Ontario Health
Cancer Care Ontario

Guideline Endorsement GL-END-C50-35

A Quality Initiative of the Surgical Oncology Program (SOP), Ontario Health (Cancer Care Ontario)

An Endorsement of the 2022 NCCN Guideline on Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL)

F.C. Wright, J. Lipa*, T. Zhong, E. Piliotis, Z. Ghorab, P. Stotland, M. Lee and the Diagnosis and Treatment of BIA-ALCL Guideline Development Group*

Report Date: August 14, 2023

This document describes the Ontario Health (Cancer Care Ontario) Surgical Oncology Program endorsement of the National Comprehensive Cancer Network (NCCN) Version 2.2022 T-Cell Lymphomas Guideline on Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL). The original publication is available at nccn.org.

For information about this document, please contact Dr. F.C. Wright at:
Phone: 416-480-4210 Fax: 416-480-6002 E-mail: Frances.Wright@sunnybrook.ca

Please visit the Ontario Health (Cancer Care Ontario) website at https://www.cancercareontario.ca/en/guidelines-advice for the most current version of all reports.

Report Citation (Vancouver Style): Wright FC*, Lipa J*, Zhong T, Piliotis E, Ghorab Z, Stotland P, Lee M. An Endorsement of the 2022 NCCN Guideline on Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL). Toronto (ON): Ontario Health (Cancer Care Ontario); *2023 August 14*. Ontario Health (Cancer Care Ontario) Guideline Endorsement No.: GL-END-C50-35.

*Co-first authors

Table of Contents

Section 1: Guideline Endorsement 1

Section 2: Endorsement Methods Overview 7

References 19

Appendix 1: Affiliations and Conflict of Interest Declarations 20

Appendix 2: Agree II Score Sheet 22

An Endorsement of the 2022 NCCN Guideline on Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL)

Section 1: Guideline Endorsement

GUIDELINE OBJECTIVES

The objectives of this guideline are to provide recommendations on diagnosing and treating Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL). The recommendations are based on the National Comprehensive Cancer Network (NCCN) Version 2.2022 T-Cell Lymphomas Guideline on BIA-ALCL [1].

TARGET POPULATION

Patients with suspected or confirmed BIA-ALCL.

INTENDED USERS

The guideline document will support providers in diagnosing and treating patients with BIA-ALCL.

ENDORSEMENT

The Diagnosis and Treatment of BIA-ALCL Guideline Development Group (GDG) of Ontario Health (Cancer Care Ontario) endorses the majority of the recommendations of the NCCN T-Cell Lymphomas Guideline on BIA-ALCL, available at nccn.org, as modified by the endorsement process described in this document. These recommendations are reprinted below with the permission of the NCCN, with modifications noted.

Fourteen of the 36 recommendations were endorsed without modifications or comments. Twenty-one recommendations were endorsed with comments and 1 recommendation (4.4) was not endorsed (with explanation) as listed in Table 1-1.

Table 1-1. NCCN T-Cell Lymphomas guideline recommendations: BIA-ALCL [1]

Recommendations	Assessment
1. Clinical Presentation	
1.1 Physical signs (effusion, enlargement, mass, ulceration) >1 y post implantation (Average 7-9 y post implantation)	**ENDORSED**
1.2 Rare cases with parenchymal breast or nodal involvement may have an aggressive course more in line with systemic ALK-positive ALCL. Optimal treatment of these cases is not well defined and management should be individualized	**ENDORSED**

2. Initial Workup	
2.1 Ultrasound of breast and axilla, or Breast MRI in selected cases, or PET/CT scan in selected cases Patients with T-cell lymphomas often have extranodal disease, which may be inadequately imaged by CT. PET scan may be preferred in these instances. **Comment:** Contrast-enhanced breast MRI with implant specific sequences may be performed in selected cases during initial workup. Mammogram is not indicated in the workup of the involved breast as it is not accurate in the diagnosis of BIA-ALCL; however, if the contralateral breast remains and does not have fluid collection, then contralateral mammogram should be performed. PET scan should be considered only after diagnosis. Imaging should ideally be done at a diagnostic imaging department in a hospital or cancer centre with breast imaging expertise.	**ENDORSED with comment**
Any effusion	
2.2 FNA biopsy of fluid around breast implant Larger volume of fluid yields a more accurate diagnosis. If possible, obtain >50 mL for cytology and cell block; >10 mL for flow cytometry immunophenotype. **Comment:** Volumes are minimum volumes and the entire large volume first aspirate should be sent for pathology. In the laboratory requisition, it should be indicated that lymphoma is a diagnostic consideration. As specimen should get to pathology optimally within an hour, recommend that this is done in a diagnostic imaging department in a hospital or cancer centre with breast imaging expertise.	**ENDORSED with comment**
2.3 Prior serial aspirations may decrease or dilute tumor burden and make diagnosis more challenging; therefore, pathology review of the first aspiration is advisable	**ENDORSED**
Mass	
2.4 Biopsy of mass **Comment:** Core biopsy of suspicious lymph nodes when considering a diagnosis of BIA-ALCL should also be performed ideally at a diagnostic imaging department in a hospital or cancer centre with breast imaging expertise. False negative results of lymph node FNA may occur in the setting of BIA-ALCL.	**ENDORSED with comment**
Ultrasound inconclusive	
2.5 Breast MRI, if not previously done, and follow pathway above for any effusion or mass (as appropriate) **Comment:** See NCCN pathway (nccn.org). If ultrasound is inconclusive, perform contrast-enhanced breast MRI with implant specific sequences. This should be performed ideally at a diagnostic imaging department in a hospital or cancer centre with breast imaging expertise.	**ENDORSED with comment**
3. Pathologic Workup following FNA biopsy of fluid around breast implant or biopsy of mass	
ESSENTIAL pathologic workup	
3.1 Cytology with cell block preparation Larger volume of fluid yields a more accurate diagnosis. If possible, obtain >50 mL for cytology and cell block.	**ENDORSED**

