haematologica
Journal of the Ferrata Storti Foundation

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Received: May 26, 2026.
Accepted: November 9, 2026.

Citation: Marco Lucioni, Arianna Di Napoli, Elena Sabattini, Stefano Lazzi, Claudio Agostinelli, Umberto Gianelli, Stefano Ascani, Raffaella Santi, Claudio Tripodo, Gaia Goteri, Ada Maria Florena, Emanuele D'Amore, Fabio Facchetti, Maurilio Ponzoni, Marco Paulli and Stefano A. Pileri.
The preanalytical phase in hematopathology: sampling as a critical step for an appropriate diagnosis. A position paper from the Italian Group of Haematopathology (GIE).
Haematologica. 2026 Nov 19. doi: 10.3324/haematol.2026.301310 [Epub ahead of print]

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DECLARATION OF COMPETING INTERESTS

M.L. received speaker honoraria from Roche and Exact Sciences and travel expenses from Eusa Pharma.

A.D.N. received honoraria from Recordati Rare Disease and Takeda for educational events and for participating in advisory board, from Novartis, Incyte, Sobi, Gentile and Blueprint for educational events and from Menarini Stemline for participating in advisory boards.

M.P. received honoraria from Roche Ventana Diagnostics as a consultant and from Astra Zeneca for participating in advisory boards.

M.Pa. received honoraria from Recordati Rare Disease.

RUNNING HEAD

“The preanalytical phase in hematopathology”

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DATA-SHARING STATEMENT

Not Applicable.

AUTHOR CONTRIBUTIONS

Conceptualization: F.F., M.P, M.Pa., S.P.; writing-original draft preparation: M.L., A.D.N., E.S., S.L.; writing-review editing: C.A., U.G., S.A., R.S., C.T., G.G., A.M.F., E.D.A; supervision: F.F., M.P., M.Pa., S.P. All authors have read and agreed to the submitted version of the manuscript.

ACKNOWLEDGMENTS

We thank Dr. Edoardo D'Este (Department of Molecular Medicine, University of Pavia, Pavia) and Dr. Giuseppe Neri (Pathology Unit Foundation IRCCS Policlinico San Matteo, Pavia) for their assistance in editing the manuscript and preparing the accompanying figure.

FUNDING INFORMATION

Not applicable

ETHICS APPROVAL STATEMENT

The study respects the ethical rules of the country in which it has been performed (Italy).

PATIENT CONSENT STATEMENT

Not applicable

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

Not applicable

AI DISCLOSURE

No AI-assisted technology was used in the writing of this manuscript.

ABSTRACT

Lymphoma diagnosis relies on morphological, immunophenotypical and molecular analyses of lesional tissue biopsies. Expert guidelines recommend surgical excision biopsy (SEB) of lymph nodes as the standard approach, as it provides adequate tissue for definitive diagnosis, accurate subtyping, and treatment selection, but core needle biopsy (CNB) is increasingly used in clinical practice because of its practical advantages. However, a critical analysis of most published series reveals that CNB may have lower diagnostic accuracy than SEB, with a high risk of inadequate/insufficient material and tissue artifacts, leading to non-definitive diagnoses and lymphoma subtype misclassification, which may delay diagnosis and/or adversely affect clinical management. The limited tissue obtained by CNB may hinder lesional architectural assessment and comprehensive ancillary testing, particularly when tissue is rapidly exhausted. In contrast, SEB generally provides more tissue for diagnostic evaluation, also favoring biobanking for future diagnostic and therapeutic needs and research purposes.

We believe that SEB remains the preferred approach for accurate lymphoma characterization and subtyping when feasible. SEB and CNB should be considered complementary rather than mutually exclusive approaches, with CNB particularly useful in patients at increased surgical risk or presenting with deep-seated, surgically inaccessible lesions. When CNB results are inconclusive or discordant with clinical findings, repeat sampling, preferably by SEB whenever possible, should be recommended to establish a reliable diagnosis. Regardless of the sampling approach, careful tissue handling and appropriate pre-analytical procedures remain essential to ensure both the quality and the sustainability of the histopathological diagnostic process.

