implant checking service -Women with specific concerns about implant integrity should consult their GP -Screening should not take place

CCA AHS 2017	Guideline	Women with breast implants	-No conclusive evidence to show the potential benefits of asymptomatic breast implant screening outweigh risks and costs to the patients.
John Hopkins Medicine.org	Webpage	Silicone Breast Implants	-Recent silicone implants, whether for cosmetic or reconstruction purposes, require the patient to agree to undergo MRI to assess implant integrity every 3 years
IOM 2000	Report	Silicone Breast Implants	-Insufficient evidence to support systematic implant rupture screening in asymptomatic women -Recommends the use of mammography and ultrasound if signs of loss of implant integrity are observed on clinical examination -MRI recommended in all cases where the mammography and ultrasound results are inconclusive.
Netherlands Health Council, 1999 (Gezondheidsraad) Not English	Report	Silicone Breast Implants	-Recommends setting up of a national registry and the close monitoring of all women with silicone gel breast implants in order to detect any ruptures as soon as possible -No recommendations about the follow-up method or modalities
French agency ANDEM, 1996 Book-no full text (summary of recommendations found here)	Guideline	Silicone Breast Implants	-Sensitivity and specificity off the imaging techniques and the feasibility problems, instituting a systematic imaging-based screening program could not be recommended -A clinical follow -up should be provided, with use made of mammography on a first-recourse basis in order to guide the explantation decision as soon as a rupture is suspected
White Literature			
Pineau, V. 2015	Multicenter, retrospective study *(Level IV)*	Silicone gel Breast implant ruptures, n=130	**Sensitivity:** Ultrasound 0.83 (96 /116) vs MRI 0.92 (81/88) -clinical abnormality led to an imaging assessment in only 19.7% of cases; rupture was mainly discovered during a systematic breast screening (59.8%) or during a preoperative examination for an aesthetic surgery (20.5%) p=0.0291 **Conclusions:** the results suggest that silicone breast implant ruptures may be underdiagnosed. Clinical surveillance does not appear to be a sufficient means in the diagnosis of ruptures. Ultrasound monitoring ± MRI can be offered at 4 years, 7 years and 10 years of implant placement. It does not seem appropriate to propose a systematic implant change without any rupture.
Rietjens, M. 2014	Prospective *(Level III)*	Post-mastectomy patients requiring implant change for aesthetic purposes, n=102 -single lumen silicone gel implants	**Age (mean):** 50 years (range 25-73) **Time to implantation (med):** 57 months (range 6 to 166 months) **Implants Ruptured:**36 implants (27.7%) vs 94 undamaged implants (72.3%) **Sensitivity:** MRI 83% (95% CI, 66 to 93%) vs Ultrasound 69% (95% CI, 50 to 84%) **Specificity:** MRI 98% (95% C, 92 to 100 %) vs Ultrasound 73% (95% CI, 62 to 83%)

			Positive Predictive Value: MRI (94%, 95% CI, 87 to 98%) vs Ultrasound 52% (95% CI, 36-68%) **Negative predictive value:** MRI 94% (95% CI, 87-98%) vs Ultrasound 85% (96% CI, 74 to 92%) **Diagnosis of breast implant rupture overall accuracies:** MRI 94% (95% CI, 88 to 97%) vs Ultrasound 72% (95% CI, 62 to 80%) **Conclusion:** MRI should be considered the method of choice for investigating silicone gel implant rupture in postmastectomy patients, and the standardization of MRI criteria may improve MRI accuracy. The authors suggest a strategy of screening asymptomatic women with ultrasound q1y and with MRI q5y.
Maijers, M.C. 2014	Prospective cohort study *(Level III)*	Poly Implant Protheses silicone breast implants (recalled) who underwent MRI screening, n=112	**Implant time (mean):** 10 years **Chosen Explant:** 107 women **At least 1 ruptured implant**: 29, 27% **MRI correct diagnosis:** 154 intact and 35 ruptured implants **Sensitivity:** 80% **Specificity:** 91% **Positive predictive value:** 69% **Negative predictive value:** 95%
Chung, K.C. 2012	Economic Analysis *(Level IV)*	Silicone gel breast implants	-FDA 2006 recommendation that screening of all women with silicone gel breast implants with MRI 3 years after implantation and q2y thereafter to assess their integrity ***Analysis*** **Ultrasound symptomatic women:** Sensitivity (82%), Specificity (81%), Positive predictive value (68), Negative predictive value (90) **Ultrasound asymptomatic women:** Sensitivity (64%), Specificity (77%), Positive predictive value (19), Negative predictive value (96) **MRI symptomatic women:** Sensitivity (85%), Specificity (90%), Positive predictive value (81), Negative predictive value (92) **MRI asymptomatic women:** Sensitivity (78%), Specificity (71%), Positive predictive value (20), Negative predictive value (97) ***Cost per rupture of screening and management of rupture*** -Ultrasound in asymptomatic women: $1090 -Ultrasound in symptomatic women: $1622 -MRI in asymptomatic women: $2067 -MRI in symptomatic women: $2143 -Ultrasound followed by MRI in asymptomatic women: $637 -Ultrasound followed by MRI in symptomatic women: $2908 **Conclusion:** Screening with ultrasound followed by MRI was optimal for asymptomatic women, and screening with ultrasound was optimal for symptomatic women

McCarthy, C.M. 2008	Review *(Level V)*	Silicone Breast Implants	-U.S. FDA recommends regular MRI for the purpose of screening for silicone implant rupture -Evidence is lacking in support of screening. -Currently no conclusive evidence to show that MRI screening of asymptomatic women leads to a reduction in patient morbidity -Existing data show it's unclear whether screening benefits outweigh the risks and potential costs for the patient -Shared medical decision making is recommended in the face of this uncertainty
Cher, D.J. 2001	Meta-Analysis *(Level IV)*	Silicone Breast Implants 18 studies with n~1039	**Summary Sensitivity:** 78% (95% CI, 71-83) **Summary Specificity:** 91% (95% CI, 86-94) **Odds Ratio:** 40.1 (range, 18.8-85.4) **Conclusion:** MRI is moderately accurate in detecting silicone breast rupture and should remain a confirmatory diagnostic test and no be used to screen asymptomatic women

CI, confidence interval; FDA, Food and Drug Administration; GP, general practitioner; IV, intravenous; med, median; MRI, magnetic resonance imaging; NHA, National Healthcare Association; US, Ultrasound.

Table 6: What is the Canadian take on routine screening guidelines for patients with implants?