3.2 IHC and/or flow cytometry may include CD2, CD3, CD4, CD5, CD7, CD8, CD30, CD45, and ALK Larger volume of fluid yields a more accurate diagnosis. If possible, obtain >10 mL for flow cytometry immunophenotype. **Comment**: BIA-ALCL is CD30 positive and ALK negative. Flow cytometry/immunohistochemistry should also include CD20.	**ENDORSED with comment**
USEFUL UNDER CERTAIN CIRCUMSTANCES during pathologic workup	
3.3 If there is solid mass associated with the implant, biopsy (excisional or incisional or core needle) may be required for diagnosis **Comment:** When suspicion of BIA-ALCL, core biopsy or incisional biopsy should be the goal. If due to the location of the lesion, this cannot be carried out, recommend discussion at a Multidisciplinary Cancer Conference (MCC). Biopsy should be performed ideally at a diagnostic imaging department in a hospital or cancer centre with breast imaging expertise.	**ENDORSED with comment**
If indeterminate of lymphoma on pathologic workup	
3.4 Second pathology consultation by tertiary cancer center **Comment:** In Ontario, a tertiary cancer centre is a regional cancer centre. Second pathology consultation should be done by a hematopathologist/pathologist with expertise in lymphoma.	**ENDORSED with comment**
Negative for lymphoma	
3.5 Refer to plastic surgeon for management **Comment**: For cosmetic implants, patients should be referred to the community/cosmetic surgeon who placed the implant. For reconstructions, patients should be referred to the implanting surgeon.	**ENDORSED with comment**
Histologic confirmation or suspicion of BIA-ALCL	
3.6 The histopathologic findings of BIA-ALCL need to be correlated with a clinical presentation and history of a breast implant to achieve a definitive diagnosis [2] **Comment**: All confirmed or highly suspicious cases should be discussed at a MCC. In Ontario, we recommend a multidisciplinary team at a cancer centre with a special interest in BIA-ALCL (e.g., malignant hematologist, plastic surgeon, hematopathologist/pathologist with expertise in lymphoma, and a surgeon with a specialized interest in breast cancer) be involved in a patient's care who has been diagnosed with BIA-ALCL.	**ENDORSED with comment**
3.7 The FDA recommends reporting all BIA-ALCL cases to the PROFILE Registry: www.thepsf.org/PROFILE **Comment**: Canada does not have an equivalent PROFILE registry. Report cases of BIA-ALCL by completing the Consumer Medical Device Report Form found here: https://health.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/problem-reporting/medical-device-consumer.html.	**ENDORSED with comment**

<table>
<tr><th colspan="2">4. Lymphoma Workup and Staging</th></tr>
<tr><td>4.1 Recommend discussion of treatment options with multidisciplinary team (e.g., medical oncologist/hematologist, surgical oncologist, plastic surgeon, hematopathologist)
<u>Comment</u>: Treatment options should be discussed with a multidisciplinary team at a cancer centre with a special interest in BIA-ALCL (e.g., malignant hematologist, plastic surgeon, hematopathologist/pathologist with expertise in lymphoma, and a surgeon with a specialized interest in breast cancer).</td><td>ENDORSED with comment</td></tr>
<tr><td>4.2 H&P examination, including complete skin examination</td><td>ENDORSED</td></tr>
<tr><td>4.3 CBC with differential, comprehensive metabolic panel and LDH
<u>Comment</u>: Metabolic panel includes blood glucose, electrolytes, creatinine, liver function tests (AST, ALT, bilirubin).</td><td>ENDORSED with comment</td></tr>
<tr><td>4.4 Assessment of HTLV1/2 by serology or other methods
<u>Explanation</u>: BIA-ALCL is not associated with HTLV1/2 infection and testing for this virus is not indicated.</td><td><u>Not ENDORSED</u> (with explanation)</td></tr>
<tr><td>4.5 PET/CT scan
Patients with T-cell lymphomas often have extranodal disease, which may be inadequately imaged by CT. PET scan may be preferred in these instances.
<u>Comment</u>: PET-CT should be performed prior to surgery to allow a baseline for the surgical site and assist with operative planning in the case of a tumor mass.</td><td>ENDORSED with comment</td></tr>
<tr><td>4.6 Echocardiogram or MUGA scan if anthracycline-based regimen is indicated</td><td>ENDORSED</td></tr>
<tr><td>4.7 Pregnancy testing in patients of childbearing potential (if chemotherapy or RT planned)</td><td>ENDORSED</td></tr>
<tr><td>4.8 Bone marrow biopsy is only needed in selected cases (e.g., extensive disease or unexplained cytopenia)</td><td>ENDORSED</td></tr>
<tr><td>4.9 Proposed TNM Staging for BIA-ALCL [3]
<table>
<tr><th>TNM</th><th>Description</th></tr>
<tr><td>T: tumor extent</td><td></td></tr>
<tr><td>T1</td><td>Confined to effusion or a layer on luminal side of capsule</td></tr>
<tr><td>T2</td><td>Early capsule infiltration</td></tr>
<tr><td>T3</td><td>Cell aggregates or sheets infiltrating the capsule</td></tr>
<tr><td>T4</td><td>Lymphoma infiltrates beyond the capsule</td></tr>
<tr><td>N: lymph node</td><td></td></tr>
<tr><td>N0</td><td>No lymph node involvement</td></tr>
<tr><td>N1</td><td>One regional lymph node (+)</td></tr>
<tr><td>N2</td><td>Multiple regional lymph nodes (+)</td></tr>
<tr><td>M: metastasis</td><td></td></tr>
<tr><td>M0</td><td>No distant spread</td></tr>
<tr><td>M1</td><td>Spread to other organs/distant sites</td></tr>
</table>
<table>
<tr><th>Stage Designation</th><th>Description</th></tr>
<tr><td>IA</td><td>T1 N0 M0</td></tr>
<tr><td>IB</td><td>T2 N0 M0</td></tr>
<tr><td>IC</td><td>T3 N0 M0</td></tr>
<tr><td>IIA</td><td>T4 N0 M0</td></tr>
<tr><td>IIB</td><td>T1–3 N1 M0</td></tr>
<tr><td>III</td><td>T4 N1–2 M0</td></tr>
<tr><td>IV</td><td>T any N any M1</td></tr>
</table>
Bilateral breast implantation for ALCL is not considered in this staging system. Complete excision of bilateral disease may be recommended if it is determined that 2 independent primaries are present (one on each side). Pathologic staging should be assessed in both sides. Identification of clonal abnormalities in bilateral cases is desirable and may help in determining if the disease represents metastasis.</td><td>ENDORSED</td></tr>
</table>

