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Clinical recommendations for diagnosis and treatment according to current updated knowledge on BIA-ALCL

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ABSTRACT

Shared strategies and correct information are essential to guide physicians in the management of such an uncommon disease as Breast Implant–Associated Anaplastic Large Cell Lymphoma (BIA-ALCL). A systematic review of the literature was performed to collect the most relevant evidence on BIA-ALCL reported cases. A panel of multidisciplinary experts discussed the scientific evidence on BIA-ALCL, and updated consensus recommendations were developed through the Delphi process. The lastest reported Italian incidence of BIA-ALCL is 3.5 per 100.000 implanted patients (95% CI, 1.36 to 5.78), and the disease counts over 1216 cases worldwide as of June 2022. The most common presentation symptom is a late onset seroma followed by a palpable breast mass. In the event of a suspicious case, ultrasound-guided fine-needle aspiration should be the first step in evaluation, followed by cytologic and immunohistochemical examination. In patients with confirmed diagnosis of BIA-ALCL confined to the capsule, the en-bloc capsulectomy should be performed, followed by immediate autologous reconstruction, while delayed reconstruction applies for disseminate disease or radically unresectable tumor. Nevertheless, a multidisciplinary team approach is essential for the correct management of this pathology.

1. Introduction

The Food and Drug Administration (FDA) heralded in 2011 the possible connection of breast implants with an uncommon form of a Non-Hodgkin Lymphoma, the Anaplastic Large Cell Lymphoma (ALCL) [1,2]. In 2016, the World Health Organization (WHO) recognized and defined this emerging clinical condition as a new form of lymphoma, the Breast Implant–Associated Anaplastic Large Cell Lymphoma (BIA-ALCL), framing it as a distinct entity and as subtype of anaplastic lymphoma kinase–negative (ALK-) ALCL [3]. Competent Authorities on medical devices are joined in an International Taskforce aimed to monitor and manage the number of new cases since 2011. The actual knowledge about BIA-ALCL presents several limits due to the lack of data derived from large prospective cohort studies with long follow-up [4]. Furthermore, the little evidence gathered from actual reports, along with multiple, and sometimes contradicting interpretations, may result in misleading narratives, which do not facilitate the physicians in the understanding and management of BIA-ALCL cases. A recent report

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of the World Consensus 2022 paper on BIA-ALCL supported the causal relationship of BIA-ALCL with all types of textured implants based on the Scientific Committee on Health, Emerging and Environmental Risks (SCHEER) of the European Health Commission reported opinion [5,6]. However, it is worthwhile to note that the SCHEER final opinion published in 2021 did not argue the presence of a "sufficient evidence" but only ascertained a moderate weight of evidence for a causal relationship between textured breast implants and ALCL, particularly in relation to implants with an intermediate to high surface roughness. In addition, the SCHEER has recognized the numerous limitations due to the various types of textured implants, different manufacture of breast implant surface textures, and benefits provided by diverse surface textures, eventually adding that there is the need for further research to better understand the aetiology and pathogenesis of BIA-ALCL [7]. Based on these considerations, shared guidelines are needed to guide all physicians involved in the diagnosis, treatment, and follow-up of this pathology in the light of actual best evidence. This study was aimed to develop comprehensive clinical recommendations on the management of BIA-ALCL – from diagnosis to treatment and reconstruction - through the discussion by a panel of experts on updated literature evidence on BIA-ALCL and previous clinical recommendations provided by the Italian Ministry of Health, build further on the United States National Comprehensive Cancer Network (NCCN) [8] and UK guidelines [9]. The presented recommendations provide an evidence-based guide for the care of such an uncommon disease.

2. Methods

2.1. Search strategy, selection criteria and process to consensus agreement

A systematic review of the literature and official reports on BIA-ALCL was conducted up to May 2022 utilizing PubMed, MEDLINE, and Cochrane databases. English language articles providing data on epidemiology, clinical aspects, molecular and genetic biomarkers, diagnosis and management of BIA-ALCL were included. Previously published official reports, recommendations and guidelines were searched, assessed, and included in the review. Search terms included: "BIA-ALCL", "breast implant associated anaplastic large cell lymphoma", and "breast implant cancer". Selected articles included original case reports, systematic reviews, and official guidelines and recommendations [Fig. 1]. All the information collected was summarized in a report and discussed by a multidisciplinary work group, which included experts in plastic surgery, oncology, haematology, presidents of Italian scientific associations and representatives of the Italian Ministry of Health Group of Experts on BIA-ALCL. All participants were asked to provide critical feedbacks and to express their agreement or disagreement on the discussed issues (Tables 1–3). The Delphi method was utilized to build consensus for each statement. All participants were asked to evaluate each statement expressing their agreement/disagreement through comments or assertions in each dedicated section of the manuscript. After a further discussion among the expert group, a final consensus has been reached for each issue and assumed as representative statement. The consensus statements developed through the Delphi process were deemed to be in accordance with the latest directives of the Italian Ministry of Health on BIA-ALCL, with the addition of reconstructive indications [10]. There was no funding source for this study.