<table>
<tr><th>Author, Date</th><th>Study Type</th><th>Patient Characteristics (n)</th><th>Outcomes/Recommendations</th></tr>
<tr><td>Health Canada 2019</td><td>Panel Discussion</td><td>Breast implants</td><td>-The 2005 Canadian Expert Advisory Panel on Silicone Gel-filled Breast Implants advised a six-step process for determining implant integrity should be related to clinical signs and symptoms:
1. patient self-examination,
2. new symptom or sign suspected,
3. physician physical exam,
4. ultrasound, mammogram or both,
5. MRI if ultrasound is negative or inconclusive, and
6. explantation of suspected implant in consultation with surgeon
-Since 2006 when the silicone gel-filled breast implants were approved, this six-step process was included in the Canadian labelling for all silicone gel-filled breast implants
-Health Canada is currently again exploring the feasibility of a national breast implant registry with the Canadian stakeholders under the principles established by the International Collaboration of Breast Registry Activities (iCOBRA)</td></tr>
<tr><td>Quebec 2002: Agence d’évaluation des technologies et des modes d’intervention en santé (AETMIS)</td><td>Report</td><td>Silicone Breast Implants</td><td>-In Quebec:
Systematic, periodic implant rupture screening is not performed in asymptomatic women
Radiologist may examine the integrity of an implant during breast cancer screening
Accessibility to MRI is quite limited, waiting list is a few months to more than a year
Recommendation:
-If there is a clinical presumption of rupture, the course of action should be mammographic examination followed by breast ultrasound
<table>
<tr><th>Technique</th><th>Sensitivity mean % (range)</th><th>Specificity mean % (range)</th><th>PPV mean %</th><th>NPV mean %</th></tr>
<tr><td>Mammography</td><td>25 (5-81)</td><td>97 (82-100)</td><td>88</td><td>63</td></tr>
<tr><td>Ultrasound</td><td>56 (25-100)</td><td>77 (55-96)</td><td>60</td><td>73</td></tr>
<tr><td>MRI</td><td>77 (46-100)</td><td>94 (55-100)</td><td>90</td><td>85</td></tr>
</table>
-if result is normal→ clinical follow-up
-if reveals intracapsular rupture→ keep implants and undergo periodic clinical follow-up
-if reveals extracapsular rupture→ implant removed
-if result is equivocal or suspicious or do not agree with the findings of the clinical examination, MRI is performed.</td></tr>
</table>

	Advantages	Limitations
Mammo	-Rapid and inexpensive -Currently performed on many women of different ages -Very sensitive in detecting extracapsular ruptures; good specificity, low false-positive rate and therefore a lower risk of unnecessary removal	-Risk associated with irradiation -Low sensitivity, risk of false-negative result, that is, of considering a ruptured implant intact -Poor ability to detect intracapsular ruptures, which are more frequent but often clinically silent -Low sensitivity in examining the posterior wall of an implant -Potential cause of intracapsular or extracapsular rupture because of the compression of the breast
US	-Inexpensive -No radiation -Detects intracapsular and extracapsular ruptures -Useful when MRI is contraindicated	-Results depend on the operator and the technique used -Low sensitivity -Lower specificity than mammography -Difficult to examine the posterior wall of an implant
MRI	-No radiation -Very good sensitivity and specificity -Detection of intracapsular and extracapsular ruptures. More accurate determination of the extent of a rapture -Good visualization, in all cases, of the entire prosthesis, especially posterior wall	-Expensive and time-consuming -Low accessibility to scanners -Cannot detect the presence of small quantities of free silicone outside implant -requires the use of surface coils specially designed for breast examinations -Contraindications: pacemaker, aneurysm clips or other metallic foreign objects, and claustrophobia

MRI, magnetic resonance imaging; NPV, negative predictive value; PPV; positive predictive value; US; ultrasound.

Table 7: Mammographic views for implants

Author, Date	Study Type (level of evidence)	Patient Characteristics (n)	Outcomes/ Recommendations
Up to Date 2021	Guideline	Patients with breasts, screening for cancer.	Standard craniocaudal (CC) and mediolateral oblique (MLO) projections of each breast are obtained with the implant included. These views permit evaluation of the implant as well as the deep breast tissues adjacent to the implant. The two views are repeated after the implant is displaced back against the chest wall and the breast tissue is pulled forward (Eklund View)
UpToDate 2021	Guideline	Patients with Implant based breast reconstruction and augmentation	Eklund views (displacement techniques) should be used when obtaining mammograms in augmented patients and should be interpreted by radiologists experienced in the evaluation of augmented patients.
ACR 2018	Guideline	Screening and Diagnostic Mammography	- Evaluation of the augmented breast should include, when possible, standard CC and MLO views as well as implant displaced views in 2 projections - Digital breast tomosynthesis (DBT) may be used in women with implants. Its utility is limited on full views, thus is typically only performed on implant-displaced views
NHS, 2017	Guideline	Breast Implants	All women attending for breast cancer screening that present with breast augmentation must be offered the Eklund technique. The recommended views include the following: -Standard mediolateral-oblique (MLO) views first to establish the position of the implant (subpectoral or subglandular). This will help with decisions about imaging of that client -If the implant is subglandular, perform standard cranial-caudal (CC) views to get as far back onto the chest wall as possible -Perform Eklund CC views to demonstrate the anterior breast tissue with the implant displaced posteriorly -If the implant is subpectoral, it is still considered beneficial to perform both standard CC views and Eklund CC views, the only difference being the implant edge is less likely to be felt during positioning. -If the implant is immobile (encapsulated), a true lateral view may be considered a helpful alternative. There is no evidence to support this as an alternative however and it remains a local decision. Clear guidance should be given by the clinical lead and protocols should be in place prior to undertaking this. It is not acceptable that this view is undertaken instead of the Eklund CC view just as an easier positioning option for the radiographer. -In addition to routine views, the Eklund technique may be used to pull the breast tissue forward and away from the implant to improve breast tissue visualization. However, if the implant feels firmly fixed in position, this technique may not be suitable. Even under ideal circumstances, such as a 'soft' breast and an experienced radiographer, some breast tissue may still be obscured by the implant.
Canadian Association of Radiologists,	Practice Guideline and Technical Standards	Breasts	Mammography -Implant evaluation should include craniocaudal and mediolateral oblique projections, as well as implant displacement views.

2016			- If displacement views cannot be performed due to immobility of the implant, 90-degree lateral images should be added to the standard views
Bondurant et al. 1999	Report	Silicone breast Implants	- The current standard for mammography of women with implants is both a nondisplaced and an implant-displaced view for each of the routine views. - four views per breast: the CC and MLO views in both the implant-displaced and the standard modes - If the capsule is hard and immobile, it may be impossible to perform the implant-displaced views. - The MLO view may be replaced by the 90- degree lateral view if the latter depicts more breast tissue in individual patients. -When there is clinical concern for lesions cephalad to the implant between the 11 and 1 o'clock positions or caudad to the implant between the 5 and 7 o'clock positions, the 90 degree lateral view can be helpful
White Literature			
Shah 2016	Pictorial essay *(Level III)*	Breast implants	-The screening mammogram should include implant displaced (Eklund technique), craniocaudal (CC), and mediolateral oblique (MLO) views, in addition to the standard CC and MLO views -Displacing the implant allows more breast tissue to be visualized than the standard compression views
Uematsu, T. 2008	Review *(Level V)*	Augmented Women	-Implant displacement technique (Eklund technique) in conjunction with the standard implant compression technique has been widely practiced to visualize more of the breast.
Eklund, G.W. 1988	Case Series *(Level V)*	Augmented Breasts, n=50 -excluded: patients with reconstruction after mastectomy	(Eklund technique) -Standard 45 degree mediolateral oblique and craniocaudal views, with the implant included in the compression field, were obtained in similar oblique and craniocaudal projections. -The two-step modified compression technique used for all patients in the study consisted of first pulling breast tissue over and in front of the implant while the compression paddle was applied. -The second step, performed simultaneously with the first, involved posterior displacement and flattening of the implant against the chest wall while compressing breast tissue, with little or none of the implant included under the paddle. -A 90 degree mediolateral view was added for those patients in whom the implant was rigidly encapsulated. -The presence of firm encapsulation was determined by the technologist if not already indicated by the referring physician. -The hard, incompressible character of the encapsulated implant is obvious to the technologist as the patient is positioned. -Encapsulation often prevents adequate compression of the breast tissue and posterior displacement of the implant.

