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*Original paper*

## ***Associated anaplastic large cell lymphoma (bia-alcl) with silicone breast implants***

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### **Abstract**

Non-Hodgkin’s lymphoma of the breast is extremely rare. Most of these lymphomas are type B, including large B cell diffuse lymphoma, extra-nodal marginal lymphoma, follicular lymphoma, primary effusion lymphoma and lympho-plasma-cytic lymphoma. BIA-ALCL is negative anaplastic lymphoma kinase (ALK) and is characterized by cells with horseshoe-shaped eccentric nuclei called “hallmark cells”. Unlike other types of ALCL, BIA-ALCL rarely invades your breast in depth. By contrast, non-Hodgkin’s T-cell lymphoma (NHL) found in breasts without implants is mostly B cell lymphoma. Due to the increasing number of cases and the fact that the first case also appeared in Romania, we consider it advisable to take information and prevention measures as well as to adopt a treatment protocol in our country. The present paper aims at adopting a unitary diagnosis and treatment protocol for all plastic surgeons. We also consider it advisable to inform patients before surgery on risk. Through this paper we want to propose a national protocol to follow and also to argue its choice.

### **Keywords**

Silicone, breast, lymphoma, implants, BIA-ALCL.

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## Introduction

Non-Hodgkin's lymphoma of the breast is extremely rare. Most of these are type B, including large B cell diffuse lymphoma, extra-nodal marginal lymphoma, follicular lymphoma, primary effusion lymphoma and lympho-plasma-cytic lymphoma (AL-ROHIL & al [1]). T-cell peripheral lymphoma represents only 10% of all breast lymphomas. In breast implant patients, over 90% of these are anaplastic lymphoma kinase (ALK)<sup>-</sup> compared to breast implant-free patients with only 37% (ALK)<sup>-</sup> (BIZJAK & al [2]).

The appearance of high-cell anaplastic lymphoma in patients with mammary implants is a novel issue. Today, about 1.7 million mammary implants are performed each year around the world. To date, over 500 cases of BIA-ALCL have been reported in the world, of which 16 deaths (KRICHELDORFF & al [3]). BIA-ALCL may occur one year after breast augmentation/reconstruction up to 32 years after that (STORY & al [4]). The average duration of implant exposure varied on average from 7 to 13 years. The incidence of BIA-ALCL is estimated at 2.03 per 1 million people, or 1 per 30,000 women with breast implants (DOREN & al [5]). The first case of BIA-ALCL was published in 1997 by Keech and Creech (KEECH & al [6]). In 2016, the World Health Organization defined BIA-ALCL as a distinct entity (SWERDLOW & al [7]).

Anaplastic large cell lymphoma (ALCL) subtypes can be grouped according to the presence or absence of surface receptors for ALK and also the primary site of tumour development in cutaneous ALCL and ALCL associated with mammary implants BIA-ALCL (CHIHARA & al [8]).

- Primary systemic ALCL: anaplastic lymphoma kinase (ALK) positive
- Primary systemic ALCL: ALK-negative
- Primary cutaneous ALCL (PC-ALCL)
- BIA-ALCL: ALK-negative, CD30 positive

Large-cell anaplastic lymphoma (ALCL) represents approximately 2-3% of all non-Hodgkin T-cell lymphoma (NHL) peripheral lymphoma [9].

BIA-ALCL is negative ALK and is characterized by cells with horseshoe-shaped eccentric nuclei called "hallmark cells". Unlike other types of ALCL, BIA-ALCL rarely invades your breast in depth. By contrast, non-Hodgkin's T-cell lymphoma (NHL) found in breasts without implants is mostly B cell lymphoma.

Most often, BIA-ALCL manifests itself as an encapsulated peri-prosthetic serum and can rarely develop as a solid tumour that can infiltrate the thoracic wall or the large pectoral, in which case the prognosis depends on the invasion of the loco-regional ganglia. The cause of this type of tumour remains uncertain. It appears to develop against a background of chronic inflammation or toxins coming out from the implant. The presence of the subclinical bi-film on the implant surface, the capsular contracture, the direct implant toxicity, and the host's immunological response are considered as contributing

factors in the development of BIA-ALCL (KAARTINEN & al [10]). From the treatment point of view, it is generally acknowledged today that in the incipient stages, simple capsulectomy is sufficient to eradicate the disease, while advanced stages include chemotherapy.

## Materials and Methods

Due to the increasing number of cases and the fact that the first case also appeared in Romania, we consider it advisable to take information and prevention measures as well as to adopt a treatment protocol in our country.

Thus, as a measure of information we have introduced in the assumed consent of patients information about BIA-ALCL: what it is, how it manifests itself, how it is treated and how it can evaluate.