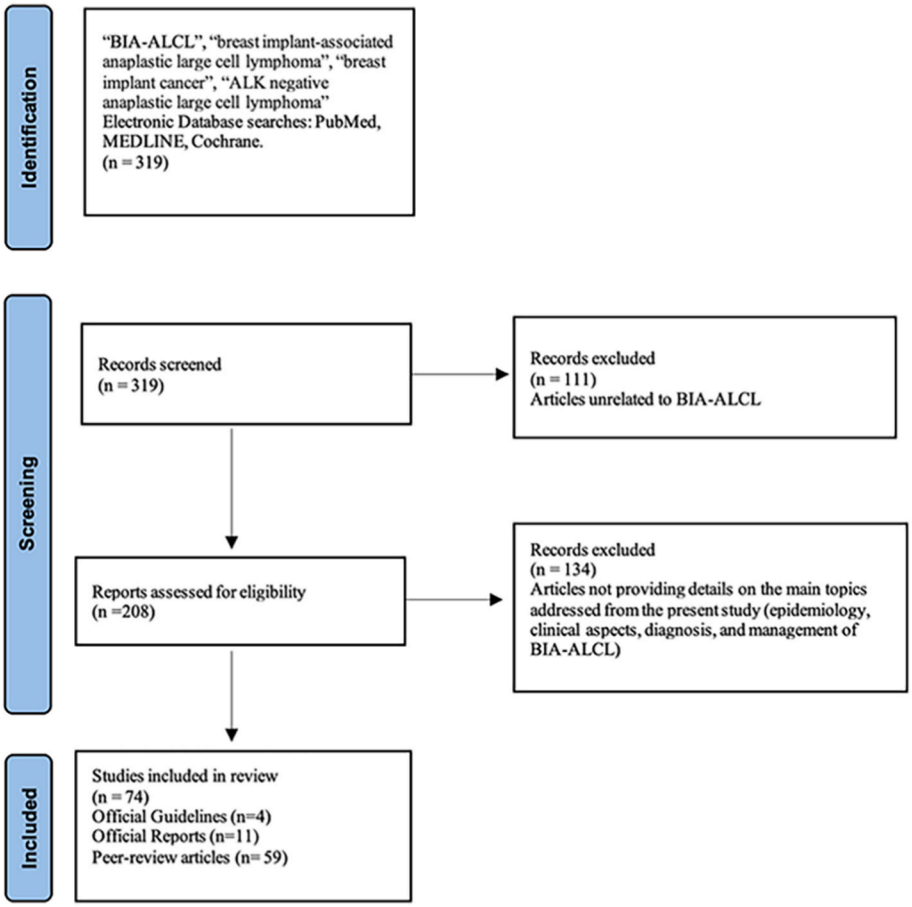

Fig. 1. Study selection process.

Table 1
Consensus statements on the management of patients with suspected Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL).

1	If any of the symptoms associated with BIA-ALCL is detected in a woman with breast implants placed ≥1 year, any physician should refer the patient to perform a breast ultrasound (US) as first-step evaluation
2	If the US detection of a periprosthetic fluid accumulation in a woman with breast implants at ≥ 1 year from implant placement, an US-guided fine-needle aspiration should be performed.
3	To ensure accurate pathological examination, ≥20 ml of serum should be collected with US-guided fine-needle aspiration and submitted to the reference pathology centre.
4	To ensure accurate pathological examination, the aspirated serum should be submitted to the reference pathology centre, as soon as possible, preferably within 12 h. In case of delivery delay, 10% neutral buffered formalin should be added to fix the aspirated serum.
5	If > 20 ml can be safely collected with US-guided fine-needle aspiration, a part of the collected fluid must be sent to the microbiology laboratory for cultural examination.
6	If the US assessment of a woman suspected with BIA-ALCL (implant placement ≥1 year + clinical signs/symptoms associated with BIA-ALCL) reveals or is suspicious for breast implant rupture, further evaluation with MRI is advised.
7	If the US assessment of a woman suspected with BIA-ALCL (implant placement ≥1 year + clinical signs/symptoms associated with BIA-ALCL) reveals lymphadenomegaly, a lymph node biopsy with cytologic, immunohistochemical and cultural analysis is advised.
8	If the US assessment of a woman suspected with BIA-ALCL (implant placement ≥1 year + clinical signs/symptoms associated with BIA-ALCL) reveals the presence of mass, surgical excision with cytologic, immunohistochemical and cultural analysis is advised.
9	If the US assessment of a woman suspected with BIA-ALCL (implant placement ≥1 year + clinical signs/symptoms associated with BIA-ALCL) reveals Type IV capsular contracture (with seroma or locoregional lymphadenopathy), implant removal with en-bloc capsulectomy with cytologic, immunohistochemical and cultural analysis of the implant capsule is advised.

3. Results

The database search strategy yielded 319 publications, which were screened by title and abstract. After removal of 111 reports not pertaining BIA-ALCL, 208 reports were screened as full-text. Seventy-four records (i.e., 59 peer-reviewed articles, 4 official guidelines and 11 official records) were included [Fig. 1]. From the information gathered from literature search an updated review of the epidemiology, pathogenesis, clinical characteristics, and management of BIA-ALCL was drafted. The issues of management of suspected BIA-ALCL cases, management of confirmed cases of BIA-ALCL and breast reconstruction in patients diagnosed with BIA-ALCL were discussed among the panel experts utilizing the Delphi methodology. A consensus was developed for 41 statements (9 for management of suspected BIA-ALCL cases, 26 for management of confirmed BIA-ALCL cases and 6 for breast reconstruction in patients diagnosed with BIA-ALCL). Three distinct process flows for the management of suspected and confirmed cases of BIA-ALCL were built on the consensus statements [Figs. 2–4].