Introduction

Histopathological examination is crucial for diagnosing lymphoma and other lymphoproliferative disorders, enabling accurate subtyping and driving treatment selection in the era of personalized medicine. An accurate pathological diagnosis is supported by a series of phenotypic, genetic and biological data.[1-3]

The morphological diagnosis and subtyping of lymphoma rely on a careful evaluation of the architectural “pattern” of the involved tissue, coupled with the identification of the cytological and phenotypic features of neoplastic cells and their microenvironment.[4-5] Beyond immunohistochemistry, ancillary investigations are essential for lymphoma characterization, including fluorescence in situ hybridization (FISH) for genomic rearrangements, PCR-based immunoglobulin and T-cell receptor gene rearrangement analysis, targeted and/or high-throughput mutational analyses of DNA and RNA by means of next generation sequencing (NGS), and gene expression profiling (GEP).[1-7] These investigations require careful pre-analytical management and adequate lesional tissue, in both quantity and quality, to achieve an integrated diagnosis by combining morphological assessment with ancillary tests.[8-10]

Both the fifth edition of the WHO Classification of Haematolymphoid Tumours and the International Consensus Classification (ICC) of Myeloid and Lymphoid Tumors, as well as guidelines from major scientific societies, including the European Society of Medical Oncology (ESMO), the National Comprehensive Cancer Network (NCCN), the British Society of Hematology and the French Lymphoma Study Association (LYSA), recommend surgical excision biopsy (SEB) of lymph nodes whenever feasible for lymphoma diagnosis and subtyping as well as for the identification of several reactive lymphadenopathies and lymphoproliferative disorders, including Castleman disease (CD) and IgG4-related lymphadenopathies.[1-4,11-16] Although these recommendations are primarily based on empirical data, they reflect the real-life experience accumulated by reference

hematopathologists and underscore the diagnostic importance of evaluating tissue architecture and obtaining representative samples.

Nevertheless, over the past decades minimally invasive approaches, particularly core needle biopsy (CNB), have gained increasing acceptance for lymph node sampling, mainly because of their practical advantages.[17-31] CNB is generally faster and safer to perform, with a lower risk of complications, such as bleeding, scarring and potential nerve injury. Conversely, SEB is a surgical procedure that requires surgical, nursing, and anesthesia staff, as well as operating room personnel, along with the associated challenges of managing a surgical patient.[32]

On this basis, some authors have proposed image-guided CNB as the first-line diagnostic procedure, reserving SEB for cases in which diagnostic uncertainty persists.[32-37] Some Italian centers use ultrasound (US)-guided 16-gauge CNB, with at least two passes yielding two tissue cores with a combined length of 30-60 mm, as the initial procedure for suspected lymphoma; the same centers reported a rate of inconclusive CNB diagnoses, requiring subsequent SEB, between 2.1 and 3%.[24,30]

We acknowledge the potential advantages and effectiveness of CNB in selected clinical settings: CNB may be appropriate for deep-seated or not easily surgically accessible lesions, for elderly patients or those in a compromised general condition (poor performance status) and/or with significant comorbidities, as well as in situations in which access to SEB would entail an excessive delay. Conversely, SEB remains the preferred approach for lymphoma diagnosis and subtyping whenever feasible, particularly when comprehensive assessment of lesional architectural pattern and infiltrate composition is important.

The present work is based on a review of articles retrieved from PubMed, Scopus and Web of Science, in compliance with the ethical standards of the country in which it was conducted (Italy).

Limitations of the studies comparing the accuracy of CNB and SEB

Most studies comparing the accuracy of CNB and SEB in the diagnosis of lymphoma have potential biases and limitations that should be considered when interpreting the diagnostic yield of CNB. **a)** Many published series are based on single-institution experiences, often involving a limited number of patients and where CNB was performed by highly trained radiologists with expertise in both diagnostic ultrasound and CNB techniques.[17-21, 23-29, 33-38] **b)** Most studies lack a control group of paired SEB specimens obtained concomitantly from the same patients and analyzed using the same methods. Not surprisingly, patients who preferentially undergo CNB are often older and have a higher clinical suspicion of lymphoma than those undergoing SEB in routine practice, introducing selection bias and limiting the generalizability of the findings.[17-23, 27-29, 31-41] **c)** Criteria for defining CNB diagnostic adequacy vary across studies. Some authors consider CNB successful even when it yields a diagnosis of unclassified lymphoma, thereby underestimating the importance of lymphoma subtyping, currently essential for appropriate clinical management and therapeutic decision-making in the era of precision medicine.[23,29] Other studies excluded non-diagnostic cases due to insufficient or poor-quality tissue,[18,19,21,22,27-29,33,36,40] potentially underestimating a scenario often encountered in real-life practice. Moreover, some series also included many patients with relapsing lymphoma previously diagnosed on surgical specimens.[17,21,26-28,37,39] Some centers perform flow cytometry (FC) analysis that may significantly increase the diagnostic reliability of CNB, at least for lymphoma subtypes whose diagnosis relies more on cytomorphology and immunophenotype than on architectural features, but this technique is not routinely available in all pathology laboratories.[42-43] **d)** Although cost-effectiveness analyses generally favor CNB, they may underestimate pathology-related costs and workload. Johl et al. interestingly compared the number of immunohistochemical tests required for a final diagnosis in nodal CNB and SEB, respectively, concluding that it was higher in CNB.[38] Similarly, some CNBs may require NGS or FISH analyses that would have