As a preventative measure, we decided to use almost exclusively smooth implants, and we recommend patients an annual breast ultrasound. We also explain to patients what the first signs are and when they should come to us for a consultation.

Until now, although initially patients have a retention in making breast augmentation, in the end there were no patients to give up this procedure. The present study relates to a number of about 60 patients, since the information about BIA-ALCL was introduced in the information consent.

Regarding the diagnosis and treatment protocol, we decided to follow the NCCN protocols reported in figures 2 and 3. However, we also recommend annual mammary ultrasound even in the absence of any signs or symptoms.

## Results and Discussion

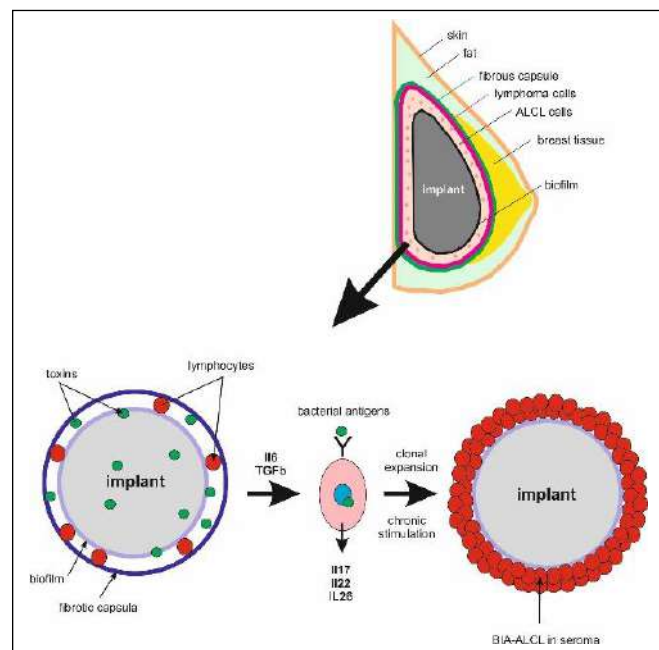
Since 1997, cases of ALCLs associated with mammary implants have been published, so in 2011 the FDA was aware of 63 cases of BIA-ALCL. However, at that time, a number of breast implants around the world were estimated at around 5-10 million, and the Food and Drug Administration (FDA) considered the 63 cases irrelevant (SWERDLOW & al [11]). Only in 2016, the World Health Organization (WHO) recognizes this pathological entity as a distinct one associated with the presence of mammary implants, and one year later the FDA recognizes this pathogenic entity, 414 cases of BIA-ALCL known worldwide and 9 deaths (Administration UFaD [12]). At that time, a new pathology of non-Hodgkin's anaplastic lymphoma associated with the presence of breast implants -ALCL was defined and accepted. Since 2017, the FDA has named this new form of non-Hodgkin anaplastic lymphoma as BIA-ALCL. There have been numerous studies in different countries, with more and more BIA-ALCL cases reported: 41 in the UK (JOHNSON & al [13]), 22 in Italy (CAMPANALE & al [14]), 43 in the Netherlands (De BOER & al [15]), 19 in France (LAURENT & al [16]), 7 in Germany (BfArM [17]) and 149 in the United States (DOREN & al [5]). Until now, no BIA-ALCL case has been confirmed in Romania, but no screening study has been conducted. The exact incidence of BIA-ALCL numbers is very difficult to estimate, but the opinion of some experts shows that in Australia and

New Zealand the incidence would be 1: 2832 for women with polyurethane implants, in the UK 1: 24,000 and in the US incidence would be 1: 30,000 (DOREN & al [5]; LOCH-WILKINSON & al [18]). In 2016, with the acknowledgement by the WHO of BIA-ALCL as a distinct pathological entity, the National Comprehensive Cancer Network (NCCN) developed the first diagnostic and treatment guide for BIA-ALCL (SWERDLOW & al [7]; CLEMENS & al [19]). For over 25 years, NCCN has been developing diagnostic and treatment guidelines for various forms of cancer in the US, all of which have been recognized by both the FDA and the WHO (CLEMENS & al [20]). NCCN clinical guides are always up to date data and research, so we can consider this guide as the gold standard in treating BIA-ALCL (CLEMENS & al [21]).