5. Treatment	
5.1 Total capsulectomy and excision of associated mass with biopsy of suspicious node(s), explantation **Comment**: Biopsy of suspicious node(s) should be done pre-operatively. If lymph node is indeterminate or positive on core biopsy, then a targeted lymph node removal for diagnosis can be completed at the time of surgery by a surgeon with a specialized interest in breast cancer. A plastic surgeon with a specialized interest in breast diseases who works at a regional cancer centre should do the total capsulectomy and explantation. Recommend review at a MCC to determine extent of excision.	**ENDORSED with comment**
5.2 Removal of contralateral implant **Comment**: Recommend with total capsulectomy by a plastic surgeon with a specialized interest in breast diseases who works at a regional cancer centre.	**ENDORSED with comment**
5.3 Consultation with surgical oncologist recommended for patients with preoperative tumor mass **Comment**: Consultation with a surgeon with a specialized interest in breast cancer recommended for patients with preoperative tumor mass and/or nodal involvement for coordination of care.	**ENDORSED with comment**
5.4 As BIA-ALCL is not a disease of the breast parenchyma, there is no role for mastectomy or sentinel lymph node biopsy	**ENDORSED**
5.5 May consider immediate (early stage) or delayed (advanced stage) breast reconstruction with autologous tissue or smooth surface breast implants [4] **Comment**: Safety of doing an immediate breast reconstruction should also be discussed at a MCC prior to surgery.	**ENDORSED with comment**
6. Follow-up/Additional Therapy	
Localized disease to capsule/implant/breast – Complete excision with no residual disease	
6.1 Clinical: H&P for every 3-6 mo for 2 y and then as clinically indicated	**ENDORSED**
6.2 Surveillance imaging (no more often than every 6 mo for 2 y and then annually for 5 y or as clinically indicated) Patients with T-cell lymphomas often have extranodal disease, which may be inadequately imaged by CT. PET scan may be preferred in these instances. **Comment**: If breast tissue remains, follow appropriate breast screening guidelines. For surveillance of BIA-ALCL, PET 6 months post-op should also be performed to ensure resolution of FDG activity. Once FDG activity resolves, no further body imaging is required, unless there is clinical suspicion of recurrence.	**ENDORSED with comment**
Localized disease to capsule/implant/breast – Incomplete excision or partial capsulectomy with residual disease ± regional lymph node involvement	
6.3 Discuss adjuvant treatment options with multidisciplinary team: RT for local residual disease ± systemic therapy (as listed below), if node positive or RT not feasible **Comment**: Treatment options should be discussed with a multidisciplinary team at a cancer centre with a special interest in BIA-	**ENDORSED with comment**

ALCL (e.g., malignant hematologist, plastic surgeon, hematopathologist/pathologist with expertise in lymphoma, and a surgeon with a specialized interest in breast cancer).	
6.4 If CR is achieved after systemic therapy, treat as ALCL, ALK-	**ENDORSED**
Extended disease (stage II-IV)	
6.5 Consider systemic therapy (see suggested treatment regimens below)	**ENDORSED**
6.6 If CR is achieved after systemic therapy, treat as ALCL, ALK-	**ENDORSED**
6.7 Local disease relapse may be amenable to re-excision surgery alone without requiring systemic therapies **Comment**: All treatment options (surgery, radiation, systemic therapy) should be discussed with a multidisciplinary team at a cancer centre with a special interest in BIA-ALCL (e.g., malignant hematologist, plastic surgeon, hematopathologist/pathologist with expertise in lymphoma, and a surgeon with a specialized interest in breast cancer).	**ENDORSED with comment**
6.8 Suggested treatment regimens, systemic therapy [5,6,7]: • Brentuximab vedotin - Brentuximab vedotin may be appropriate for low-burden disease in selected patients • Brentuximab vedotin + CHP (cyclophosphamide, doxorubicin, and prednisone) • CHOP • CHOEP - Oral etoposide dose of 200 mg/m^2 (PO dosing of etoposide is 2x the IV dose) may be substituted on days 2 and 3 for IV etoposide. Consider splitting the daily doses of oral etoposide over 200 mg • Dose-adjusted EPOCH **Comment**: At the present time (2023), Brentuximab vedotin + CHP is the standard therapy.	**ENDORSED with comment**

An Endorsement of the 2022 NCCN Guideline on Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL)

Section 2: Endorsement Methods Overview

BACKGROUND FOR GUIDELINE

Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL) is an uncommon, but emerging T-cell non-Hodgkin lymphoma, almost exclusively arising in patients with textured surface breast implants. The disease can present with swelling or asymmetry of the breast, pain, capsular contracture, a breast lump or mass, and/or involvement of the lymph nodes [8].

There is currently no established guideline, specific to Ontario, in this area. The purpose of this endorsement document is to provide clinicians with evidence-based guidance on how to diagnose and treat patients with BIA-ALCL.

GUIDELINE ENDORSEMENT DEVELOPERS

This endorsement project was developed by the Diagnosis and Treatment of BIA-ALCL Guideline Development Group (GDG) (Appendix 1), which was convened at the request of the Surgical Oncology Program (SOP) at Ontario Health (Cancer Care Ontario). The project was led by a small Working Group of the GDG, which was responsible for reviewing the evidence base and recommendations in the National Comprehensive Cancer Network (NCCN) Version 2.2022 T-Cell Lymphomas Guideline on BIA-ALCL [1] in detail and making an initial determination as to any necessary changes, drafting the first version of the endorsement document, and responding to comments received during the document review process. The Working Group members had expertise in general surgery, plastic surgery, hematology and hematopathology. Other members of the Diagnosis and Treatment of BIA-ALCL GDG served as the Expert Panel and were responsible for the review and approval of the draft document produced by the Working Group. Conflict of interest declarations for all GDG members are summarized in Appendix 1.

ENDORSEMENT METHODS

The SOP endorses guidelines using the process outlined in Ontario Health (Cancer Care Ontario)'s Guideline Endorsement Protocol [9]. This process includes selection of a guideline, assessment of the recommendations (if applicable), drafting the endorsement document by the Working Group, and internal review by content and methodology experts.

The SOP assesses the quality of guidelines using the AGREE II tool [10]. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour and transparency of guideline development and to improve the completeness and transparency of reporting in practice guidelines.

Selection of Guidelines

As a first step in developing this document, a search for existing guidelines was undertaken to determine whether any guideline could be endorsed. A literature search in Google was performed on March 8, 2021 with the search terms "guidelines + patients + management + implant associated ALCL." A total of two organizational guidelines were found and two additional were recommended by a Working Group member, all of which were reviewed by the SOP. The guideline that was deemed to be the most relevant and comprehensive was a supplement to the 2019 NCCN Guideline on BIA-ALCL. However, for the guideline endorsement,

the SOP chose to endorse the original, most recent version, of the NCCN guideline (version 2.2022) as potentially useful and relevant to guide practice in Ontario.