4. Discussion

4.1. Epidemiology

The first case of BIA-ALCL was reported by Keech and Creech in 1997 [11]. The incidence of BIA-ALCL is considered low and typically associated with macrotextured surface implants (according to International Organization for Standardization [ISO] classification) [7,12,13].Nevertheless, further investigation is required to clarify the etiopathogenesis

Table 2
Consensus statements on the management of patients with confirmed diagnosis of Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL).

1	In patients with confirmed diagnosis of BIA-ALCL, PET scan evaluation should be performed to assess for systemic disease, prior to treatment planning.
2	In case PET scan was not performed prior to the oncologic surgery, a PET scan evaluation should be performed post-operatively.
3	Postoperative PET-scan evaluation can be postponed at 2–3 months from surgery, after multidisciplinary single-case evaluation, to avoid equivocal results and interpretation yielded from post-operative inflammation.
4	All patients diagnosed with BIA-ALCL requires implant removal and en bloc capsulectomy.
5	In the presence of suspicious enlarged lymph nodes, surgical lymphadenectomy and bone marrow biopsy should be performed, with implant removal and en-bloc capsulectomy, to assess disease dissemination.
6	After performance of en-bloc capsulectomy, orientation sutures should be placed at the upper pole and anterior margin of the implant capsule and the capsule analysed from the pathologist.
7	In case of capsule fragmentation during removal, the surgeon should mark the fragments with orientation sutures and provide topographical indications of the single fragments.
	Stage I BIA-ALCL
8	Implant removal and en-bloc capsulectomy is the gold-standard of care in patients with Stage I BIA-ALCL
9	Patients diagnosed with stage I BIA-ALCL, and with evidence of negative resection margins (R0) after oncologic surgery, should receive clinical-radiological follow-up evaluation every 3–6 months for the first 2 years.
10	Patients diagnosed with stage I BIA-ALCL, and with evidence of negative resection margins (R0) after oncologic surgery, should receive annual clinical-radiological follow-up evaluation from the 2nd postoperative year up to 5 years.
	Stage II BIA-ALCL
11	A multidisciplinary team evaluation is necessary to plan adequately the treatment of Stage II BIA-ALCL.
12	Implant removal, en-bloc capsulectomy and complete resection of the tumor mass is the recommended surgical approach in patients with stage II BIA-ALCL.
13	Surgical lymphadenectomy should be added to implant removal, en-bloc capsulectomy and tumor mass resection as part of the surgical treatment of patients with locally advanced disease with lymph node involvement (stage IIB T1-N1M0).
14	Patient diagnosed with BIA-ALCL localized to the capsule with lymph node involvement, stage IIB (T1-3N1M0), should be treated with adjuvant chemotherapy and immunotherapy.
15	Patients diagnosed with stage II BIA-ALCL, and with evidence of negative resection margins (R0) after oncologic surgery, should receive annual clinical-radiological follow-up evaluation from the 2nd postoperative year up to 5 years.
16	In case of incomplete tumor surgical excision (R1 and R2), patients with Stage II BIA-ALCL should be evaluated as candidates for adjuvant chemotherapy and immunotherapy.
	Stage III BIA-ALCL
17	A multidisciplinary team evaluation is necessary to plan adequately the treatment of Stage III BIA-ALCL.
18	Implant removal, en-bloc capsulectomy, complete resection of the tumor mass and lymphadenectomy is the recommended surgical approach in patients with stage III BIA-ALCL (T4N(1–2)M0).

(*continued on next page*)

Table 2 (*continued*)

19	Patients diagnosed with BIA-ALCL extending beyond the capsule and with lymph node involvement, stage III BIA-ALCL (T4N(1–2)M0) should be treated with adjuvant chemotherapy and immunotherapy.
Stage IV BIA-ALCL	
20	A multidisciplinary team evaluation is necessary to plan adequately the treatment of Stage IV (AnyT; AnyN; M1) BIA-ALCL.
22	In light of the lack of prospective trials, therapeutic management of disseminated stage IV BIA-ALCL should be guided by current experience and protocols utilized in the treatment of ALCL lymphomas.
22	Tumor debulking surgery should be considered as initial approach in the treatment of disseminated stage IV BIA-ALCL
23	In patients diagnosed with stage IV BIA-ALCL systemic therapy (chemotherapy and immunotherapy) should be postponed after tumor debulking surgery.
24	In patients with stage IV BIA-ALCL local radiation therapy should be considered and evaluated on the basis of tumor response to chemotherapy assessed with PET/CT scans.
25	Patients diagnosed with stage IV BIA-ALCL, after complete treatment, should receive clinical-radiological follow-up evaluation every 3–6 months for the first 2 years.
26	Patients diagnosed with stage IV BIA-ALCL, after complete treatment, should receive annual clinical-radiological follow-up evaluation from the 2nd postoperative year up to 5 years.

Table 3
Consensus statements on breast reconstruction in patients diagnosed with Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL).