### 1. Etiology and pathophysiology

One of the possible causes seems to be the presence of infection or chronic inflammation, although breast augmentation with silicone prostheses is considered an aseptic surgery. However, there is research that supports the association between chronic inflammation and NHL (DU & al [22]) and, on the other hand, the association between BIA-ALCL and various infections (LOCH-WILKINSON & al [18]). Thus, a textured implant creates a biofilm due to bacterial colonization, which will cause the increase in the number of T lymphocytes; they will determine the appearance of the serum and later of the lymphoma (ADAMS & al [23]). Chronic infection is considered to be a contributing mechanism in some types of human lymphoma. It is assumed that a cytokine-rich environment facilitates the rapid division of host lymphocytes, causing tumour alterations leading to BIA-ALCL. The cytokine profile of BIA-ALCL cell lines, specifically interleukin (IL)-6, transforming growth factor

(TGF)- and interleukin (IL)-10, has also been shown to induce populations of immune suppressive cells that can inhibit host immunity and facilitate the development of cancer. Also, receptors were found in BIA-ALCL-developed cell lines for (HLA-DR, CD80, CD86), IL-2 (CD25, CD122) and IL-6 ( STEWART & al [24], KADIN & al [25]). Although there has been no direct correlation between chronic infections and BIA-ALCL until now, there are reported cases of association between *Ralstonia* and BIA-ALCL (HU & al [26]). Another pro argument that supports the association between a possible infection and BIA-ALCL is the presence of CD30. This is a protein that is normally found on activated T cells and is essential in the diagnosis of BIA-ALCL. In support of biofilm infection/modification theory, there is also chronic *Helicobacter pylori* infection that promotes the appearance of gastric lymphoma (WANG & al [27]) but also possible cutaneous microbiome changes induced by direct or indirect mechanisms having as a model the lymphocytoma produced by *Borrelia* species (FITZAL & al [28]) as well as possible alterations of the cut microbial by direct or indirect mechanisms like it shows in "Figure 1". Therefore, it is plausible that chronic infected mammary implants mediate inflammatory and neoplastic processes, resulting in the development of a T cell lymphoma. In conclusion, although underestimated the association between inflammation / chronic infection and the appearance of BIA-ALCL, however, a 14-point protocol was issued consisting essentially of perioperative and localized antibiotic treatment, immediate implant exposure to the air, preventing implant skin contact and drainage tube omission, and which aims at minimising the risk of infection or chronic inflammation on the implant (ADAMS & al [23]). In general, the BIA-ALCL determinism on the background of a chronic inflammation/infection can only occur in genetically susceptible persons.



**Figure 1.** BIA-ALCL pathophysiology of inflammatory/infectious etiology. Modified and adapted after F. FITZAL & al [28].

Another possible cause would be the allergenic determinism of BIA-ALCL. Eosinophilis were found in implant capsules, and tumour cells expressed the GATA 3 transcription factor and produced IL13, suggesting the possible development of BIA-ALCL on an allergic background (KADIN & al [29]).

Lately, more and more genetic studies have been done on BIA-ALCL, starting from the previously known data on genetic determinants of malignant blood diseases. According to the latest studies, activation of STAT3 mutations was detected in 64% of cases, and in 25% there was also a truncating mutation of SOCS 1, which is supposed to trigger the JAK / STAT pathway by losing negative regulation. There are multiple activation pathways of STAT3 in sALCL, including activating sequence variants in JAK1 / STAT3 (in approximately 20-30% of cases) and translocations involving ROS1 and TYK2 (BLOMBERG & al [30]; CRESCENZO & al [31]). Although STAT3 Ser614Arg mutations, as well as DNA binding (STAT3 His410Arg) have been observed, the explanation for the predilection of JAK/ STAT3 activation in BIA-ALCL by STAT3 activation mutations is unclear, the genomic mechanism by which this aberration signalling seems to be different (BLOMBERG & al [30]). There were also observed mutations on the TP53 gene in patients who had been breast cancer treated and had breast implant reconstruction, plus a history of familial breast cancer ( BLOMBERG & al [30]; AJORE & al [32]). TP53 gene mutations can also lead to Li-Fraumeni syndrome, which is a syndrome of multiple cancers predisposed to young age (very common before 30 years). The most common forms of cancer that occur in Li Fraumeni syndrome are osteosarcoma (bone cancer), breast cancer, soft-tissue sarcoma, acute leukemia, brain cancer, and adrenocortical carcinoma. Recently a case was reported in which BIA-ALCL was associated with Li-Fraumeni

syndrome, although only about 500 cases of Li-Fraumeni syndrome are known in the world (PASTORELLO & al [33]). Cases reported with this genetic anomaly are very few, and until now, a direct link between this mutation and the presence of the implant could not be achieved. It has also been demonstrated that most cases of ALK-negative lymphomas sALCL do not express a T-cell receptor, despite having rearranged TRG and TRB sites, which also appears to be counterbalanced in BIA-ALCL (BONZHEIM & al [34]; M. SHUGAY & al [35]). As a brief conclusion on the genetic determinism of BIA-ALCL, we can say that the aberrant signalling pathways in BIA-ALCL are similar to those in sALCL including abnormalities of the TP53, MYC and JAK / STAT3 models, and are characterized by a high recurrence in activation STAT3 mutations and recurrent deletions of 1p22 involving RPL5 (which have not been identified in sALCL to date); genetic alterations of the anomalies of TGF-β, PKC, Wnt / β-catenin, MYC, P2RX7, TMEM119 as well as high-level amplification of TNFRSF11A and PDGFRA (BLOMBERG & al [30]; FANCELLO & al [36]).