			-When there was clinical concern for lesions cephalad to the implant between the 11 o'clock and 1 o'clock positions or caudad to the implant between the 5 and 7 o'clock position, the 90 degree lateral view was useful. -An additional view was obtained tangential to the areas of clinical or radiographic concern, which were not projected free of the implant on other views. -Focal compression and magnified images were obtained when needed to resolve areas in question and to better evaluate microcalcifications. -Lead markers were applied to the skin surface to identify areas of clinical concern. -Manual techniques were used for all standard views of the breast. Photo timing was used for the modified compression views.

CC, craniocaudal; DBT, digital breast tomosynthesis; MLO, mediolateral oblique.

Table 8: What are the effects of radiation on an implant?

Author, year	Study Type (level of evidence)	Patients Characteristics (n)	Outcome
Oliver, J.D. 2019	Systematic review (11 studies included) *(Level II)*	Post mastectomy radiation therapy (PMRT), n=1565 -before 2-stage expander-implant breast reconstruction, n=1145 -after 2-stage expander-implant breast reconstruction, n=420	• Significantly higher likelihood of infection following pre-implant placement PMRT vs PMRT after implant placement (21.03% vs 9.69%; p=0.000079) • No different in the rate of explantation between pre-implant placement PMRT and postimplant placement PMRT (12.93% vs 11.43%) **Conclusion:** patients receiving PMRT before implant placement in 2-stage expander-implant based reconstruction may have a higher risk of developing an infection
Molinar, V.E. 2018	Case Report *(Level V)*	Late breast implant rupture with seroma and history of prior radiation, n=1	• Cause of implant rupture remains unknown BUT it is very likely that delayed onset fibrosis and capsular contracture secondary to radiation therapy played a role
Ricci, J.A. 2017	Systematic Review and Meta-analysis (20 studies) *(Level IV)*	Implant-based breast reconstruction and PMRT, n=2348 -PMRT to tissue expander, n=1479 -PMRT to permanent implant, n=869	**Reconstructive failure:** PMRT to tissue expander 20% vs PMRT to implant 13.4% (RR=2.33, p=0.0083, 95%CI 1.24-4.35) **Capsular Contracture:** PMRT to tissue expander 24.5% vs tissue expander 49.4% (RR-0.53, p=0.083, 95% CI 0.26-1.09)
Cordeiro, P.G. 2014	Prospective study *(Level III)*	Patients with 2-stage implant-based reconstruction, n=2133 -postmastectomy radiation to the permanent implant, n=319	**Follow-up (mean):** 56.8 months (range, 12-164 months) **Implant loss:** 9.1 % of irradiated implants vs 0.5% of nonirradiated implants (p<0.01) **Grade IV capsular contracture:** 6.9% of irradiated vs 0.5% of nonirradiated (p<0.01) **Predicted implant loss at 12 years:** 17.5% of irradiated vs 2.0% for nonirradiated (p<0.01) **Predicted implant replacement rates at 8 years:** 12.7% irradiated vs 8.8% nonirradiated (not significant)
Kronowitz, S.J. 2012	Review (19 studies) *(Level V)*	Implant-based reconstruction and irradiation, n not stated	• Most recent studies find a significant need for unplanned or major corrective surgery in irradiated breasts reconstructed with implants • Approximately 1/3 of patients develop Baker grade III or IV capsular contracture • Patients who underwent one-stage reconstruction and post mastectomy radiation therapy had a significantly higher need for revision and lower aesthetic outcome score than patients who had 2-stage implant reconstruction with implant placement after radiation treatment • In the setting of postmastectomy radiation therapy, implant-based reconstruction continues to be associated with a higher incidence of major corrective surgery than autologous tissue-based reconstruction
Hvilsom, G.B. 2012	Retrospective study	Delayed breast implant reconstruction, n=717	• Failure: 6% • >90% of failures were due to extrusion of the implant and/or infection

	(Level IV)	1-stage procedures with expandable implants, n=288
		• 49 w/ radiation, 239 without
		2-stage procedures with temporary expanders followed by second implant exchange, n=429
		• 79 with radiation, 353 without
			• In 2 -stage reconstruction failure was higher among radiated women (p=0.06 not significant)
			• In 1-stage reconstruction there was no difference observed between those with and without radiation therapy (p=0.8)
			• In univariate analyses for 1 stage procedures, the risk of severe capsular contracture was significantly higher for the procedures with radiation therapy (10-year risk=20.5%; 95% CI: 14.7-26.3) as compared with those without (10-year risk= 7.0%; 95% CI: 5.3-8.7)
			• In univariate analyses for 2-stage procedures, the risk of severe capsular contracture was significantly higher for the procedures with radiation therapy (10-year risks= 17.1%; 95% CI: 12.8-21.4) as compared with those without 10-year risk= 8.2%; 95% CI: 6.6-9.8)
			• Reoperation was more frequent among radiated than nonradiated women (no statistically significant)
			  • 1 stage: 10-year risk=44% nonradiated (95% CI: 41.5-48.3) vs radiated 52.0% (95% CI: 44.8-59.3)
			  • 2 stage: 10-year risk=31.9% nonradiated (95% CI:29.1-34.8) vs radiated 38.3% (95% CI: 32.7-43.9)
			• In Cox regression analyses a record of radiation therapy was associated with increased risk of both reoperation and severe capsular contracture for both 1 and 2 stage procedures compared with no record of radiation therapy
			• In restricted cohort (questionnaire data available)
			  • Adjusted HR for severe capsular contracture among 1-stage procedures with a record of radiation therapy was 3.3% (95% CI: 0.9-12.4) compared with nonradiated
			  • Risk estimate for 2 stage procedure was 7.2% (95% CI: 2.4-21.4)
			• HR for reoperation after 1-stage procedures with a record of radiation therapy was 1.4 (95% CI: 0.7-2.5) compared with nonradiated, and the corresponding HR estimate for the 2-stage procedure was 1.6 (95% CI: 0.9-3.1)

Roostaeian, J.R. 2011	Retrospective Chart Review
	
	(Level IV)
		Patients who underwent immediate breast reconstruction with silicone implants, n=35
		Radiation before reconstruction, n=4
		Radiation after reconstruction, n=2
			• Radiation before reconstruction:
			  • 3(75%) required revision surgery, 2 were major revisions secondary to complications
			• Post-operative adjuvant radiation treatment
			  • 2 (100%) developed asymmetry: 1 required a change in implant size and the other needed adjustment of the contralateral inframammary fold to achieve symmetry.