1	In patients diagnosed with BIA-ALCL, immediate or delayed breast reconstruction should be considered and provided to patients after being submitted to multidisciplinary team assessment.
2	In patients diagnosed with BIA-ALCL, with disease limited to the implant capsule, stage $\leq$ IIAb, and no signs of chest wall infiltration, immediate reconstruction should be considered.
3	In patients diagnosed with BIA-ALCL and disease stage $\geq$ IIAcw delayed breast reconstruction is recommended.
4	Delayed breast reconstruction in patients diagnosed with BIA-ALCL and disease stage $\geq$ IIAcw must always be preceded by a radiological evaluation which rules out tumor relapse.
5	The use of implants, either textured or smooth, in immediate or delayed breast reconstruction of patients diagnosed with BIA-ALCL, is not advised after both aesthetic and reconstructive procedures.
6	In patients diagnosed with BIA-ALCL, autologous tissue reconstruction, either immediate or delayed (see recommendations 1,2,3) should be preferred over implant placement.

of the disease and the association with different implant types and textures [14,15]. In order to accurately estimate the incidence and risk by country, the single country prevalence of women having breast implants should be known, which is difficult due to the lack of centralized databases and surgical tourism [16,17]. In a study published in 2018 and conducted in The Netherlands, de Boer et al. found a cumulative risk of BIA-ALCL in women with implants of 29/million at 50 years and 82/million at 70 years [18]. They concluded that the number of women with any type of implant needed to cause one BIA-ALCL case was 6920. A retrospective Italian study found an incidence of BIA-ALCL of 2.8 per 100.000 implanted patients (95% CI, 0.88 to 4.84), with 22 confirmed BIA-ALCL cases in Italy, up to 2015 [19]. A new clinical case assessment, updated in June 2019, showed an incidence of 3.5 cases per 100.000 (95% CI, 1.36 to 5.78) in Italy, revealing a slight increase due to increased awareness of the disease [20]. The Italian ministerial database records 79 cases of BIA-ALCL (from 2010 to February 2022), including two deaths [21]. The average time from implantation to the time of diagnosis was 7.77 $\pm$ 4.33 years and the most common symptom at presentation was seroma, detected in 90.6% of patients diagnosed with breast-ALCL [22]. In 40.6% of cases the implants had been placed for aesthetic purposes, while in 59.4% for breast reconstruction. At the time of diagnosis, the mean age was 54.7 $\pm$ 11.8 years. Since the first case report in 1997, the American Society of Plastic Surgeons (ASPS) has recognized a total of 1216 worldwide cases of BIA-ALCL as of June 2022 [23]. The consensus moves towards central registration of cases should enable the collection of more accurate data and epidemiological analysis.

4.2. Pathogenesis

Similar to other anaplastic lymphoma kinase (ALK)-negative ALCL (i.e. systemic and primary cutaneous), BIA-ALCL is composed by large anaplastic tumor cells strongly positive for CD30 and commonly for CD4 and cytotoxic markers, but negative or only occasionally positive for other T-cell associated markers such as CD3, CD5, CD7, and CD8 [24,25]. Despite the morphologic similarities, its distinction from the other types of ALK-negative ALCL is based on both clinical and molecular characteristics [26,27]. The exact cause of BIA-ALCL is not established yet, but current research supports the idea that the development of this lymphoma has a multifactorial aetiology. There are two proposed hypotheses regarding the aetiology of the disease, not necessarily mutually exclusive [28].

1. Genetic predisposition;
2. Chronic inflammation.

Regarding genetic predisposition, few studies highlighted the germline TP53 BRCA 1/2 genes mutations as a possible risk factor for the development of BIA-ALCL, based on the reported higher incidence of BIA-ALCL in patients with Li-Fraumeni Syndrome and BRCA 1/2 carriers [29–33]. However, larger cohorts are needed before any conclusion could be drawn. Local chronic inflammation seems to play a central role in the pathogenesis of the disease [34,35]. Conditions which have been hypothesized as local triggers of chronic inflammation include bacterial contamination, shell shedding of particulates, shell surface friction, and implant-associated reactive compounds [28,36–39]. Regardless of the primary triggers, chronic inflammation could represent the determining factor driving lymphomagenesis by favoring the accumulation of malignancy-promoting mutations into the chronically stimulated T cells [40–46]. To date, there is no general agreement to exclude any of these factors or on how they cooperate in the pathogenesis of BIA-ALCL.

4.3. Disease characteristics

Symptoms usually associated with BIA-ALCL arise at the site of breast implant, whether positioned for aesthetic or reconstructive purposes. In most cases, only one breast is involved, and the most common presentation is a late onset periprosthetic effusion, causing swelling and increase in breast volume and tenderness. These symptoms often appear at least 1 year after and on average 7–10 years following breast implant surgery, with a negative history of trauma or infection. A large spontaneous effusion surrounding the breast implant could be misdiagnosed as an implant rupture. However, implant ruptures do not determine an increase in overall breast volume. The presence of a palpable breast mass is the second most common clinical sign and is associated with a more advanced stage of the disease [47]. Axillary lymphadenopathy may also represent an initial symptom of BIA-ALCL. Less frequently, BIA-ALCL may present as a “Baker IV” capsular contracture with deformation of the breast profile. Rarely described are local signs including skin rash and skin ulceration (<5% of cases) [48–50]. A recent report of thoracic pain in association with pleural effusion as first symptoms of the disease has been described in literature [51]. Although Non-Hodgkin lymphomas are usually staged utilizing the Lugano modification of the Ann Arbor staging system, currently the NCCN guidelines propose the tumor, lymph node, metastasis (TNM) solid tumor staging system for BIA-ALCL,