Assessment of Guideline(s)

The Working Group selected the 2022 NCCN T-Cell Lymphomas Guideline on BIA-ALCL because it outlines evidence-based recommendations for the full treatment pathway, from clinical presentation to follow-up/additional therapy [1]. In addition, the guideline was selected because the rigor of development domain, which assesses the methodological quality of the guideline, had a high score.

Details of the AGREE II assessment can be found in Appendix 2. The overall quality of the guideline was rated as "6" by both appraisers (on a scale from 1 to 7). Both appraisers stated that they would recommend this guideline for use. The AGREE II quality ratings for the individual domains were varied; they were assessed at 97% for scope and purpose, 61% for stakeholder involvement, 89% for rigor of development, 89% for clarity of presentation, 25% for applicability, and 100% for editorial independence.

DESCRIPTION OF ENDORSED GUIDELINE(S)

The 2022 NCCN T-Cell Lymphomas Guideline presents updated recommendations on the diagnosis and treatment of patients with BIA-ALCL, including clinical presentation, initial workup, pathologic workup, lymphoma workup and staging, treatment, and follow-up/additional therapy. Prior to the update of this version of the guideline, a literature search of the PubMed database was performed to obtain literature since the previous guideline update in 2021. The results were narrowed to studies in humans published in English and restricted to Clinical Trials (Phase II to IV), Guidelines, Randomized Controlled Trials, Meta-Analyses, Systematic Reviews, and Validation Studies [1].

The PubMed search results were examined and data from key articles deemed relevant by the NCCN Guidelines Panel were included. Recommendations that lacked high-level evidence were based on expert opinion and the Guideline panel's review of lower-level evidence [1]. Further details on the Development and Update of NCCN Guidelines can be found at nccn.org.

ENDORSEMENT PROCESS

The Working Group reviewed the 2022 NCCN T-Cell Lymphomas Guideline on BIA-ALCL [1] in detail and reviewed each recommendation to determine whether it could be endorsed, endorsed with changes, or rejected. This determination was based on the agreement of the Working Group with the interpretation of the available evidence presented in the guideline, and whether the recommendation was applicable and acceptable to the Ontario context, whether it was feasible for implementation, and whether new evidence reported since the guideline was developed might change any of the recommendations.

For each of the recommendations, the Working Group considered the following issues:

1) Does the Working Group agree with the interpretation of the evidence and the justification of the original recommendation?
2) Are modifications required to align with the Ontario context?
3) Is it likely there is new, unidentified evidence that would call into question the recommendation?
4) Would additional statements of qualification/clarification be valuable in Ontario?

ENDORSEMENT AND MODIFICATIONS

Fourteen of the 36 recommendations were endorsed without modifications or comments. Twenty-one recommendations were endorsed with comments and 1 recommendation (4.4) was

not endorsed (with explanation) as listed in Table 2-1 (see Section 1, Table 1-1 for a list of all 36 recommendations).

Table 2-1. NCCN T-Cell Lymphomas guideline recommendations: BIA-ALCL [1]

Recommendations	Assessment
2. Initial Workup	
2.1 Ultrasound of breast and axilla, or Breast MRI in selected cases, or PET/CT scan in selected cases Patients with T-cell lymphomas often have extranodal disease, which may be inadequately imaged by CT. PET scan may be preferred in these instances. **Comment:** Contrast-enhanced breast MRI with implant specific sequences may be performed in selected cases during initial workup. Mammogram is not indicated in the workup of the involved breast as it is not accurate in the diagnosis of BIA-ALCL; however, if the contralateral breast remains and does not have fluid collection, then contralateral mammogram should be performed. PET scan should be considered only after diagnosis. Imaging should ideally be done at a diagnostic imaging department in a hospital or cancer centre with breast imaging expertise.	**ENDORSED with comment**
Any effusion	
2.2 FNA biopsy of fluid around breast implant Larger volume of fluid yields a more accurate diagnosis. If possible, obtain >50 mL for cytology and cell block; >10 mL for flow cytometry immunophenotype. **Comment:** Volumes are minimum volumes and the entire large volume first aspirate should be sent for pathology. In the laboratory requisition, it should be indicated that lymphoma is a diagnostic consideration. As specimen should get to pathology optimally within an hour, recommend that this is done in a diagnostic imaging department in a hospital or cancer centre with breast imaging expertise.	**ENDORSED with comment**
Mass	
2.4 Biopsy of mass **Comment:** Core biopsy of suspicious lymph nodes when considering a diagnosis of BIA-ALCL should also be performed ideally at a diagnostic imaging department in a hospital or cancer centre with breast imaging expertise. False negative results of lymph node FNA may occur in the setting of BIA-ALCL.	**ENDORSED with comment**
Ultrasound inconclusive	
2.5 Breast MRI, if not previously done, and follow pathway above for any effusion or mass (as appropriate) **Comment:** See NCCN pathway (nccn.org). If ultrasound is inconclusive, perform contrast-enhanced breast MRI with implant specific sequences. This should be performed ideally at a diagnostic imaging department in a hospital or cancer centre with breast imaging expertise.	**ENDORSED with comment**

3. Pathologic Workup following FNA biopsy of fluid around breast implant or biopsy of mass	
ESSENTIAL pathologic workup	
3.2 IHC and/or flow cytometry may include CD2, CD3, CD4, CD5, CD7, CD8, CD30, CD45, and ALK Larger volume of fluid yields a more accurate diagnosis. If possible, obtain >10 mL for flow cytometry immunophenotype. **Comment**: BIA-ALCL is CD30 positive and ALK negative. Flow cytometry/immunohistochemistry should also include CD20.	**ENDORSED with comment**
USEFUL UNDER CERTAIN CIRCUMSTANCES during pathologic workup	
3.3 If there is solid mass associated with the implant, biopsy (excisional or incisional or core needle) may be required for diagnosis **Comment:** When suspicion of BIA-ALCL, core biopsy or incisional biopsy should be the goal. If due to the location of the lesion, this cannot be carried out, recommend discussion at a Multidisciplinary Cancer Conference (MCC). Biopsy should be performed ideally at a diagnostic imaging department in a hospital or cancer centre with breast imaging expertise.	**ENDORSED with comment**
If indeterminate of lymphoma on pathologic workup	
3.4 Second pathology consultation by tertiary cancer center **Comment:** In Ontario, a tertiary cancer centre is a regional cancer centre. Second pathology consultation should be done by a hematopathologist/pathologist with expertise in lymphoma.	**ENDORSED with comment**
Negative for lymphoma	
3.5 Refer to plastic surgeon for management **Comment**: For cosmetic implants, patients should be referred to the community/cosmetic surgeon who placed the implant. For reconstructions, patients should be referred to the implanting surgeon.	**ENDORSED with comment**
Histologic confirmation or suspicion of BIA-ALCL	
3.6 The histopathologic findings of BIA-ALCL need to be correlated with a clinical presentation and history of a breast implant to achieve a definitive diagnosis [2] **Comment**: All confirmed or highly suspicious cases should be discussed at a MCC. In Ontario, we recommend a multidisciplinary team at a cancer centre with a special interest in BIA-ALCL (e.g., malignant hematologist, plastic surgeon, hematopathologist/pathologist with expertise in lymphoma, and a surgeon with a specialized interest in breast cancer) be involved in a patient's care who has been diagnosed with BIA-ALCL.	**ENDORSED with comment**