An exciting and consistent feature of BIA-ALCLs is their complex cytogenetics. This suggests that genomic instability may play a role in the formation or progression of tumours. For example, the genetic mutation on chromosome 17 induces the disruption of the P53 gene located on chromosome 17 (17p13.1), which results in increased tumour aggression (MULLER & al [37]). Human P53 plays an important role in apoptosis, genomic stability and inhibition of angiogenesis (WADE & al [38]; NWABUDIKE & al [39]). Another etiopathogenic model may be that one described related to altered epigenetic pathways and cell cycle dysregulation in healthy appearing skin of patients with koebnerized squamous cell carcinomas following skin surgery, “Table 1”.

**Table 1.** Tumor cells *in vivo* cytogenetic evolution. Modified and adapted after GERORGE & al [40].

Cell Source	Clonal Cytogenetic Abnormalities
Tumor cells from seroma fluid	45, XX [cp19] dup(X)(q11q28), +1, del(1)(q32), i(1)(q10), add(3)(p11), der(3) t(2,3)(p12,p26), +6, der(6)t(6,8)(q12,q21.3)x2, add(8)(q11.2), add(11)(q23), add(14)(p11.1), -15, -17, -20, 80~91, idem [cp2]
Cells from lymph node	34, XX [1]* +1, del(1)(q32)x2, +2, -3, der(3)t(2,3)(p12,p26), +6, der(6)t(6,8) (q12,q21.3)x2, add(9)(p22), -10, -12, -12, -13, -14, -15, add(15) (p11.2), -16, add(16)(q11.2), -17, -18, -20, -20, -21, -21, -22 [1] 78-79, XX [cp3]* +X, +X, +1, +1, del(1)(q32)x2, i(1)(q10), +2, add(3)(p11), add(4) (q21), +6, +6 der(6)t(6,8)(q12,q21.3)x2, -8, add(9)(p22)x1-3, -10, add(10)(p13), add(11)(q23), +14, -15, add(15)(p11.2), +16, add(16)(q11.2)x2, -17, -17, -18, +19, -20, -22, i(22)(q10), +mar1-2 46, XX [16]

George E.V. et al. studied and correlated several tumour factors in BIA-ALCL: CD30, Ki67, CD8, CD15, CD45, CD25, CD20, TP53. It found that the combination of CD30 with strongly positive Ki67 suggests an increased proliferative index, while CD15 positivity was increased in the recurrent tumour, suggesting that CD15 may mark a more aggressive sub-clone of the basal tumour (GERORGE & al [40]).

Another possible contributing cause would be textured implants. Considered to be more stable and with a much lower rotation risk, textured implants were used with predilection. However, most of the BIA-ALCL cases appeared on textured implants, “Table 2” (LOCH-WILKINSON & al [18]; GERORGE & al [40]).

**Table 2.** Aggressive cases of BIA-ALCL: Int., interval, Rt, right, Lt, left, BI, breast implant, CA, carcinoma, LN, lymph node, LAD, lymphadenopathy, LyP, lymphomatoid papulosis, CPT, capsulectomy, RT, radiation therapy, CT, chemotherapy, ASCT, autologous stem cell transplantation, CHOP, PBC, primary biliary cirrhosis, ALK-, anaplastic lymphoma kinase gene rearrangement negative (GERORGE & al [40]).