on the model of the American Joint Committee on Cancer (AJCC) TNM, proving that this staging system predicts patient overall survival more accurately than the Lugano staging system [52]. In a recent study by Campanale et al. stage IIA with chest wall infiltration (IIAcw) showed interestingly a similar prognosis to stage IV, rather than IIA without chest wall infiltration (IIAb) [22] [Fig. 5]. The authors concluded that tumor cells infiltrating chest wall are the critical factor influencing the prognosis, since it prevents the possibility of radical surgical excision. The prognosis of BIA-ALCL is excellent when a proper therapeutic management is performed. It is globally recognized that patients presenting with a mass or with tumor extending beyond the implant capsule have a worse prognosis [53]. To date, in the light of the 35 deaths reported on a total of 1148 confirmed cases, the mortality rate is 1:30.5 [54]. Clemens et al., in 2016 reported an overall survival rate of 91% at 5 years among 87 BIA-ALCL patients [52].

4.4. *Process flow for suspected BIA-ALCL*

According to the 2021 National Comprehensive Cancer Network guidelines, if any physician finds a suspicion of BIA-ALCL with one or more of the symptoms listed above, ultrasonography should be the first step in evaluation [55–57]. In presence of periprosthetic fluid accumulation, ultrasound-guided fine-needle aspiration should be performed in an appropriate healthcare facility. Freshly aspiration fluid should include at least 20 ml of serum and should be submitted as soon as possible, preferably within 12 h, to the pathology reference centre. Otherwise, in case of delivery delay, an adequate amount of 10% neutral buffered formalin could be added to fix the aspirated liquid. Cytological smear and cell block preparation allow morphological examination and immunocytochemical characterization of the inflammatory infiltrate [57,58]. Although CD30 immunohistochemistry is essential for BIA-ALCL diagnosis, it not sufficient alone, since rare CD30 positive activated lymphocytes could be observed in non-neoplastic effusions. Indeed, only the presence in the fluid of more than 10% of large $CD30^{+}$ cells with atypical/anaplastic morphology rises the suspicious of a BIA-ALCL. Besides the uniform positivity to CD30, additional markers should also be investigated to make the definitive diagnosis of BIA-ALCL. In particular, the negativity for ALK protein is essential, whereas the partial expression of pan-T-cell antigens and/or of a clonal rearrangement of the T-cell receptor genes exclude the possible diagnosis of the recently reported Epstein Barr virus-positive B-cell lymphomas associated with breast implants [59,60]. If the effusion is more than 20 ml, a part must be sent to the microbiology laboratory for a cultural examination. Ultrasound guidance must always be used to avoid implant damage. If a suspicion of implant rupture arises from ultrasonography, magnetic resonance imaging (MRI) is also recommended. In presence of periprosthetic mass and/or locoregional lymphadenopathy or type IV capsular contracture associated with seroma or locoregional lymphadenopathy, computed tomography associated with positron emission (CT/PET) is strongly recommended. The patient should be referred to a Breast Unit for a multidisciplinary evaluation, planning a surgical program to perform a biopsy of the mass and/or of any suspicious lymph nodes, and/or to remove the implant along with the periprosthetic capsule. Fig. 2 shows the BIA-ALCL diagnostic algorithm in