been unnecessary with SEB to achieve the correct diagnosis, potentially making the diagnostic work-up more expensive overall. **e)** Non-diagnostic or insufficiently informative CNB results may delay definitive diagnosis by necessitating subsequent surgical excision. **f)** Incomplete, uncertain, or incorrect diagnoses may lead to repeat sampling and additional investigations, resulting in diagnostic delay and/or inappropriate treatment. **g)** Hematopathology is one of the most difficult diagnostic fields in pathology; lymphoma diagnosis is often challenging even for expert hematopathologists, particularly when dealing with lymph node CNB. The histological interpretation of small biopsy samples requires a higher level of expertise and experience to establish an accurate lymphoma diagnosis, supported by a targeted selection of ancillary tests. The absence of centralized expert hematopathology review in most of the above-mentioned studies may have led to underestimation of the risk of lymphoma misdiagnosis. [5,17-29, 39-42]

Intrinsic diagnostic limitations of CNB

Despite the fact that various studies aimed at assessing the role of image-guided CNB in lymphoma diagnosis have suggested this method as a valid alternative strategy for obtaining diagnostic pathological material, a critical analysis of the published data reveals that diagnostic precision of CNB is significantly lower than that of SEB, and the putative advantages of CNB (lower cost and fewer complications) may not compensate for its lower diagnostic accuracy. A recent meta-analysis of 13 studies, including a total of 9049 patients undergoing CNB alone for suspected lymphoma,[32] found that the diagnostic yield of CNB ranged between 79% and 97% (median 91.7%). In those studies that also included a SEB series, the diagnostic yield of SEB ranged between 93.5% and 100%, with a median of 97.5% (Table 1). The median proportion of patients with an unsuccessful diagnosis based on CNB and SEB was 8.2% and 2.8%, respectively, thus meaning that CNB fails to yield a conclusive diagnosis in approximately four times as many cases as SEB. However, the

overall CNB performance estimates should be interpreted with even more caution, as they are likely influenced by the high prevalence of diffuse large B-cell lymphoma (DLBCL), which may be quite easily diagnosed also on limited tissue samples more often than other lymphoma subtypes, that require adequate assessment of tissue architecture and microenvironment [i.e. Hodgkin lymphoma (HL) and peripheral T-cell lymphoma (PTCL)]. Notably, studies analyzing CNB accuracy in different lymphoma subtypes reported a higher sensitivity for non-Hodgkin lymphoma (NHL) than HL (97.2% vs 88.7%)[36] and for aggressive B-cell lymphoma (100%) than other lymphoma subtypes, including indolent B-cell lymphoma (95%), HL (93%) and PTCL (90%).[30] Therefore, the reported aggregate metrics of CNB effectiveness probably substantially underestimate the risk of a missed or incorrect lymphoma diagnosis in many lymphoma subtypes other than aggressive B-cell lymphoma.