Case/Ref.	Age/Int. at ALCL, PMH	Textured BI filled with	Presentation/Sites of disease	Markers	Genetics/ALK Status	Treatment/Outcome
Alobeid et al. 2009	68/16, history of Rt breast ductal CA and PBC	silicone	Rt axillary LAD/Rt axillary LNs, Rt BI capsule, Lt axillary LNs	CD30+, CD45-/+ , CD15+, CD2+, CD4+, EMA+, MUM1+	complex ALK-	CPT, 6 cycles CHOP/No known relapse
Carty et al. 2011	57/32, multiple BI revisions due to capsular contraction and implant rupture	silicone	B-symptoms, Lt axillary LAD/Lt BI capsule with chest wall invasion and pleural thickening	CD30+, CD4+	Complex ALK-	CPT, RT, 5 cycles CHOP, salvage CT, ASCT/ Death from progressive disease 3 yrs after diagnosis
Gaudet et al. 2002	50/10, Lt breast CA, remote history of HL	Silicone	Mass overlying Rt BI/Dermal involvement overlying Rt BI	CD30+, CD2+, LCA+, weakly positive for CD3, CD5, CD43	Complex ALK-	CHOP/Relapse 1 year later with pleural and pericardial effusions, mediastinal LAD, Unknown current status
Aladily et al. 2012	63/6+1, L breast CA, 3 yr history of lyP	saline	Effusion & mass in Rt breast/Rt breast	CD30+, CD3+, CD4+, CD2+, CD43+	Complex ALK-	CPT/Died at 12 yrs post ALCL diagnosis
Aladily et al.	47/9, breast CA	saline	Rt BI mass/Rt breast with effusion	CD30+, CD45+, CD43+, CD4+, EMA+, Granzyme B	Complex ALK1-	CPT, RT, CT/ Died at 2 yrs post ALCL diagnosis
George E.V.	67/8, breast CA	Silicone	Enlargement and Effusion in Rt breast/Rt breast	CD30+, CD15+, CD25+, CD8+,	Complex with genetic evolution ALK-	CPT at diagnosis, CHOP/ Etoposide at relapse. Patient is well without detectable disease

In 2017, the FDA reported that of 231 cases of BIA-ALCL, 203 were on textured implants and only 28 on smooth implants (BERLIN & al [41]). On the other hand, in the structure of the silicone gel in the implants, many chemicals, such as vinyl derivatives, aromatic hydrocarbons (benzene, xzyl) and traces of metals. Some of these substances can cross the implant capsule and reach the tissues around the implant causing a chronic inflammation and implicitly an increased T lymphocyte influx, which may theoretically favour a BIA-ALCL (C. HILLARD & al [42]). Moreover, on an existing chronic inflammation, aromatic hydrocarbons can cause cytoplasmic and aryl hydrocarbon transcription factor activation (AHR) activation to turn cytochrome P450 transformation (CYP1Aa / 2 and 1B1 enzymes), the latter resulting in mutagenic DNA changes (ANDERSON & al [43]) also explained by the Wolf phenomenon (TATU & al [44]) but, on the other hand, AHR exhibits high levels in most forms of BIA-ALCL (KOLLURI & al [45]), and the bacteria attach much more easily to textured implants than the smooth ones, which would explain the higher incidence of BIA-ALCL on textured implants.

## 2. Diagnosis

BIA-ALCL is one of the 4 types of ALCL. All of these ALCL forms are positive for CD 30, but the clinical prognosis and prognosis is different, with BIA-ALCL having a rare evolution that can lead to death. BIA-ALCL is characterized by elevated levels of CD30, even in the absence of anaplastic lymphoma kinase (ALK) (FERRUFINO-SCHMIDT & al [46]).

From a clinical point of view, in most cases, it is manifested by the appearance of a periprosthetic serum with thickening of the capsule and signs of capsular contraction. The average occurrence interval is 7-8 years

after implant insertion (CLEMENS & al [47]). Can also present chronic breast dermatitis, breast deformities and axillary adenopathies. A minimal number of cases have been reported in the absence of a collection of peri-protheses in combination with a severe capsular contraction, a mass or a nodule. BIA-ALCL can also occur bilaterally, although this can occur even less frequently. The axillary invasion of the lymph nodes is quite frequent, according to some authors, reaching 93%, with the invasion of internal and supraclavicular mammary lymph nodes (FERRUFINO-SCHMIDT & al [46]). Very rarely, it can manifest itself as a solid capsular tumour (J. XU & al [48]).

From para-clinical investigations, any serum starting more than 1 year associated with an implant should be investigated by mammary and axillary ultrasonography and by highlighting the structure of the thoracic wall, as it shows in "Figure 2". The sensitivity of ultrasound for detecting a BIA-ALCL is estimated to be 84% for serum and 46% for solid tumours. The specificity of ultrasound for detection of a BIA-ALCL is estimated to be 75% for serum and 100% for solid tumours (ADRADA & al [49]). If mammary echography is inconclusive, the next step is to perform, magnetic resonance imaging (MRI). Positron emission tomography-computed tomography (PET / CT) may also be an option in the diagnosis of advanced BIA-ALCL, especially in the detection of metastasis or invasion of the thoracic wall, it is also a postoperative follow-up method, but at least 3 months after surgery (BRODY & al [50]).