3.7 The FDA recommends reporting all BIA-ALCL cases to the PROFILE Registry: www.thepsf.org/PROFILE **Comment**: Canada does not have an equivalent PROFILE registry. Report cases of BIA-ALCL by completing the Consumer Medical Device Report Form found here: https://health.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/problem-reporting/medical-device-consumer.html.	**ENDORSED with comment**
4. Lymphoma Workup and Staging	
4.1 Recommend discussion of treatment options with multidisciplinary team (e.g., medical oncologist/hematologist, surgical oncologist, plastic surgeon, hematopathologist) **Comment**: Treatment options should be discussed with a multidisciplinary team at a cancer centre with a special interest in BIA-ALCL (e.g., malignant hematologist, plastic surgeon, hematopathologist/pathologist with expertise in lymphoma, and a surgeon with a specialized interest in breast cancer).	**ENDORSED with comment**
4.3 CBC with differential, comprehensive metabolic panel and LDH **Comment**: Metabolic panel includes blood glucose, electrolytes, creatinine, liver function tests (AST, ALT, bilirubin).	**ENDORSED with comment**
4.4 Assessment of HTLV1/2 by serology or other methods **Explanation**: BIA-ALCL is not associated with HTLV1/2 infection and testing for this virus is not indicated.	**Not ENDORSED (with explanation)**
4.5 PET/CT scan Patients with T-cell lymphomas often have extranodal disease, which may be inadequately imaged by CT. PET scan may be preferred in these instances. **Comment**: PET-CT should be performed prior to surgery to allow a baseline for the surgical site and assist with operative planning in the case of a tumor mass.	**ENDORSED with comment**
5. Treatment	
5.1 Total capsulectomy and excision of associated mass with biopsy of suspicious node(s), explantation **Comment**: Biopsy of suspicious node(s) should be done pre-operatively. If lymph node is indeterminate or positive on core biopsy, then a targeted lymph node removal for diagnosis can be completed at the time of surgery by a surgeon with a specialized interest in breast cancer. A plastic surgeon with a specialized interest in breast diseases who works at a regional cancer centre should do the total capsulectomy and explantation. Recommend review at a MCC to determine extent of excision.	**ENDORSED with comment**
5.2 Removal of contralateral implant **Comment**: Recommend with total capsulectomy by a plastic surgeon with a specialized interest in breast diseases who works at a regional cancer centre.	**ENDORSED with comment**

5.3 Consultation with surgical oncologist recommended for patients with preoperative tumor mass **Comment**: Consultation with a surgeon with a specialized interest in breast cancer recommended for patients with preoperative tumor mass and/or nodal involvement for coordination of care.	**ENDORSED with comment**
5.5 May consider immediate (early stage) or delayed (advanced stage) breast reconstruction with autologous tissue or smooth surface breast implants [4] **Comment**: Safety of doing an immediate breast reconstruction should also be discussed at a MCC prior to surgery.	**ENDORSED with comment**
6. Follow-up/Additional Therapy	
Localized disease to capsule/implant/breast – Complete excision with no residual disease	
6.2 Surveillance imaging (no more often than every 6 mo for 2 y and then annually for 5 y or as clinically indicated) Patients with T-cell lymphomas often have extranodal disease, which may be inadequately imaged by CT. PET scan may be preferred in these instances. **Comment**: If breast tissue remains, follow appropriate breast screening guidelines. For surveillance of BIA-ALCL, PET 6 months post-op should also be performed to ensure resolution of FDG activity. Once FDG activity resolves, no further body imaging is required, unless there is clinical suspicion of recurrence.	**ENDORSED with comment**
Localized disease to capsule/implant/breast – Incomplete excision or partial capsulectomy with residual disease ± regional lymph node involvement	
6.3 Discuss adjuvant treatment options with multidisciplinary team: RT for local residual disease ± systemic therapy (as listed below), if node positive or RT not feasible **Comment**: Treatment options should be discussed with a multidisciplinary team at a cancer centre with a special interest in BIA-ALCL (e.g., malignant hematologist, plastic surgeon, hematopathologist/pathologist with expertise in lymphoma, and a surgeon with a specialized interest in breast cancer).	**ENDORSED with comment**
Extended disease (stage II-IV)	
6.7 Local disease relapse may be amenable to re-excision surgery alone without requiring systemic therapies **Comment**: All treatment options (surgery, radiation, systemic therapy) should be discussed with a multidisciplinary team at a cancer centre with a special interest in BIA-ALCL (e.g., malignant hematologist, plastic surgeon, hematopathologist/pathologist with expertise in lymphoma, and a surgeon with a specialized interest in breast cancer).	**ENDORSED with comment**
6.8 Suggested treatment regimens, systemic therapy [5,6,7]: • Brentuximab vedotin - Brentuximab vedotin may be appropriate for low-burden disease in selected patients • Brentuximab vedotin + CHP (cyclophosphamide, doxorubicin, and prednisone) • CHOP • CHOEP - Oral etoposide dose of 200 mg/m^2 (PO dosing of etoposide is 2x the IV dose) may be substituted on days 2 and 3 for IV etoposide. Consider splitting the daily doses of oral etoposide over 200 mg	**ENDORSED with comment**

• Dose-adjusted EPOCH **Comment**: At the present time (2023), Brentuximab vedotin + CHP is the standard therapy.	