In 2022, Syrykh et al. reported the experience of the French Lymphopath network, analyzing the diagnostic performance of lymph node CNB compared with SEB in 32285 samples (10285 CNB and 22000 SEB) from patients undergoing pathological evaluation for primary lymphoma diagnosis.[8] These cases were diagnosed at local institutions, including university, public, and private hospitals, and all were reviewed by expert hematopathologists through the French Lymphopath network, which provides systematic expert review of all lymphoma diagnoses in France. The rate of definitive diagnosis following central expert review was significantly lower with CNB (92.3%) than with surgical excision (98.1%), with non-definitive diagnoses occurring in 7.7% of cases with CNB vs 1.9% of cases with SEB. Similarly, discordance rates between referral and expert diagnoses were higher for CNB (23.1%) than for SEB (21.2%; P = 0.004), and referral pathologists reported more cases with unclassified lymphomas or equivocal lesions with CNB. Reclassification of reactive lesions as lymphoma or non-definitive diagnoses following expert review was more frequent with CNB. In the selected group of 125 patients who underwent SEB within 3 months following a non-definitive CNB diagnosis after expert review, only 7/11 lesions suspected by experts to be

reactive upon CNB examination were confirmed as reactive on SEB, whereas all referral reactive lesions were reclassified as lymphoma (7/7). These data may suggest that the negative predictive value of CNBs should also be interpreted with caution in an unselected population.

Diagnostic uncertainty associated with CNB concerns not only the distinction between lymphoma and reactive lymphadenopathy, but also the accurate classification of lymphoma subtypes. Studies including paired CNB and SEB specimens report widely variable concordance rates between provisional CNB and definitive SEB diagnoses, ranging from 19.2% to 97% (Table 1). In the study by Syrykh et al., most discordant expert diagnoses involved PTCL, including nodal T follicular helper cell lymphoma, angioimmunoblastic type (nTFHL-AI); indolent B-cell lymphomas, particularly nodal marginal zone lymphoma (NMZL); and misclassification between nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) and T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL), as well as between nTFHL-AI and HL.[8] Other studies reported similar diagnostic challenges. In the series by Li et al., the equivocal or nondiagnostic CNB group included two cases of NLPHL, three of classical HL (cHL), four of DLBCL, one each of mantle cell lymphoma (MCL), follicular lymphoma (FL), and Burkitt lymphoma (BL), and seven T-cell lymphomas (one PTCL, one angioimmunoblastic lymphoma, and five anaplastic lymphomas).[22] Picardi et al. reported 30 patients with equivocal or inconclusive CNB findings whose subsequent SEB established a diagnosis of cHL in 11 cases, NLPHL in three, indolent B-cell lymphoma in 13, and nodal PTCL in three.[30] False-negative or equivocal HL diagnoses were also reported by Groneck et al. (5/20)[28] and Skelton et al. (3/26).[19] Amador-Ortiz et al and Assaf et al reported diagnostic discrepancies mainly involving HL, FL, NMZL and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)[42-43], whereas He et al described 8 cases misdiagnosed on CNB as reactive processes or non-lymphoid malignancies, including CLL/SLL, NMZL, DLBCL, and T-cell lymphoma.[44] In the series by Ingersoll et al.,

discordance occurred in 5/28 paired specimens and involved inaccurate FL grading, misclassification of cHL as a T-cell lymphoma, failure to recognize EBV-positive DLBCL, failure to identify the neoplastic T-cell component of a composite T and B-cell lymphoma, and misclassification of a small B-cell lymphoma with a prominent reactive T-cell infiltrate as a T-cell lymphoma.[39]

The above-mentioned findings cannot be used to definitively estimate the diagnostic performance of CNB for individual lymphoma subtypes since, in most paired CNB/SEB series, excision was preferentially performed in patients with inadequate, equivocal, or discordant CNB findings. However, these data suggest that reliable lymphoma diagnosis and subtyping via CNB may be challenging when neoplastic cells are sparse within a polymorphic background, or when diagnosis depends on tissue architecture evaluation and microenvironmental characterization. These limitations seem to be particularly relevant to follicular large B-cell lymphoma (grade 3B FL), FL variants with atypical growth patterns (e.g., diffuse FL and inguinal-type FL), NMZL, lymphoplasmacytic lymphoma (LPL), EBV-driven lymphoproliferative disorders, PTCL (particularly nTFHL-AI), THRLBCL, NLPHL, and cHL.[1-4, 8-10] Even FC may not overcome these limitations in entities whose classification depends on tissue architecture or the identification of sparse neoplastic cells within an extensive inflammatory background.[45] Furthermore, CNB may preclude assessment of clinically relevant morphological features, including FL grading and architectural patterns in NLPHL.