Anderson, P.R. 2009	Retrospective Study *(Level III)*	Breast cancer patients who underwent modified radical mastectomy and breast reconstruction followed by RT to either a temporary tissue expander (TTE n=62) or	• Follow-up (med): 48 months • Rate of major complications: PI (0%) vs TTE (4.8%) • Lost the reconstruction: PI (0%) vs TTE (4.8%) • Excellent/good cosmetic score: PI 90% vs TTE 80%; p=0.22

		permanent breast implant (PI n=12), total n=74	**Conclusion:** no significant difference in the overall rate of major or minor complications between TTE and PI group

Wong, J.S. 2008	Retrospective study
	
	(Level IV)
		Modified radical mastectomy, immediate breast reconstruction, postoperative radiation and ≥1 follow-up or procedure ≥2 months after radiation, n=62
		Non-implant, n=47
		Implant, n=15
			• Follow-up (med): 10 months (range: 4-57)
			• Major corrective surgery (MCS): 16% between 1-28 months after radiation (med 8 months)
			  • Non-implant: 4, 9% vs Implant: 6, 40%
			• Of patients followed ≥6 months after RT
			  • Non-implant: 0, 0% vs Implant: 3, 23% (p=0.01)
			• Of patients followed ≥12 months after RT
			  • Non-implant:1, 4% vs Implant: 2, 29%; p=0.12)
			Conclusion: Patients who undergo immediate reconstruction after mastectomy using an implant followed by radiation have a high rate of subsequent major corrective surgery

CI, confidence interval; HR, hazard ratio; MCS, major corrective surgery; med, median; PI, permanent implant; PMRT, post mastectomy radiation therapy; RT, radiation therapy; TTE, temporary tissue.

Table 9: Squamous cell carcinoma and patients with breast implants

Author, year	Study Type (level of evidence)	Patients Characteristics (n)	Outcome
Soni, S.E. 2022	Case Study/Viewpoint *(Level V)*	-46-year-old woman, at 26 weeks gestation, presented with 4 month history of pain and swelling in her right breast -prior breast augmentation with submuscular, smooth, round saline implants and two previous revisions for capsular contracture	**Case:** -Squamous cell carcinoma of the breast implant capsule is even rarer than BIA-ALCL with only 8 cases reported previously in the English-language literature - Cytologic evaluation of a recurrent, complex, periprosthetic fluid collection revealed abundant squamous cells, mostly enucleated, and no CD30-positive lymphocytes -Biopsy of capsular mass was positive for squamous cell carcinoma -Modified radical mastectomy with en bloc excision of the implant and capsule was performed on right breast with SLNB - Final pathological analysis of right breast revealed an ill-defined, firm mass measuring 6x4x3cm • Determined to be well-differentiated squamous cell carcinoma arising from the medial breast implant capsule and invading the adjacent breast parenchyma and skeletal muscle -Implant was intact Mentor smooth, round saline implant -periprosthetic fluid: opaque, tan with pasty, white debris -Capsule was studded with tan-white nodules and had extensive squamous metaplasia and atypia -Breast tissue was benign showing only lactational changes -All sentinel and nonsentinel lymph nodes were negative for metastatic squamous cell carcinoma. -The mass itself was negative for estrogen, progesterone, and HER2-neu receptors. -The patient underwent induction of labor at 35 weeks' gestation to expedite adjuvant chemotherapy and radiotherapy, which she tolerated well. -She was in remission 12 months after initiation of adjuvant therapy. -Patient DID have textured implants at one time -Patient had transaxillary, periareolar, and inframammary incisions used in her previous augmentation and subsequent revisions, putting her at risk for ductal transection, implant colonization with biofilm-producing organisms, and subsequent chronic inflammation, which may have led to squamous metaplasia and subsequent dysplasia -In 2016 at this patient's most recent revision, there was periprosthetic fluid and a mass on her capsule at the same site where her SCC ultimately developed - Reported as benign but no pathology report was available **Breast Implant Capsule- Associated Squamous Cell Carcinoma:** -Shares presenting symptoms with BIA-ALCL: late-onset breast edema in the setting of breast implants present for 15 years or longer.

			-The outcomes for breast implant capsule–associated squamous cell carcinoma seem to be worse than those for BIA-ALCL, with multiple patients having metastases reported within 2 years of diagnosis -The limited published data suggest that this has a much more aggressive pathology with more aggressive surgical management, as well as adjuvant therapy, necessary for disease management
Goldberg, M.T. 2021	Case Study *(Level V)*	Patients with long-standing implants (>10 years), routine pathologic evaluation of capsulectomy specimens revealed squamous cell carcinoma associated with the breast implant capsule, n=2	**Case 1:** -40-year-old healthy woman with no personal of family history of cancer -bilateral breast augmentation with sub muscular 350mL smooth saline implants 11 years before presentation. -presented with sudden onset swelling and erythema of the left breast 10 days after sustaining blunt trauma to her chest, and experiencing clear liquid from her nipple at the time of trauma -Examination: bilateral Baker grade IV capsule with left breast swelling, erythema, and thinning of overlying skin -Pre-op CT: periprosthetic fluid with surrounding inflammatory changes but no other abnormality of the breast parenchyma, chest or lung -At Surgery: both smooth round saline implants intact in subpectoral pockets • Right complete capsulectomy was performed • Left capsule was thickened with surrounding keratinaceous debris and adherent to perichondrium directly over 2nd and 3rd ribs- near complete capsulectomy was performed, leaving behind the posterior portion • Due to magnitude of inflammation new implants were not placed -Pathology from the capsule: acute and chronic inflammation, calcifications, and keratinized squamous metaplasia with focal atypia concerning for carcinoma -4wks later another surgery found extensive granulomatous, keratinaceous material behind the pectoralis major and extending into the axillary region which was not present at the first surgery -Final pathology of the tissue revealed moderately differentiated infiltrating, keratinizing SCC -No occult primary found -MRI and repeat CT scan demonstrated that the mass was separate from the breast parenchyma and was invading the pectoralis minor, chest wall, manubrium, and 4th rib -patient started neoadjuvant chemotherapy with cisplatin and fluorouracil to decrease the tumor burden before chest wall resection -patient developed malignant pleural effusions secondary to invading mass while on chemo and died within 3 months of diagnosis **Case 2:** -62 year old healthy woman with no personal or family history of cancer -Bilateral subcutaneous mastectomies for fibrocystic disease with implant-based reconstruction in 1983