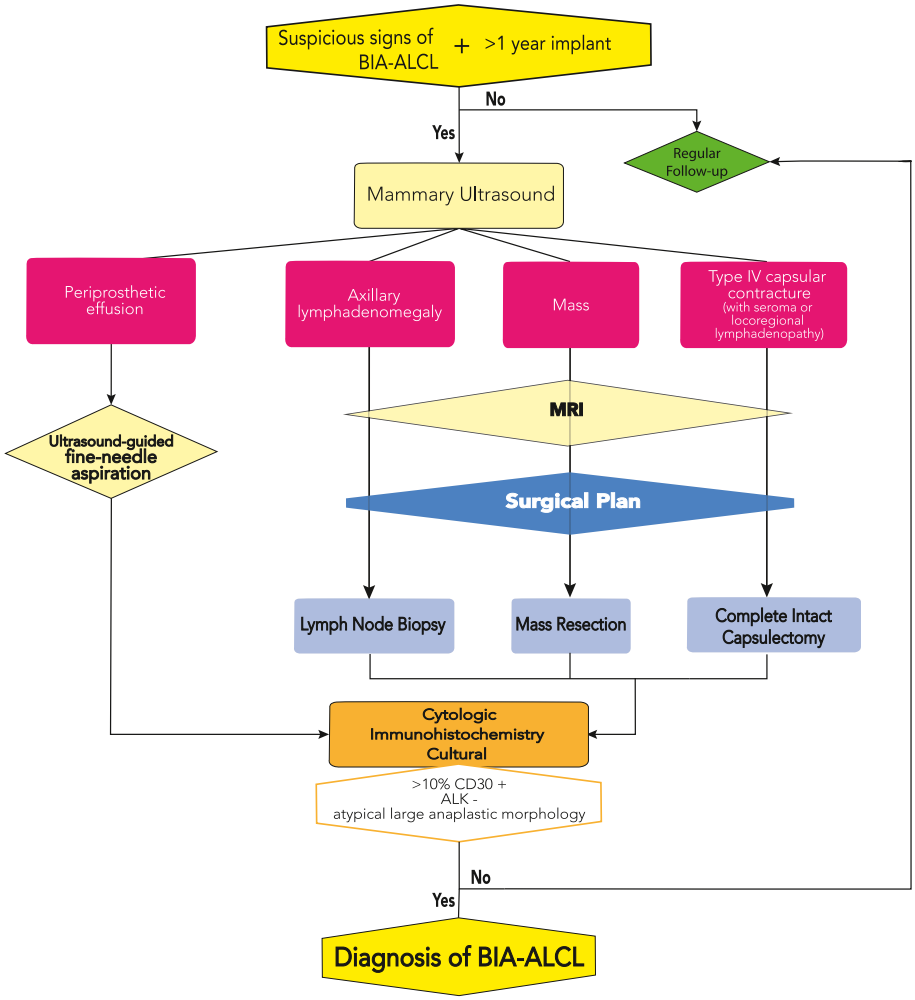

Fig. 2. Diagram showing process flow for suspected BIA-ALCL.

the context of any suspicious clinical signs.

4.5. Process flow for confirmed diagnosis of BIA-ALCL

In presence of a confirmed diagnosis of BIA-ALCL made on fluid, periprosthetic capsule, mass or lymph node, positron emission tomography computed tomography (PET/CT) scan should be planned to develop a program for the following treatments and to assess for systemic disease. If PET/CT scan has been not performed before surgical treatment, it should be postponed 1–3 months after surgery to reduce any possible surgery-induced inflammation. In case PET/CT reveals that the disease is confined to the fluid accumulation or periprosthetic capsule (Stage I, T1/T2/T3N0M0), an en-bloc capsulectomy is required as gold standard procedure. There is much confusion regarding terminology of capsulectomy. As described by Gerzenshtein J., "partial capsulectomy" is the removal of the thickened or calcified portion of the breast capsule only, while "complete capsulectomy" the complete removal of the breast capsule but not together with the implant [61]. Further, the "complete intact capsulectomy" is the total removal of the intact breast capsule along with the implant and as the only oncological excision procedure there is the "en-bloc capsulectomy", or rather the complete removal of the capsule together with implant, with a defined margin of healthy tissue around it. In an elegant study conducted by Clemens et al. emerged that complete surgical excision prolonged overall survival ($p = 0.001$) and event-free survival ($p = 0.001$) compared with the other therapeutic interventions [52]. The specimen should be then oriented with surgical sutures indicating the upper pole and the anterior margin to allow subsequent pathological evaluation of resection margins. If the capsule is mistakenly removed in fragments, the surgeon should indicate their topographical location. After surgery and in case of BIA-ALCL confined only in the periprosthetic capsule with negative margins (R0), clinical-radiological follow-up should be performed every 3–6 months for the first 2 years and annually up to 5 years.

In the case of locally advanced disease with the presence of mass or chest wall infiltration (stage IIA, T4N0M0), a multidisciplinary evaluation is required to set up therapeutic modalities. In this scenario the surgical approach should be en-bloc capsulectomy along with removal of the mass with malignant-free surgical margins. Removal of the posterior part of capsule could be the hardest part of the procedure, especially in subpectoral implant, but it is the key to prevent the recurrence of the disease [62]. After surgical treatment, the patient should perform a clinical-radiological follow-up every 3–6 months for the first 2 years, then annual checks up to 5 years. Patients with positive margins of surgical resection (R1 = microscopic cancer residue; R2 = macroscopic cancer residue) should be candidates for adjuvant chemotherapy and immunotherapy (Brentuximab vedotin) [63]. Moreover, if residual disease is present, the multidisciplinary team should consider whether to refer the patient to post-operative radiotherapy in addition to chemo/-immunotherapy. In the case of patients with suspected enlarged lymph nodes, surgical lymphadenectomy and bone marrow biopsy are required in addition to the en-bloc capsulectomy to allow assessment of disease dissemination to lymph nodes (stage IIB and III) and/or to the bone marrow (stage IV). Patients with BIA-ALCL localized to the capsule but with lymph nodes involved (stage IIB T1-3N1M0) or extended beyond the capsule and disseminated to the lymph nodes (stage III T4N1-2M0), after en-bloc capsulectomy, the multidisciplinary team should indicate to administer adjuvant systemic chemotherapy and immunotherapy (Brentuximab vedotin). There are no still prospective trials to guide the management of patients with distant disseminated disease, so the therapeutic management is entrusted to the experience on the treatment of primary cutaneous and systemic ALCL. The most frequent used therapeutic protocol is CHOP or CHOEP (cyclophosphamide, hydroxydaunorubicin (doxorubicin), (etoposide) vincristine and prednisolone), based on experience with this regimen from other types of ALCL lymphomas [60,64–66]. Multidisciplinary team can also evaluate to perform local consolidation radiotherapy, based on the response to chemotherapy revealed at PET/CT scans. After appropriate treatment, the patient should perform a clinical-radiological follow-up every 3–6 months for the first 2 years, then annual checks up to 5 years. Surgical treatment should be performed as first in order to resect as much tumor as possible, and, whenever deemed feasible, also in disseminated disease (stage IV – $T_{any}N_{any}M_1$) [20,22]. Nevertheless, in the light of limited evidence on treatment of stage IV disease, appropriate treatment should always be tailored by the multidisciplinary team on the basis of the extent of metastatic dissemination and neoadjuvant systemic therapy might be considered [67,68]. In all cases, patients with BIA-ALCL should be treated and followed-up by a multidisciplinary team, guaranteed within the reference Breast Unit. Each new diagnosis of BIA-ALCL including its clinical-pathological staging must be obligatorily notified to the respective Competent Authorities on medical devices. Fig. 3 depicts the therapeutic algorithm in presence of confirmed diagnosis of BIA-ALCL.