Sensitivity/specificity for serum:

- Ultrasound: 84 / 75%
- Computer tomography (CT): 55 / 83%
- MRI: 82 / 33%
- PET-CT: 38 / 83%

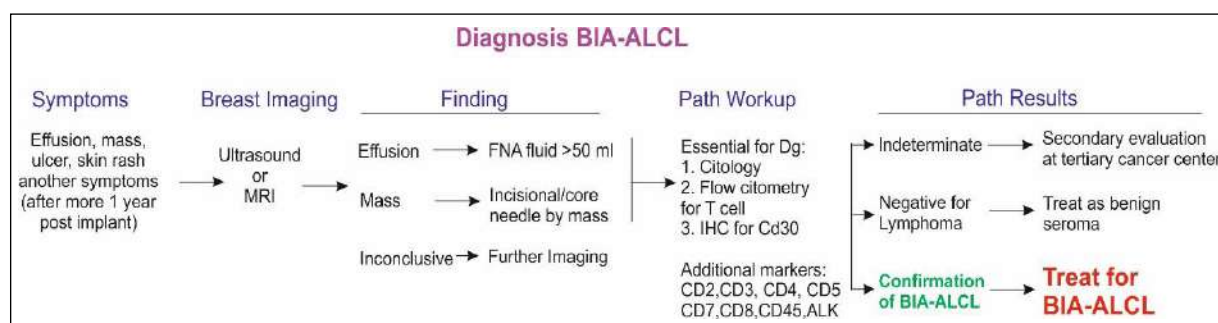
Sensitivity/specificity for solid tumours:

- Ultrasound: 46/100%
- CT: 50/100%
- MRI: 82/33%
- PET-CT: 64/88%

Mammography is inferior to breast ultrasound and MRI, both as sensitivity and specificity, without being able to differentiate solid tumor serum (73/50%) [49].

These investigations raise the suspicion of a BIA-ALCL, but the diagnosis of certainty is supported by the

exogenous aspiration of the periprosthetic fluid with cytology and immunohistochemistry for CD30 and ALK. In the case of patients with axillary adenopathies or chronic dermatitis, the biopsy with the histopathological and immunohistochemical examination is indicated for CD30 and ALK (CLEMENS & al [51]). Since the implant capsule drains through various lymphatic tracts and to various lymph nodes, it is not recommended to make the sentinel ganglion. Only lightened lymph nodes detected by palpation will be excised.



**Figure 2.** BIA-ALCL, diagnosis management. Modified and adapted after NCCN (National Comprehensive Cancer Network) (M.W. CLEMENS & al [51]).

The differential diagnosis of a seroma within one year old includes infection, trauma, hematoma, implant rupture, double capsule, synovial metaplasia, breast cancer and idiopathic causes. Differential diagnosis with other breast malignancies may require other tumour markers such as CD2, CD3, CD4, CD5, CD7, CD8, CD45 and anaplastic lymphoma kinase (ALK), BIA-ALCL is always ALK-negative (QUESADA & al [52]).

### 3. Treatment

Treatment of BIA-ALCL depends on the clinical stage of the disease, and the National Comprehensive Cancer Network proposed a very comprehensive algorithm, “Figure 3”.

Non-Hodgkin’s lymphomas are classified most

frequently according to the staging of Ann Arbor, modified by Lugano. According to this classification, stage IE is defined by the invasion of a single extranodal site (E), such as the implant capsule, while stage IIE appears to spread to nearby tissues or local lymph nodes invasion (B.D. CHESON & al [53]). Thus, if we follow this classification, almost all BIA-ALCLs are diagnosed at an early stage, either in stage 1E (83-84%) or stage IIE (10-16%), while in advanced stages only 0-7% of cases are diagnosed (CLEMENS & al [21]). This classification does not take into account the capsular invasion in BIA-ALCL, which makes it less usable in this form of lymphoma, which is why NCCN adopted the TNM classification of BIA-ALCL, and we revealed in “Table 3”.

**Table 3.** TNM Classification by NCCN guidelines (2019). (CLEMENS & al [51])

TNM Classification		TNM Stage	
T: Tumour extent		IA	T1N0M0
T1	Confined to effusion or a layer on luminal side of a capsule	IB	T2N0M0
T2	Early capsule infiltration	IC	T3N0M0
T3	Cell aggregates or sheets infiltrating the capsule	IIA	T4N0M0
T4	Lymphoma infiltrates beyond the capsule	IIB	T1-T3N1M0
N: Lymph node		III	T4N1-N2M0
N0	No lymph node involvement	IV	T any, N any, M1
N1	One regional lymph node		
N2	Multiple regional lymph nodes		
M: Metastasis			
M0	No distant spread		
M1	Spread to other organs/distant sites		