			- Chronic wounds and implant exposure complications - Underwent 8 surgeries before placement of permanent silicone implants without use of autologous flaps in 1986 -2015: presented with right breast swelling and pain for 2 months after falling on her chest -Physical exam: bilateral Baker grade IV capsules with swelling and erythema of the right breast -both implants malposition being costal margin (long-standing) -US revealed 4cm collection consistent with an organized hematoma and intact implants -Due to history of infections and the malposition of both implants, bilateral implant removal and capsulectomies was offered and accepted. -Surgery: - Left breast smooth silicone implant and capsule without signs of inflammation - Right breast: small amount of turbid fluid and an intact smooth silicone implant with a yellow-tinted shell; substantial granulomatous material and calcifications within the capsule in the axillary and posterior portions of the capsule -Pathology of left breast capsule: well differentiated, invasive, keratinizing SCC arising from the capsule lining and invading the basement membrane; granulomatous material from the posterolateral aspect of the capsule showed sheets of well-differentiated SCC. -Workup: breast MRI, thoracic spine MRI, bone scan, positron emission tomography scan, and CT scan of the neck, chest, abdomen, and pelvis failed to demonstrate an occult primary **-R**ecommended treatment: involved neoadjuvant cisplatin and 5-FU to decrease tumor size; Adjuvant radiation therapy was recommended for locoregional control. -This patient underwent concurrent cisplatin 40 mg/m2 weekly and radiotherapy of 50 Gy, both over 5 weeks, with stabilization of the chest mass - after completion of chemotherapy and radiation, the patient declined the planned surgical resection and was offered palliative care. - She was ultimately lost to follow-up
Buchanan, P.J. 2018	Case Report *(Level V)*	65-year-old woman with subglandular bilateral breast augmentation: 200 cc foam-covered silastic implants (Hyer Schulte) 31 years ago	**Presented:** an enlarging left breast after a mechanical fall **Exam:** breast mound about twice the size of the right and extremely tender to palpation **Mammogram**: showed edema vs hemorrhage around the left breast implant with superior extravasation of silicone material **Ultrasound:** circumferential hypoechogenicity concerning for edema vs hemorrhage without a defined mass **Treatment Plan:** complete capsulectomy with implant exchange via an inframammary approach **During surgery:**

			- Periprosthetic milky fluid collection was encountered→ aspirated and sent for ALCL CD-markers and histological examination - Implant capsule and ruptured implant were completely removed and sent for permanent pathology - The posterior capsule was well adhered to the underlying pectoralis major musculature. The implant pocket was thoroughly irrigated, and a new 375 cc saline implant was placed **Pathology:** - Periprosthetic fluid → keratinized squamous cells - Capsule → well-differentiated SCC arising from the fibrous capsule **Follow up 1 month later:** - PET scan showed FDG uptake surrounding the left breast implant, axillary lymph nodes, and internal mammary lymph node chain **Treatment:** - Left radical mastectomy and medial chest wall resection - Postoperative RT 50Gy **Follow up:** - Alive and disease free 8 years (to current)
Zhou, Y.M. 2018	Case Report *(Level V)*	46-year-old female with silicone gel breast implantation for breast augmentation 21 years prior to presentation. The implantation was surgically revised 7 years later and again and 4 years after that.	**Presentation:** - hardening, swelling and pain in her right breast for a year - MRI: showed a large fluid collection surrounding the intact right silicone implant **Treatment:** - Surgical drainage of fluid collection and capsulectomy. - A month later underwent bilateral prosthesis explantation and bilateral capsulectomy. - 4-cm moderately differentiated invasive SCC, extended into the muscle, and in situ tumor was noted to extend to the peripheral margin - There was no perineural or lymphovascular invasion - Pathology of the left breast capsule showed chronic inflammation - CT of chest, abdomen and pelvis revealed absence of metastatic disease - Month later underwent re-excision of the remaining chest wall - well differentiated SCC with negative margins - Chest wall fluid was negative for malignant cells - On slide review, there was squamous epithelialization of the implant capsule with benign squamous epithelium on both sides. (tumor is likely SCC of the implant capsule rather than primary SCC of the breast) - Estrogen and progesterone receptor markers were negative - External beam radiation (supine with free breathing)

			- Four tangent beams were used to target the right breast with 50 Gray in 25 fractions, followed by a 10 Gray boost to the tumor bed delivered in five fractions. - Radiation was delivered using opposed tangents completed - No adjuvant chemotherapy was offered due to the rare histology and paucity of data. **Followed up:** 1 month after RT without complications or clinical recurrence. - CT scan performed 3 months after RT: displayed a right upper lobe lung nodule and findings were suspicious for local recurrence - She underwent right video thoracoscopy and right upper lobe wedge resection. - pathology consistent with metastatic moderately differentiated SCC - patient declined chemotherapy at this time. - CT chest and abdomen at another hospital showed new cavitary lung nodules and right renal and psoas abscess. - 7 months later, retroperitoneal fine needle aspiration of the right renal collection was positive for SCC. - 4 months later, admitted to the hospital for abdominal pain→ was progressive disease. - CT abdomen and pelvis with IV and oral contrast demonstrated a 6.1 cm x 5.7 cm heterogeneous lesion in the right kidney lower pole with invasion into the adjacent right psoas muscle - Progressive metastases to the liver, lungs and retroperitoneum were noted as well. - Ultrasound-guided fine-needle aspiration and core biopsy of the liver was positive for metastatic SCC with keratinization and necrosis. - Her hospital course was complicated by non-ST elevation myocardial infarction, recurrent anemia requiring transfusions, atrial fibrillation with rapid ventricular rate and hypotension. - She was noted to have leptomeningeal spread. - She was ultimately transferred from the medical intensive care unit to the palliative care unit for comfort care. She expired of her disease in July 2017, one year after her initial diagnosis of cancer.
Olsen, D.L. 2017	Case Series *(Level V)*	Case 1: 56-year-old woman undergone bilateral silicone breast implants for cosmesis 28 years prior, replaced both implants with 300-mL textured saline implants 10 years later (18 years b/f presentation) due to capsular contracture	***Case 1:*** **Presentation:** 4-week history of painful, enlarged left breast with associated red purple skin discoloration. **Treatment Plan:** surgical removal of the implants **Surgery:** - Both implants were intact. - Large volume of thick white fluid in left breast implant capsule - Mass on the posterior surface of the implant capsule. - Tumor invaded through the capsule into the surrounding breast parenchyma and chest wall skeletal muscle