EXPERT PANEL REVIEW AND APPROVAL

For the endorsement document to be approved, 75% of the content experts who comprise the GDG Expert Panel must cast a vote indicating whether or not they approve the document, or abstain from voting for a specified reason, and of those that vote, 75% must approve the document. The Expert Panel may specify that approval is conditional, and that changes to the document are required.

The endorsement document was evaluated by the GDG Expert Panel of clinical content experts representing general surgery, plastic surgery, hematology, radiology, hematopathology, and radiation oncology (Appendix 1). Of the 7 members of the GDG Expert Panel, 7 members voted and 0 abstained, for a total of 100% response in February 2023. Of those who voted, 7 approved the document (100%). The main comments from the Expert Panel and the Working Group's responses are summarized in Table 2-2.

Table 2-2. Summary of the Working Group's responses to comments from the Expert Panel.

Comments	Responses
1. Recommendation 2.1: Expert Panel Member 1: The comment in Table 1.1. sub 2.1 is misleading and could be construed as a recommendation to avoid mammography in any patient with implants, which is not supported by the literature. Breast MRI should be clarified to be contrast-enhanced to distinguish it from implant protocol MRIs that are done without contrast. However, it is important to note that contrast-enhanced breast MRIs should be done with implant-specific sequences to assess for other causes of symptoms such as implant rupture. A better way to word it is Contrast-enhanced breast MRI, with implant specific sequences may… I am concerned about the wording of the comment that Mammogram is not indicated in the workup of the involved breast (due to concern of rupture of fluid collection). There is no documentation of this in the literature with BIA-ALCL and many people with suspected BIA-ALCL have other diagnoses that require mammographic diagnosis. There is a very low risk of rupture. The reason why mammography is not recommended is that it often is not accurate for the diagnosis of BIA-ALCL.	Comment has been updated to specify "contrast-enhanced MRI with implant specific sequences." We have also specified that Mammogram is not indicated in the workup of the involved breast as it is not accurate in the diagnosis of BIA-ALCL.
2. Recommendation 2.2 Expert Panel Member 1: I agree with 2.2 except I would clearly state in the laboratory requisition that T cell lymphoma/ALCL is a diagnostic consideration as this is not routinely	Comment has been updated to include "in the laboratory requisition, it should be indicated that lymphoma is a diagnostic consideration."

screened for (especially important in flow cytometry sample as it is first processed by technologists and pathologist is often made aware afterwards at which point sample may no longer be viable anymore).	
3. Recommendation 2.4 Expert Panel Member 1: The recommendation to perform biopsies of masses associated with implants is problematic. Many breast cancers are diagnosed in women with implants and this recommendation would negatively impact the already overloaded hospital breast centres. The pathology is usually not done without flow cytometry, and the review by a second pathologist allows for careful review of suspected cases, after the biopsy is performed. The incidence of BIA-ALCL is between 1 in 4000 to 1 in 30,000, and 85% present as a peri-implant effusion, while 15% present as a palpable mass. In contrast, the incidence of breast cancer is 1 in 8 women. This means that more women with implants with a palpable mass or a screen-detected mass will be diagnosed with breast cancer than BIA ALCL. It is the routine clinical practice for radiologists to be familiar with and biopsy masses that are present in women with breast implants to exclude breast cancer and is done in many community hospitals and clinics in Ontario. If the recommendation is made to biopsy all women with a breast implant at a tertiary care centre, this would potentially pose a greater delay in a diagnosis of breast cancer, while waiting to refer the woman to tertiary care, Breast Health Center. Expert Panel Member 2: I do agree that biopsies of masses associated implants, unless benign on imaging on clinical exam, should be biopsied at a hospital or breast center to guide best care and minimize misdiagnosis at small volume locations. Expert Panel Member 3: Re: 2.4 False negatives can also occur on core needle biopsy but are less likely. If an FNA of lymph node is performed a portion put into formalin for cell block and another portion sent for flow cytometry (with indication to rule out T cell lymphoma/ALCL) would be important to increase diagnostic yield.	Comment has been updated to include “when considering a diagnosis of BIA-ALCL” to ensure that only women with suspicion of BIA-ALCL are being referred to a tertiary care centre for biopsy. The feedback regarding false negatives has already been addressed in the comment.

4. Recommendation 2.5 Expert Panel Member 1: As above, this is unclear. Specify contrast-enhanced breast MRI with implant specific sequences. Most MRIs – almost all in the province – are done in the Diagnostic imaging departments of hospitals not breast imaging departments. Suggest changing to the Diagnostic imaging department in a hospital or cancer centre with breast imaging expertise.	Comment has been updated to specify "contrast-enhanced MRI with implant specific sequences." We have also changed "breast imaging department located in a hospital or cancer centre" to "diagnostic imaging department in a hospital or cancer centre with breast imaging expertise." Note: this update has also been made to recommendations 2.1, 2.2, 2.4 and 3.3.
5. Recommendation 3.2 Expert Panel Member 1: Re: 3.2 I would change comment to "Flow cytometry at minimum should include T cell markers and CD30. Immunohistochemistry should include at least one positive T cell marker and CD30." CD20 is a B cell marker, not sure why that is mentioned other than to exclude B cell lymphoma, but there are other possible exclusionary stains that are of equal value so don't see why that one is mentioned.	The reason to include CD20 is to exclude B-cell lymphoma (as part of lymphoma panel), in particular EBV+ fibrin associated large B-cell lymphoma that has been described recently around breast implants. These can be misdiagnosed as BIA-ALCL. Comment has not been changed.
6. Recommendation 3.3 Expert Panel Member 1: As above, because the biopsy specimens are being placed in formalin, there is usually no flow cytometry done on them so they could also be done at an outpatient clinic. A consultation with the pathologists at a tertiary care centre will ensure quality of the interpretation. The consequence of this recommendation as worded could further negatively impact the hospitals who are already carrying a heavy burden of biopsies and this would lead to any enlarged masses in a patient with an implant being referred to breast centres or hospitals for diagnosis. Expert Panel Member 2: Same comment as above. I do agree that biopsies of masses associated implants, unless benign on imaging on clinical exam, should be biopsied at a hospital or breast center to guide best care and minimize misdiagnosis at small volume locations.	Comment has been updated to include "when suspicion of BIA-ALCL" to ensure that only women with suspected BIA-ALCL are being referred to a tertiary care centre for biopsy.