4.6. Breast reconstruction following BIA-ALCL diagnosis

In patients diagnosed with BIA-ALCL the issue arises of how to proceed with the reconstructive process. There is no consensus in the literature regarding the timing of breast reconstruction after BIA-ALCL diagnosis [69]. In our opinion an immediate breast reconstruction should be strongly considerated in cases without signs of chest wall infiltration on preoperative radiological examination and/or up to stage IIAb, or rather pathology confined to the implant capsule. In cases of more advanced disease (stage IIAcw – IV), the surgeon should strongly consider delayed reconstruction, referring the patient to scheduled radiological inspections. No evidence-based recommendation can be developed on the safe timing for delayed breast reconstruction, however based on current evidence on relapses of disseminated peripheral T-cell lymphomas (PTCL), breast reconstruction should be delayed at least 5 years from the end of complete treatment and decision must be guided by of follow-up radiological evidence [70,71]. There is no definite evidence that preclude any association between smooth implants and the pathogenesis of the BIA-ALCL. For this reason, it is not recommended and should be avoided any type of implant placement, neither textured or smooth, after the en-bloc capsulectomy both in aesthetic and reconstructive patients. Conversely, it is highly recommended to opt for an autologous breast reconstruction, using indifferently free flaps, FALD flap or autologous fat grafting alone [72–75]. Removal of the contralateral breast implant should be performed, since in a low percentage of cases BIA-ALCL also involved the contralateral breast [76]. Fig. 4 shows the decisional algorithm for breast reconstruction following BIA-ALCL diagnosis and en-bloc capsulectomy.

4.7. Process flow for patients with breast implants

There are no relevant studies regarding management of asymptomatic patients with macrotextured implants and there is no data to support the prophylactic removal of textured implants in asymptomatic patients to date [77,78]. On 2019 following macrotextured breast implant recall, ANSM did not recommend preventive explantation for women carrying these implants [79]. In October 2020, the TGA affirmed that even if breast implants are being cancelled, suspended or recalled, medical experts do not recommend removing them if patient does not have symptoms of BIA-ALCL [80]. In May 2022, also in Canada, where Biocell macrotextured breast implants have been withdrawn from the market, Health Canada declared that removing breast implants is not recommended if patient does not have any signs or symptoms suggesting BIA-ALCL. Patients should discuss risks and benefits of removal with their healthcare professional [81]. Even in patients at higher risk of BIA-ALCL, such as Allergan Biocell implants carriers, the rate of them who will develop the disease remains low [82,83]. There is no evidence in literature that suggests that a complete capsulectomy in asymptomatic patients reduces the risk of BIA-ALCL [84], being these procedures