		Case 2: 81-year-old woman, a wide local excision of a reportedly benign breast mass followed by reconstruction with a silicone breast implant (implant details are not available) 40ish years ago	**Pathologic examination:** - Invasive well- to moderately differentiated SCC associated with focally dysplastic squamous epithelium lining the implant capsule. - Left implant capsule with densely keratinizing squamous epithelialization with areas of hyperkeratosis - Focal squamous dysplasia→increased basal mitoses and nuclear hyperchromasia and atypia, adjacent to invasive keratinizing, well-to moderately differentiated SCC (forming 8 nodules ranging up to 3.5 cm in largest dimension) - No evidence of atypia, or conventional invasive or in situ mammary carcinoma within the breast parenchyma. - Surgical resection margins were negative for tumor. - Multiple (9) sentinel and nonsentinel axillary lymph nodes were negative for malignancy. - Neoplastic cells did not express estrogen or progesterone receptors and were negative for HER2 overexpression or amplification - Clinical (and radiologic staging) was negative for a primary cutaneous site or metastasis. **Further Treatment:** - Multiple cycles of chemo and RT Follow Up: - Within 8 months locoregional metastasis→ biopsy-proven invasive SCC in the subcutaneous soft tissues of the left axilla - Within a year of surgical excision of the axillary metastasis followed by RT and additional chemo→ multiple palpable nodules of biopsy-proven subcutaneous soft tissue metastases occurred in the left upper arm, axilla, and upper chest wall. - At the time of last clinical follow-up, she was being treated with palliative radiation therapy ***Case 2:*** - **Presentation:** acute onset of pain and enlargement of the left breast →a palpable left breast mass adjacent to implant. **Ultrasonographic imaging:** partially cystic 2.9-cm left breast mass with features suggestive of hematoma. -Following an initial short period of conservative therapy, she presented with increased swelling and with an interval growth of the mass to 5 cm. **Surgery:** - Intact implants were removed and biopsy of the mass on the implant capsule - Left mastectomy and sentinel lymph node biopsy - Tumor invaded into the underlying breast parenchyma. **Pathology:**

			- invasive SCC associated with focally dysplastic squamous epithelium lining the implant capsule. - The dysplastic areas showed similar cytologic features to the invasive component - Clinical (and radiologic) staging negative for distant primary site or metastasis - Histopathologic examination revealed 5-cm invasive, moderately differentiated SCC with areas of high-grade sarcomatoid/spindle cell differentiation, centered on the posterior aspect of a squamous epithelialized implant capsule with focal dysplasia - The breast epithelium showed mild proliferative fibrocystic changes but no atypia, or in situ or invasive mammary carcinoma. - Surgical resection margins negative for malignancy. - Multiple (3) sentinel axillary lymph nodes negative for malignancy] - Neoplastic cells negative for estrogen or progesterone receptors and HER2 overexpression or amplification. -The patient received adjuvant RT and chemo **Follow Up:** - At 5 months PET imaging demonstrated FDG-avid masses in the lung and liver, mediastinal and hilar lymphadenopathy, and soft tissues of the leg. - Biopsy of the hepatic mass confirmed metastatic SCC with spindle cell differentiation, confirmed with immunohistochemical cytokeratin 5/6, cytokeratin AE1/AE3, and p63 staining. - Because of poor performance status, she did not receive additional adjuvant chemo and died of disease
van Diest, P.J. 1998	Review *(Level V)*	Patients with silicone implants	Squamous Metaplasia and Carcinoma -Kitchen et al - Described a case with a thin lining of squamous epithelium around a breast implant - Second case shows focally acanthotic and hyperkeratotic squamous epithelium lining around a breast implant, but much of the capsular wall surrounding the implant was lines by strands and nests of cells with pleomorphic and hyperchromatic nuclei, and individual cell dyskeratosis and atypical mitotic figures, which infiltrated the stroma around the capsule but not the surrounding breast tissue - Immunohistochemistry showed strong reactivity for cytokeratin - Lesion interpreted as a poorly differentiated squamous cell carcinoma - There were no lymph node metastases on mastectomy with axillary dissection -Hypothesized that there may occasionally be a proliferation of ductal cells around implant capsules that develop squamous metaplasia in response to chronic irritation from the indwelling breast implant.

			-Squamous cell carcinoma has been known to arise in long standing chronic inflammation in other sites. -Squamous metaplasia may only be focally present and it may thus be missed on routine investigation. -Squamous cell carcinoma seems to be a very rare complication→the extent to which the silicones themselves play a role in the oncogenesis of such squamous cell carcinomas was felt to be unclear
Talmor, M. 1995	Case Study *(Level V)*	70-year-old woman with bilateral breast augmentation 25 years prior tp presentation	**Presentation:** enlarging, mildly painful left breast. Enlargement for past 10 year but rapid growth for 6 months. Internal pulling sensation but no pain. Left nipple became inverted. No discharge or bleeding or change in skin. Right breast lumpy but has always been this way since implants. **Work up:** - Chest x ray: revealed prior benign granulomatous disease and as asymmetry of breast shadows (left more prominent and superiorly positioned) - Mammogram (6 months prior) showed areas of dense homogeneous and nodular shadows but without significant change - Mammogram (current) left breast with large mass replacing virtually the entire breast - Ultrasound: markedly irregular architecture in both breasts without any discrete cystic or solid masses visible - MRI: large fluid filled cyst in left breast, which was of high signal intensity on T2-weighted images and dark on water suppression views. Cyst demonstrated silicone layering out on top of the fluid as well as globules of silicone within the fluid - Physical Exam: Left breast tender, 2x size of right breast. Right breast has multiple irregularities (not hard or fixed). No adenopathy in cervical or axillary regions on right breast. No bleeding or discharge. Skin overlying right breast was unremarkable. Upper 3 quadrants of left breast were substantially enlarged, no discrete mass were palpable. No fixation to chest wall. Left nipple flattened. No skin irregularities. In axilla, multiple soft, moveable nodules were palpable **Treatment**: bilateral simple mastectomy and immediate reconstruction with temporary tissue expanders. Gross exam showed a large fluid filled cyst of the left breast. Both breasts have scarring and multiple, irregularly shaped, silicone-filled cysts and nodules **Pathology:** - Right breast- granulomatous foreign body giant cell reaction associated with refractile foreign material consistent with silicone-induced mastopathy. - Left breast- infiltrating, moderately differentiated SCC with extensive necrosis. - Tumour 8cm at greatest diameter