7. Recommendation 3.4 Expert Panel Member 1: The spelling of centre is based on NCCN but the Canadian spelling is centre. It should be consistent in the document. Expert Panel Member 2: Re 3.4 and any other time a hematopathologist is mentioned I would say "pathologist with expertise in lymphoma." Most hematopathologists in Canada don't actually sign out lymphoma, as opposed to USA.	The wording or spelling of the NCCN recommendations cannot be changed. However, we can use the Canadian spelling of "centre" in our comments. We have updated "hematopathologist" to "hematopathologist/pathologist with expertise in lymphoma." Note: this update has also been made to recommendations 3.6 and 4.1.
8. **Recommendation 3.7** Expert Panel Member 1: The sentence "PROFILE may open to international cases in the future" is speculative and does not provide useful guidance.	This sentence has been removed from the comment.
9. Recommendation 4.1 Expert Panel Member 1: This recommendation is too general. A clinical malignant haematologist must be involved not just a medical oncologist. Overall this sounds like a telephone chat with multiple specialists and surgery anywhere in Ontario that does any breast surgery would all be fine. My experience at a quarternary level institution with experience with this lymphoma is that there is angst and difficulty making treatment plans so what would it be like at a community hospital. I don't think this is good enough for these patients. I think there should be a very small number of designated hospitals.	We have updated the comment to specify that multidisciplinary discussions should take place at a cancer centre with a special interest in BIA-ALCL. We also updated the list of multidisciplinary team members by changing "medical oncologist/hematologist" to "malignant hematologist," specifying "hematopathologist/pathologist with expertise in lymphoma," adding "a surgeon with a specialized interest in breast cancer," and removing "surgical oncologist." Note: these updates have also been made to recommendations 3.6, 6.3 and 6.7.
10. Recommendation 4.4 Expert Panel Member 1: This second statement "When you assess for it, you're implying that BIA-ALCL is a HTLV driven disease, which is not the case" is not needed, sounds a bit pejorative. Suggest changing comment to "BIA-ALCL is not associated with HTLV1/2 infection and testing for this virus is not routinely indicated." Need to arrive at wording that reflects lack of causal relationship.	We have updated the comment to "BIA-ALCL is not associated with HTLV1/2 infection and testing for this virus is not indicated."
11. Recommendation 4.6 Expert Panel Member 1: Not all oncologists would say this is appropriate for all patients.	Working Group agrees this is standard practice at most hospitals. Recommendation will not be changed.
12. Recommendation 6.2 Expert Panel Member 1: This is not clear. You must word that the recommendation for	Comment about yearly mammogram has been removed and updated with "if breast tissue remains, follow appropriate breast screening guidelines." We have also

surveillance imaging after a diagnosis of BIA-ALCL is annual mammogram surveillance. The way it is written suggests this is only if a woman had a past history of breast cancer. A woman who was diagnosed with BIA-ALCL should undergo annual surveillance mammogram, similar to a woman with a personal history of breast cancer. Expert Panel Member 2: If implant was for breast reconstruction, and has been removed, is there any role for imaging? I don't feel we are endorsing this part (in particular the imaging suggestion for systemic disease) and feel it should be "not endorsed."	added "for surveillance of BIA-ALCL" to the comment regarding PET 6-months post-op.
13. Recommendation 6.3 Expert Panel Member 1: This is an oversimplification in a disease for which there is no randomized clinical trial data and for which observational data is relatively sparse and replete with selection bias. For this histology of lymphoma it would be hard to argue for radiation treatment for residual disease in the absence of systemic therapy. There should be a very limited number of centres and a very limited number of MCCs with the mandate to make such recommendations. Any random breast or lymphoma MCC is not sufficient.	We have updated the comment to specify that multidisciplinary discussions should take place at a cancer centre with a special interest in BIA-ALCL and specified the team members that should be involved in the care.
14. Recommendation 6.4 Expert Panel Member 1: Not clear what this means: is this reference to how patients will be followed?	Please see recommendation 6.2.
15. Recommendation 6.7 Expert Panel Member 1: Not sure what the data are to support this? Acknowledging the difference between this lymphoma and many others but if patient has had chemo for stage II-IV and a recurrence, is surgery appropriate therapy? Do we wish to comment on role of RT here?	We have included a comment to specify that all treatment options (surgery, radiation, systemic therapy) should be discussed with a multidisciplinary team at a cancer centre with a special interest in BIA-ALCL and specified the team members that should be involved in the care.
16. Recommendation 6.8 Expert Panel Member 1: Brentuximab vedotin - This is not appropriate as there are no high quality data and this is not funded in Ontario for this indication. CHOP - Inferior to CHP BV. Would need a reason to suggest this regimen. Dose-adjusted EPOCH - Not appropriate for this condition.	We have added a comment to state that at the present time (2023), Brentuximab vedotin + CHP is the standard therapy.

DISSEMINATION

The endorsement document will be published on the Ontario Health (Cancer Care Ontario) website. Section 1 of this guideline is a summary document to support the implementation of the guideline in practice.

UPDATING THE ENDORSEMENT

The SOP at Ontario Health (Cancer Care Ontario) will review the endorsement on an annual basis to ensure that it remains relevant and appropriate for use in Ontario.

ACKNOWLEDGEMENTS

The Diagnosis and Treatment of BIA-ALCL GDG would like to thank the following individuals for their assistance in developing this report:

- Sheila McNair from the Program in Evidence-Based Care (PEBC) for assisting the SOP with the guideline endorsement process
- The NCCN for collaborating with the SOP and PEBC to facilitate endorsement of the guideline

CONCLUSION

The final endorsed recommendations contained in Section 1 reflect the integration of feedback obtained through the internal review processes with the document as drafted by the GDG Working Group and approved by the GDG Expert Panel.