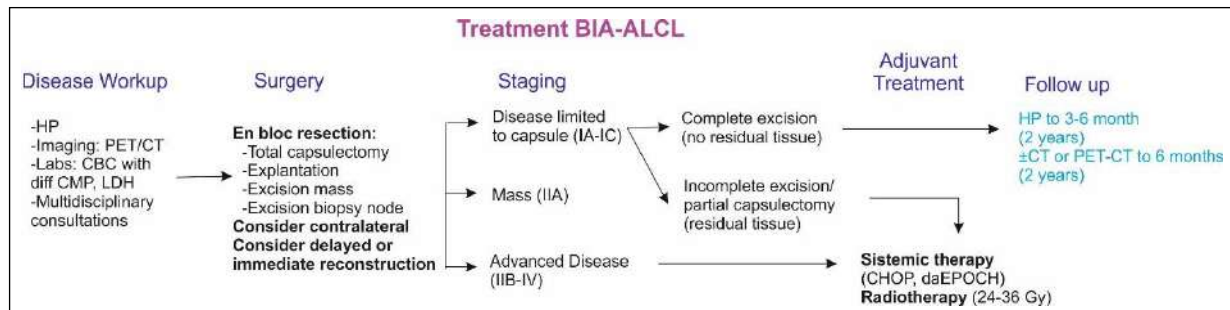
Compared to the Ann Arbor classification, TNM classification more precisely divides the disease into clinical stages, thus allowing a more accurate assessment of the therapeutic protocol and prognosis. Thus, according to some authors, the incidence of BIA-ALCL depending on the TNM stages would be: 35-70% stage I, 11% stage IB,

8-13% stage IC, 8-25% stage IIA, 3-5 % in Stage IIB, 3-9% in Stage III and only 1-2% in Stage IV (ADRADA & al [49]; DOREN & al [5]). Thus, BIA-ALCL treatment is performed according to the TNM classification.

In stage 1-3, complete removal of the implant and the surrounding fibrous capsule is sufficient to eradicate

the disease (see figure 3). In advanced stages, it is necessary to associate chemotherapy or extended surgical excisions, and very rarely the association of radiotherapy (Figure 3). At present, the role of radical mastectomy or sentinel ganglion is not clearly defined. Complete axillary dissection

was rarely used in cases where more lymph nodes were invasive. The JAK / STAT3 targeted tyrosine kinase inhibitor may be a possible treatment for infiltrative BIA-ALCL (CHIARLE & al [54]). It is estimated that 2-4% develop bilateral disease, requiring treatment for both breasts.



**Figure 3.** Treatment of BIA-ALL. Modified and adapted after NCCN (CLEMENS & al [51]). Breast implant-associated anaplastic large cell lymphoma disease algorithm.

Current evidence-based algorithm for achieving diagnosis followed by treatment by stage of the disease. Bx, biopsy, CBC, complete blood count, CHOP, cyclophosphamide doxorubicin vincristine prednisolone, CMP, complete metabolic profile, daE, dose-adjusted etoposide, FNA, fine needle aspiration, LDH, lactate dehydrogenase, MRI, magnetic resonance imaging, PET/CT, positron emission tomography-computed tomography, RT, radiation therapy.

Radiotherapy is occasionally indicated when the excision margins are positive, non-resectable tumour, chest wall invasion or relapse, with the usual doses being 24-36 Gy (CLEMENS & al [19]).

Chemotherapy is indicated in the following cases: non-resectable tumours, tumours that have spread to the breast parenchyma or chest wall, axillary lymph node invasion. Chemotherapy is performed according to the CHOP regimen, with different rates of success. In CHOP-resistant patients, Brentuximab Vedotin, which is made up of anti-CD30 monoclonal antibodies, is used as a neo-adjuvant, with encouraging BIA-ALCL results in advanced stages (ALDERUCCIO & al [55]). Advani claims that following this treatment with Brentuximab Vedotin, the response rate was 86% and the complete remission rate of 59% (B. PRO & al [56]). Systemic therapy is warranted in patients in stage II-IV Lugano or the stage IIB-IV TNM, ALK-negative lymphomas respond less well to CHOP than ALK-positive (survival rates of 5 to 40% versus 70-90%) (HAPGOOD & al [57]). After Clemens, about two-thirds of patients with BIA-ALCL showed tumor progression after CHOP (CLEMENS & al [20]). Patients who did not respond to baseline chemotherapy had a complete response to Bentuximab, but other chemotherapies but very rare chemotherapy protocols were used: ABVD (Adriamycin, Bleomycin, vinblastine, dacarbazine), hyper-CVAD (cyclophosphamide, vincristine, doxorubicin and dexamethasone alternating with methotrexate and cytarabine), and ICE (ifosfamide, carboplatin, etoposide) (CLEMENS & al [21]; LEBERFINGER

& al [58]; SHAH & al [59]; MAZILU [60]).