			- Tumour seemed to be arising from large cyst lined by keratinizing squamous epithelium - No ductal of lobular elements were noted - Nipple and skin- free of disease - Non-neoplastic breast tissue- granulomatous foreign giant cell reaction associated with refractile foreign material consistent with silicone-induced mastopathy **Further Treatment:** left axillary lymph node dissection and deep muscle biopsy. Tissue expanders were exchange for silicone implants. No evidence of disease in lymph nodes or muscles
Kitchen, S.B. 1993	Case series *(Level V)*	Case 1: 42-year-old woman with bilateral breast augmentation with silicone implants 11 years prior to presentation Case 2: 52-year-old with bilateral breast augmentation with 240ml style 2100 Heyer Schlute silicone gel prosthesis 15 years prior to presentation	***Case 1:*** **Presentation:** pain in both breasts for about a year, exacerbated by activity and exercise **Physical Exam:** minimal to moderate firmness of both breasts with no palpable masses **Surgery:** Implants were removed and found to be intact and there were no problems with capsule formation -1 year later patient reported a left breast mass - Physical exam showed 6.0 x6.0 cm solid oval mass in the upper outer quadrant of the left breast - No masses were palpable in the right breast - Mammograms showed bilateral large silicone granulomas - Bilateral breast explorations were performed, and both silicone granulomas were excised with their surrounding capsules **Pathologic Findings:** - Soft tissue mass that was not palpable on preop exam was removed from the right breast and found to be a 5.5 x 4.0 x 3.5 cm cystic structure consisting of a gray wall covered by a thin layer of fibroadipose tissue. - Cyst contained a thin, opaque, brown-yellow fluid, and the inside of the cyst was smooth and glistening. - Microscopic exam of the cyst wall showed a fibrous wall with a lining composed of a thin layer of squamous epithelium - Immunohistochemical staining for cytokeratin was strongly positive in the squamous epithelium. The capsule removed from the left breast had no epithelial lining but contained proteinaceous debris, scattered inflammatory cells, and hemosiderin ***Case 2:*** **Presentation:** enlarged and painful left breast present for 4 weeks - Left breast approximately twice as large as the right breast, firm, and tender, but no mass was palpable and no nipple discharge. - Both axillae were without adenopathy, and the right breast was unremarkable.

			- Etiologies considered: ruptured prosthesis with surrounding inflammatory reaction, a subacute hematoma, implant infection, and breast cancer. **Surgery:** - 6-cm mass contiguous with the posterior aspect of the fibrous capsule of the implant was identified and removed along with the implant. - Between 50 and 100 cc of "sebaceous" material was also evacuated - Biopsy consisted of 100 g of friable and soft gray-yellow tissue fragments as well as strips of firm, rubbery fibrous tissue with adherent lobules of adipose tissue - left and right breast implants were intact and grossly unremarkable - no extension of tumor into nonneoplastic breast parenchyma **Pathology:** - Microscopic exam of left breast mass→ fibrous capsular wall, focally surfaced by granulation tissue - Much of the capsular wall was lined by a poorly differentiated squamous cell carcinoma, with strands and nests of cells with hyperchromatic and pleomorphic nuclei infiltrating connective tissue - Individual cell dyskeratosis and scattered atypical mitoses were seen. - no evidence of ductal differentiation. - In some areas, the capsular lining was composed of acanthotic but bland stratified squamous epithelium and in still others, the lining epithelium showed nuclear atypia and disturbance of normal maturation but no extension into the surrounding fibrous capsule. - Patchy infiltrates of chronic inflammatory cells and a focal foreign body giant cell reaction noted in surrounding connective tissue. - 3- to 4-mm zone of dense connective tissue separated squamous cell carcinoma from the adjacent breast tissue - Immunohistochemical staining for cytokeratin was strongly positive in the bland and acanthotic epithelium as well as in the areas of frank carcinoma. **Further Treatment:** - left modified radical mastectomy - Gross and microscopic exam of the breast showed no residual squamous cell carcinoma. - Portion of the capsular wall remained, and sections demonstrated hyperkeratotic stratified squamous epithelium with focal atypia. - Surrounding breast parenchyma showed only fibrocystic changes, with no evidence of atypia or malignancy. - The nipple and skin of the breast were uninvolved by the tumor. Thirty axillary lymph nodes showed no evidence of metastasis.
Paletta, C. 1992	Case Report *(Level V)*	52-year-old woman with bilateral breast augmentation (Heyer Schulte 240mL style 2100 silicone gel)	**Presentation:** painful, enlarged left breast (over last 4 weeks) **Exam:** left breast 50% larger than right, tender, tense and firm. No mass palpable, no nipple discharge, no axillae adenopathy

			Diagnosis: Ruptured implant and inflammatory reaction OR subacute breast hematoma OR implant infection OR breast cancer **Surgery:** removal of both implants - Left intact, capsule had sebaceous-type mass with about 50-100 gm of sebaceous material present in the capsular space - Mass appeared to be arising from capsule, 6 cm in size - Capsule thickened and calcified **Pathology:** - The capsule has areas that were stratified squamous epithelium - Squamous material appeared to be exfoliated into keratinous debris (like a ruptured inclusion cyst) - In some areas it showed a benign quality, and in others there was a transformation into an invasive squamous cell carcinoma - Some areas had gradual transition- only in situ changed of atypical nuclei - Other areas had acanthotic pegs of invasive malignancy extending into the underlying connective tissue - Some of the tumor was well differentiated, other areas assumed a poor to an undifferentiated pattern - It was determined the squamous cell carcinoma originated in the posterior implant capsule and did no represent a metastatic lesion - No primary squamous differentiation in breast tissue to suggest the presence of a primary SCC in breast **Further Treatment:** radical mastectomy **Follow up:** Disease free 12 months later.

SCC, squamous cell carcinoma

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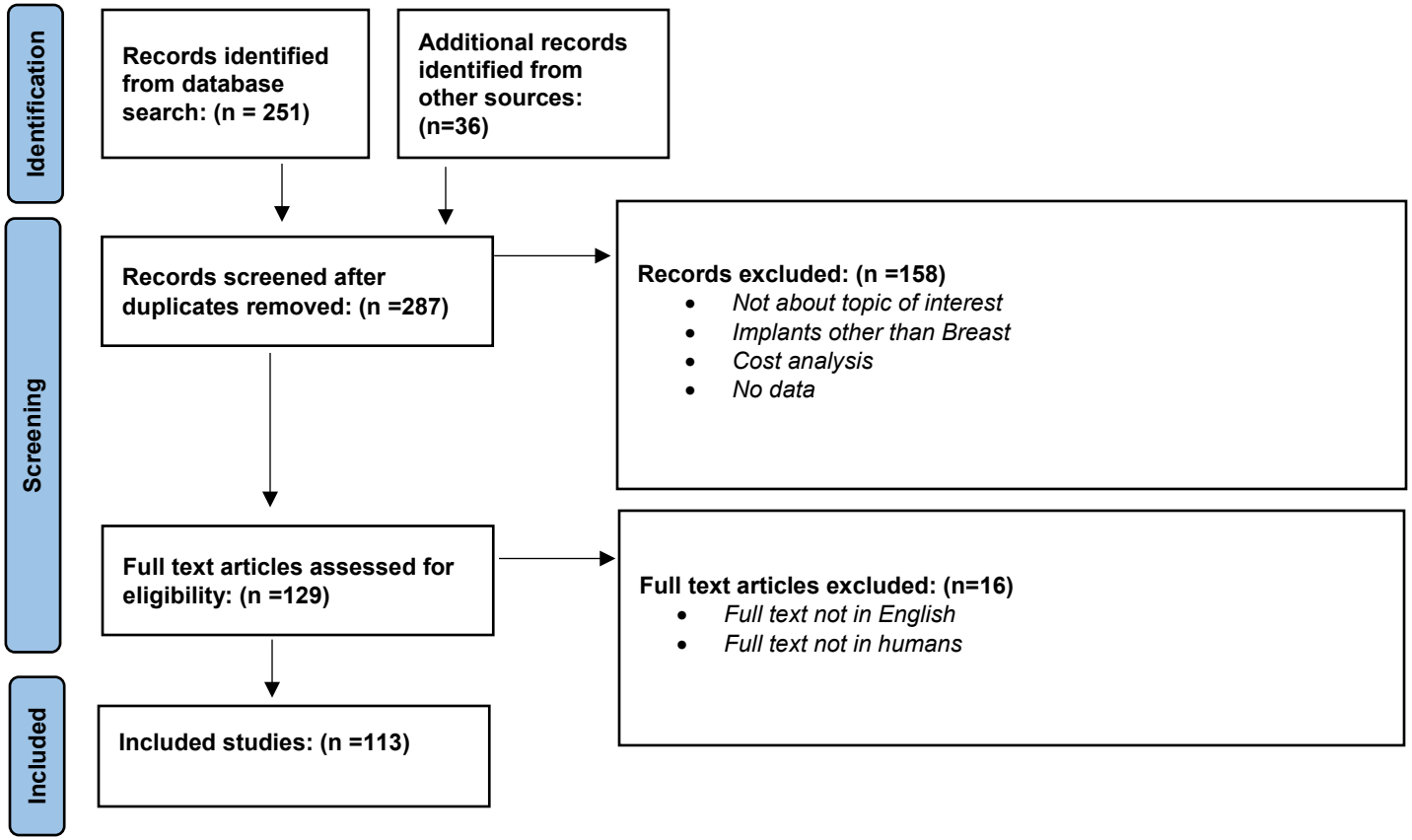
Appendix A: Search Strategy