References

1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for T-Cell Lymphomas Guideline Version 2.2022. © National Comprehensive Cancer Network, Inc. 2023. All rights reserved. Accessed [November 21, 2022]. To view the most recent and complete version of the guideline, go online to nccn.org. NCCN makes no representations or warranties of any kind regarding their content, use or application and disclaims any responsibility for their application or use in any way.
2. Quesada AE, Medeiros LJ, Clemens MW, et al. Breast implant-associated anaplastic large cell lymphoma: A review. Mod Pathol 2019;32:166-188.
3. Clemens MW, Medeiros LJ, Butler CE, et al. Complete surgical excision is essential for the management of patients with breast implant-associated anaplastic large-cell lymphoma. J Clin Oncol 2016;34:160-168.
4. Lamaris GA, Butler CE, Deva AK, et al. Breast reconstruction following breast implant-associated anaplastic large cell lymphoma. Plast Reconstr Surg 2019;143:51S-58S.
5. Pro B, Advani R, Brice P, et al. Brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large-cell lymphoma: results of a phase II study. J Clin Oncol 2012;30:2190-2196.
6. Pro B, Advani R, Brice P, et al. Five-year results of brentuximab vedotin in patients with relapsed or refractory systemic anaplastic large cell lymphoma. Blood 2017;130:2709-2717.
7. Horwitz S, O'Connor OA, Pro B, et al. Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial. Lancet 2019;393:229-240.
8. Mehta-Shah N, Clemens MW, Horwitz SM. How I treat breast implant-associated anaplastic large cell lymphoma. Blood 2018;132:1889-1898.
9. Program in Evidence-based Care. Cancer Care Ontario guideline endorsement protocol. http://pebctoolkit.mcmaster.ca/doku.php?id=projectdev:cco_endorsement_protocol Ontario, Accessed June 15, 2022.
10. Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, et al. AGREE II: advancing guideline development, reporting and evaluation in health care. CMAJ. 2010;182(18):E839-E42.

Appendix 1: Affiliations and Conflict of Interest Declarations

Table 1: Members of the Diagnosis and Treatment of BIA-ALCL Guideline Development Group

Name	Affiliation	Conflict of Interest
Working Group		
Zeina Ghorab Hematopathologist/ Cytopathologist	Sunnybrook Health Sciences Centre Toronto, ON	None declared.
Michelle Lee Team Lead, Surgical Oncology Program (SOP)	Ontario Health (Cancer Care Ontario) Toronto, ON	None declared.
Joan Lipa Plastic Surgeon	Sunnybrook Health Sciences Centre Toronto, ON	Chair and Director of The American Board of Plastic Surgery, Inc., voluntary role. President, American Society for Reconstructive Microsurgery, voluntary role. Grant-in-Aid for Educational Purposes from Allergan to University of Toronto which provides partial support for Sunnybrook Oncologic and Microvascular Reconstruction Fellow.
Eugenia Piliotis Hematologist	Kingston General Hospital Kingston, ON	None declared.
Peter Stotland Surgical Oncologist Quality Lead, SOP	North York General Hospital Ontario Health (Cancer Care Ontario) Toronto, ON	None declared.
Frances Wright Surgical Oncologist Provincial Head, SOP	Sunnybrook Health Sciences Centre Ontario Health (Cancer Care Ontario) Toronto, ON	Melanoma talk at William Osler. Funds donated to University of Toronto (UofT) from Novartis. Received donation from Merck for University of Toronto endowed fund for General Surgical Oncology fellowship program.
Toni Zhong Plastic Surgeon	University Health Network Toronto, ON	Belinda Stronach Chair in Breast Cancer Reconstruction at University Health Network. Grant-in-Aid from Johnson & Johnson for University of Toronto Breast Reconstruction and Aesthetic Fellowship.
Expert Panel		
Muriel Brackstone General Surgeon	London Health Sciences Centre London, ON	None declared.
Erin Cordeiro General Surgeon	The Ottawa Hospital Ottawa, ON	None declared.
Michael Crump Hematologist	University Health Network Toronto, ON	None declared.
Anat Kornecki Radiologist	St Joseph's Health Care London London, ON	None declared.

Aleksandra Paliga Anatomic Pathologist/ Hematopathologist	The Ottawa Hospital Ottawa, ON	None declared.
Lawrence Paszat Radiation Oncologist	Sunnybrook Health Sciences Centre Toronto, ON	None declared.
Jean Seely Radiologist	The Ottawa Hospital Ottawa, ON	President of the Canadian Society of Breast Imaging, voluntary role. Medical Advisory role, Dense Breasts-info-org.

Appendix 2: Agree II Score Sheet

Domain	Item	AGREE II Appraiser Ratings[1]	
		1	2
1) Scope and Purpose	1. The overall objective(s) of the guideline is (are) specifically described.	7	6
	2. The health question(s) covered by the guideline is (are) specifically described.	7	7
	3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	7	7
Domain score[2] – (41-6/42-6)*100 = 35/36*100 = 0.9722*100 = **97.2%**		Score 41	
2) Stakeholder Involvement	4. The guideline development group includes individuals from all relevant professional groups.	6	6
	5. The views and preferences of the target population (patients, public, etc.) have been sought.	2	1
	6. The target users of the guideline are clearly defined.	7	6
Domain score[2] – (28-6/42-6)*100 = 22/36*100 = 0.6111*100 = **61.1%**		Score 28	
3) Rigor of Development	7. Systematic methods were used to search for evidence.	5	6
	8. The criteria for selecting the evidence are clearly described.	5	7
	9. The strengths and limitations of the body of evidence are clearly described.	7	5
	10. The methods for formulating the recommendations are clearly described.	7	7
	11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	7	6
	12. There is an explicit link between the recommendations and the supporting evidence.	6	5
	13. The guideline has been externally reviewed by experts prior to its publication.	7	7
	14. A procedure for updating the guideline is provided.	7	7
Domain score[2] – (101-16/112-16)*100 = 85/96*100 = 0.8854*100 = **88.5%**		Score 101	
4) Clarity of Presentation	15. The recommendations are specific and unambiguous.	6	5
	16. The different options for management of the condition or health issue are clearly presented.	7	6
	17. Key recommendations are easily identifiable.	7	7
Domain score[2] – (38-6/42-6)*100 = 32/36*100 = 0.8889*100 = **88.9%**		Score 38	
5) Applicability	18. The guideline describes facilitators and barriers to its application.	2	2
	19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	2	4
	20. The potential resource implications of applying the recommendations have been considered.	2	3

	21. The guideline presents monitoring and/or auditing criteria.	2	3
Domain score[2] – (20-8/56-8)*100 = 12/48*100 = 0.25*100 = **25.0%**		Score 20	
6) Editorial Independence	22. The views of the funding body have not influenced the content of the guideline.	7	7
	23. Competing interests of guideline development group members have been recorded and addressed.	7	7
Domain score[2] – (28-4/28-4)*100 = 24/24*100 = 1*100 = **100%**		Score 28	
Overall Guideline Assessment	1. Rate the overall quality of this guideline.	6	6
Overall Guideline Assessment	2. I would recommend this guideline for use.	Yes with modifications	Yes with modifications

[1]Rated on a scale from 1 to 7, [2]Domain score = (Obtained score – Minimum possible score) / (Maximum possible score – Minimum possible score)