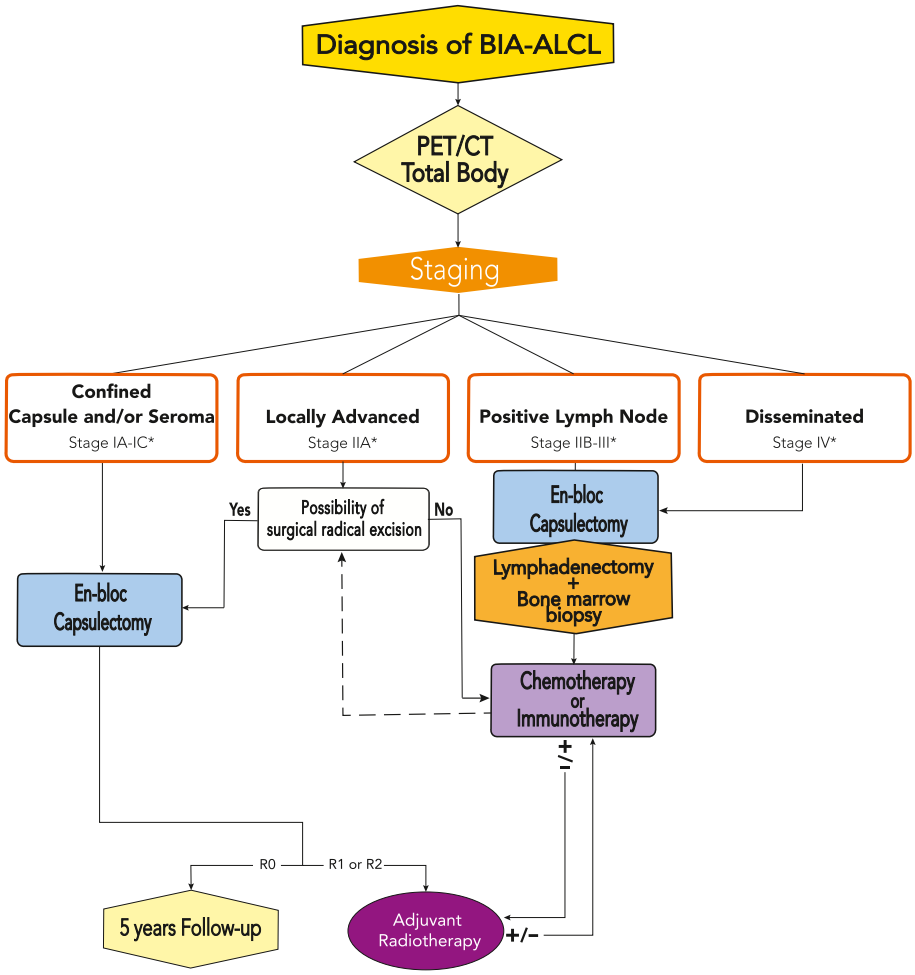

Fig. 3. Diagram showing process flow for confirmed diagnosis of BIA-ALCL.

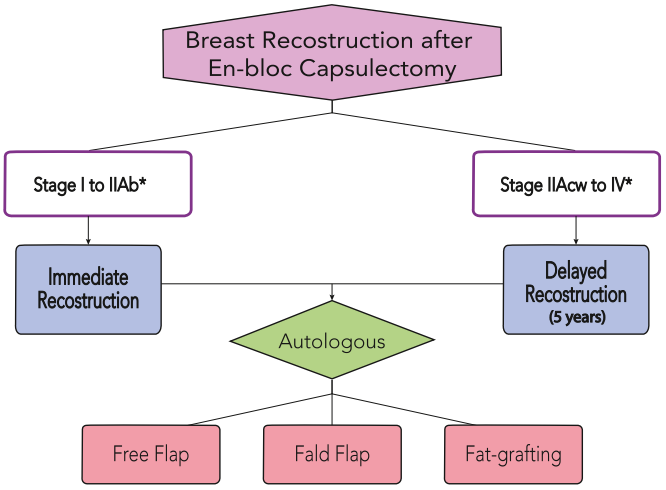

Fig. 4. Diagram showing suggested indications for breast reconstruction following BIA-ALCL diagnosis.

burdened by different degrees of morbidity and negative cosmetic impact [85]. The FDA and the American Society of Plastic Surgeons (ASPS) clarified that the prophylactic removal of textured breast implants in asymptomatic patients is not recommended [86]. In particular, the FDA has specifically stated "If you have no symptoms, we are not recommending the removal of these or other types of breast implants due to the low risk of developing BIA-ALCL" [87]. In 2019, the Italian Ministry of Health declared that there are no sufficient reasons to recommend the withdrawal from commercial availability of the textured implants. Moreover, the same Italian Ministry of Health affirmed that there is no indication to surgically remove the smooth or textured implant in the absence of clinical suspicion of BIA-ALCL [88]. It is strongly recommended to have a clear and transparent conversation with the patient, in order to inform her on the possible risks and benefits of each procedure, to achieve a shared decision to remove the implant and the periprosthetic capsule. In any case, all asymptomatic patients with breast implants should have regular follow-up with exam and imaging as indicated by oncologists and surgeons.

5. Conclusions

Clinical recommendations are needed to guide physicians in the diagnosis and management of BIA-ALCL, an uncommon disease diagnosed in women with breast implants. The present study provides updated practical recommendations, encompassing all steps of BIA-ALCL management, from diagnostic work-up to surgical treatment, developed by a group of multidisciplinary experts on BIA-ALCL. Complete information in the medical field is of utmost importance for timely diagnosis, right management including implant removal, proper selection of capsulectomy type and appropriate follow-up of BIA-ALCL. Autologous reconstruction can be performed in an immediate setting for patients with local disease, while a delayed reconstruction should be considered for patients with disseminated disease or without a radically resectable mass. Multidisciplinary team approach is crucial for the

TNM classification	TNM stage			
T: Tumor extent	IA	T1	N0	M0
T1: Confined to seroma or a layer on luminal side of capsule	IB	T2	N0	M0
T2: Early capsule infiltration	IC	T3	N0	M0
T3: Cell aggregates or sheets infiltrating the capsule	IIAb	T4b	N0	M0
T4: Lymphoma beyond the capsule; without (T4b) or with (T4cw) chest wall infiltration	IIAcw	T4cw	N0	M0
N: Lymph node	IIB	T1	N1	M0
N0: No lymph node involvement	IIB	T2	N1	M0
N1: One regional lymph node (+)	IIB	T3	N1	M0
N2: Multiple regional lymph nodes (+)	III	T4	N1	M0
M: Metastasis	III	T4	N2	M0
M0: No distant spread	IV	Any TN		M1
M1: Spread to other organs/distant sites				

Fig. 5. TNM staging system for BIA-ALCL.

correct management and follow-up. Future efforts are needed for the development of mandatory national registries and shared international guidelines.

Author contribution

BL, ADN, GC, PV, SP, MM, RDV, NF, PC, CB, VC are the members of the expert group on BIA-ALCL; all have participated to the Delphi process and contributed to the development of the consensus recommendations on BIA-ALCL. GS, GD, MG performed the systematic review of the literature, cowrote and critically revised the manuscript.

Declaration of competing interest

The authors have no conflicts of interest to declare.

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