The overall survival rate for patients diagnosed with BIA-ALCL is 89% at five years and is dependent on the stage in which the disease is diagnosed.

The relapse rate after surgical excision is 14.3% for T4 patients and 0% for patients in T1-T3 stages (CLEMENS & al [21]). Local relapse is due to the incomplete resection of the implant capsule.

There is also the possibility, reduced what is right, spontaneous remission of the disease, Fleming reporting in 2018, 2 spontaneous regression of BIA-ALCL (FLEMING & al [61]).

There are currently 4 cases reported by BIA-ALCL to transgender. Of these, 3 patients were Ann Arbor IE and treated with full surgical resection and CHOP adjuvant chemotherapy, a 4<sup>th</sup> case was diagnosed in Stage IIE (TNM Stage III) and was treated with CHOP chemotherapy (4 cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone), radiotherapy (3600 cGy in 180 cGy fractions) and surgical excision. (DE BOER & al [62]; PATZELT & al [63]; ALI & al [64]; CIUHU & al [65]). They all had textured implants.

Postoperative surveillance will be done through 6-month clinical follow-up and 2-year breast ultrasound for 5 years (ARDELEANU & al [66]).

In 2019, the National Comprehensive Cancer Network (NCCN) has updated the Consensus Guidelines on the Diagnosis and Treatment of Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL), which is the gold standard in diagnosing and treating BIA-ALCL. This guide addresses the disease in its function and is recognized by the FDA. Observing this guide assists patients with the most modern and optimal treatment, this guideline based on the latest and most complex studies in the world. (BERETTA & al [67]; DI VIRGILIO & al [68]; PANTEA STOIAN & al [69]; ROUANET & al [70]).

Exceptionally, differential diagnosis can also be made with solid tumors such as lipomatosis (ARDELEANU & al [71]), case of course the treatment and prognosis is totally different. Certainly certain diagnostic techniques used today in other forms of cancer will be extrapolated

to BIA-ALCL (ARDELEANU & al [72]; CALOTĂ & al [73]; OZEN & al [74]).

## Conclusion

The appearance of high-cell anaplastic lymphoma in patients with mammary implants is a topical issue, with more than 1.7 million implants being mounted in the world and over 500 cases of BIA-ALCL reported, of which 16 deaths. The estimated incidence of the disease is 2.03 to 1 million people or 1 in 30,000 women with mammary implants. The average duration of implant exposure varies on average from 7 to 13 years.

The causes of BIA-ALCL are still incompletely elucidated. Several possible etiologies such as chronic inflammations/infections, textured implants, host allergic terrain, genetic determinism for haematological cancers, genetic mutations, removal of implants toxins are incriminated.

Clinically, it is most often manifested by the appearance of a massive serum that appeared on the average after 7-8 of the implant, most often unilaterally, accompanied or not by other signs such as skin pruritus.

The diagnosis of certainty is supported by the tumour marker CD30 and ALK, which is harmful.

Treatment varies depending on stages. For incipient stages (I-III), implant removal and capsule excision are sufficient, while chemotherapy or radiotherapy is required for advanced or invasive stages. The most commonly used chemotherapy regimen is CHOP (cyclophosphamide doxorubicin vincristine prednisolone).

The gold standard in diagnosing and treating BIA-ALCL is the NCCN guide of 2019.

The differential diagnosis of a seroma within 1 year old includes infection, trauma, hematoma, implant rupture, double capsule, synovial metaplasia, breast cancer and idiopathic causes.

Prognosis is a good one if the disease is treated in the early stages and can become less favourable in advanced stages. The relapse rate after surgical excision is 14.3% for T4 patients and 0% for patients in T1-T3 stages. Local relapse is due to the incomplete resection of the implant capsule. There are also reports of spontaneous remission.

Due to the increasing incidence of BIA ALCL simultaneously with the increase in the number of breast augmentations with implant throughout the world but also our country, we consider very importantly, on the one hand, the knowledge by all plastic surgeons of the manifestations of this disease as well as the diagnosis and the proper treatment, but also the creation of a unique register of breast augmentations. There remains an open discussion on the type of implant chosen, smooth or textured, yet there are no definite conclusions in this regard, as there have been reported cases of BIA-ALCL on both textured and smooth implants. In November 2019, the first case of BIA-ALCL was diagnosed in Romania with a patient with Allergan Natrelle Inspira implants in dual-plane technique, and implants mounted 5 years ago.

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## Conflicts of Interest

The authors declare no conflict of interest.

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