Database	Date	Search Strategy	Limits	Results
PubMed	Mar. 2, 2021	"Breast Implant-Associated Anaplastic Large Cell Lymphoma"[All Fields] AND ("manage"[All Fields] OR "managed"[All Fields] OR "management s"[All Fields] OR "managements"[All Fields] OR "manager"[All Fields] OR "manager s"[All Fields] OR "managers"[All Fields] OR "manages"[All Fields] OR "managing"[All Fields] OR "managment"[All Fields] OR "organization and administration"[MeSH Terms] OR ("organization"[All Fields] AND "administration"[All Fields]) OR "organization and administration"[All Fields] OR "management"[All Fields] OR "disease management"[MeSH Terms] OR ("disease"[All Fields] AND "management"[All Fields]) OR "disease management"[All Fields]))	English language, full text, humans,	36
PubMed	May 17 2021	("breast implants"[MeSH Terms] OR ("breast"[All Fields] AND "implants"[All Fields]) OR "breast implants"[All Fields]) AND ("augment"[All Fields] OR "augmentation"[All Fields] OR "augmentations"[All Fields] OR "augmented"[All Fields] OR "augmenting"[All Fields] OR "augments"[All Fields]) AND ("radiate"[All Fields] OR "radiated"[All Fields] OR "radiates"[All Fields] OR "radiating"[All Fields] OR "radiation"[MeSH Terms] OR "radiation"[All Fields] OR "electromagnetic radiation"[MeSH Terms] OR ("electromagnetic"[All Fields] AND "radiation"[All Fields]) OR "electromagnetic radiation"[All Fields] OR "radiations"[All Fields] OR "radiation s"[All Fields] OR "radiator"[All Fields] OR "radiators"[All Fields])	English language, full text, humans	54
PubMed	Aug. 5 2021	("breast implant"[All Fields] AND ("radiate"[All Fields] OR "radiated"[All Fields] OR "radiates"[All Fields] OR "radiating"[All Fields] OR "radiation"[MeSH Terms] OR "radiation"[All Fields] OR "electromagnetic radiation"[MeSH Terms] OR ("electromagnetic"[All Fields] AND "radiation"[All Fields]) OR "electromagnetic radiation"[All Fields] OR "radiations"[All Fields] OR "radiation s"[All Fields] OR "radiator"[All Fields] OR "radiators"[All Fields]))	English language, full text, humans	86
PubMed	Oct. 12 2021	"Breast Implant"[All Fields] OR "Breast Reconstruction"[All Fields]) AND ("diagnosis"[MeSH Subheading] OR "diagnosis"[All Fields] OR "screening"[All Fields] OR "mass screening"[MeSH Terms] OR ("mass"[All Fields] AND "screening"[All Fields]) OR "mass screening"[All Fields] OR "early detection of cancer"[MeSH Terms] OR ("early"[All Fields] AND "detection"[All Fields] AND "cancer"[All Fields]) OR "early detection of cancer"[All Fields] OR "screen"[All Fields] OR "screenings"[All Fields] OR "screened"[All Fields] OR "screens"[All Fields]) AND "implant integrity"[All Fields]	English language, full text, humans	10
PubMed	Dec.15 2021	("breast implant illness"[All Fields])	English language, full text, humans	43
PubMed	Dec. 29 2021	("mammography"[MeSH Terms] OR "mammography"[All Fields] OR "mammographies"[All Fields] OR "mammography s"[All Fields] OR ("mammography"[MeSH Terms] OR "mammography"[All Fields] OR "mammogram"[All Fields] OR "mammograms"[All Fields])) AND ("view beijing"[Journal] OR "view"[All Fields]) AND ("embryo implantation"[MeSH Terms] OR ("embryo"[All Fields] AND "implantation"[All Fields]) OR "embryo implantation"[All Fields] OR "implantation"[All Fields] OR "implant"[All Fields] OR "implant s"[All Fields] OR "implantability"[All Fields] OR "implantable"[All Fields] OR "implantables"[All Fields] OR "implantate"[All Fields] OR "implantated"[All Fields] OR "implantates"[All Fields] OR "implantations"[All Fields] OR "implanted"[All Fields] OR "implanter"[All Fields] OR "implanters"[All	English language, full text, humans	12

		Fields] OR "implanting"[All Fields] OR "implantion"[All Fields] OR "implantitis"[All Fields] OR "implants"[All Fields])		
PubMed	Oct. 04, 2022	((Breast Implants[Title/Abstract]) OR (Breast Implants [MeSH Terms])) AND ((Squamous Cell Carcinoma[Title/Abstract]) OR (Carcinoma, Squamous Cell[MeSH Terms]))	English language, full text, humans	8

PRISMA Flow Diagram



Adapted from: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. For more information, visit http://www.prisma-statement.org/

Appendix B: Levels of Evidence

- Level I – evidence from at least one large randomized controlled trial (RCT) of good methodological quality with low potential for bias or meta-analyses of RCTs without heterogeneity
- Level II – small RCTs, large RCTs with potential bias, meta-analyses including such trials, or RCTs with heterogeneity
- Level III – prospective cohort studies
- Level IV – retrospective cohort studies or case-control studies
- Level V – studies without a control group, case reports, or expert opinions