In many cases, CNB allows for a diagnosis of aggressive B-cell lymphoma,[30,46] but prognostic stratification and treatment selection in DLBCL are increasingly based on extensive phenotypic and molecular characterization.[1-3,9,47,48] The feasibility of immunohistochemistry, FISH, GEP, and mutational analysis depends on the amount and quality of available tissue. Moreover, the limited nodal sampling provided by CNB may

represent a major limitation for detecting high-grade lymphoma transformation.[38,43,49] The diagnosis of high-grade lymphoma transformation relies on the detection of two lymphoma components (high- and low-grade), which may not be appreciated in small tissue fragments obtained via CNB. This limitation may particularly affect FL: Johl et al. found that transformation was identified in 3.3% of cases by CNB, compared with 7.6% by SEB.[38] Similarly, identifying histologically accelerated CLL/SLL may be important in distinguishing these cases from Richter transformation.[1] Synchronous or collision lymphomas and solid tumors have also been reported at nodal sites, although rarely.[50] In such cases, partial nodal sampling may fail to capture divergent neoplastic components.[39]

In various non-neoplastic reactive conditions and lymphoproliferative disorders, including Castleman disease (CD), immunodeficiency-associated and immune dysregulation-associated lymphoid proliferations, and histiocytic disorders, the diagnosis may be challenging on CNB samples alone, as it requires an assessment of the lymph node architecture and the characterization of tissue cell populations.[1] Accurate diagnosis has important clinical implications: idiopathic multicentric CD (iMCD), for example, can be life-threatening, and specific anti-IL-6 therapies are available and recommended in current treatment guidelines.[51] Other conditions, including granulomatous and IgG4-related disease, also require appropriate recognition to facilitate timely treatment.[52] Thus, although CNB may provide useful diagnostic information in selected cases, SEB generally enables a more comprehensive assessment of nodal architecture and cellular distribution, which may be critical for establishing these diagnoses.

Handling and processing of pathologic specimens

The accuracy of histopathological diagnoses, including hematopathological ones, depends not only on the type and size of samples but also on a careful pre-analytical phase, which encompasses the adequate fixation, embedding, cutting, and staining of the submitted

samples. We focused in particular on the sampling procedures because the availability of adequate diagnostic material, in terms of both quantity and quality, remains a cornerstone of diagnosis, although its yield also depends on the quality of subsequent pre-analytical steps.

Crushing artifacts, characterized by overlapping, crowded, and elongated nuclei with loss of cellular detail, may be encountered, particularly in small biopsy specimens. These artifacts can be particularly problematic in large B-cell lymphoma and other fragile lymphoid proliferations, including MCL, CLL/SLL, BL and lymphoblastic lymphoma, which are especially sensitive to mechanical distortion. Tissue ischemia and delayed fixation may further affect specimen quality, although their effects differ according to the tissue characteristics and the diagnostic assays performed.

In CNB samples, the number and size of cores available for diagnosis are often limited, making tissue allocation particularly important. The amount of tissue available may determine whether sufficient material remains for immunohistochemistry and additional ancillary investigations, while tissue quality may independently influence the reliability of these analyses. Depending on specimen characteristics and local laboratory protocols, submitting individual cores in separate blocks may facilitate tissue allocation and preserve material for subsequent investigations, while reducing the risk of exhausting the available material. When lymphoma is suspected, effective communication between the clinical team and the pathology laboratory can facilitate proper handling of the specimen, allowing a portion of the fresh tissue to be allocated for analysis by FC or other ancillary techniques, when indicated and feasible.

For SEB specimens, small lymph nodes should generally be submitted entirely for histopathological examination. Larger specimens may be selectively sampled to provide material for additional procedures, such as cell culture, advanced molecular testing, and

tissue cryopreservation, thereby avoiding the unnecessary depletion of material with diagnostic value.

Standardized fixation and processing are essential for preserving morphological detail, immunohistochemistry reliability, and nucleic acid integrity for molecular investigations. Although no single fixative is optimal for every purpose, fixation in 10% neutral buffered formalin followed by paraffin embedding remains the standard practice for routine histological and immunohistochemical assessment. In addition to the type of fixative used, both cold ischemia time and fixation duration may affect the performance of selected biomarkers and molecular assays. These variables may interact with specimen size because tissue dimensions influence formalin penetration and the time required for adequate fixation. Although optimal conditions vary according to tissue type and assay, general recommendations emphasize minimizing the fixation delay (typically <1 hour) and ensuring that the fixation duration falls within validated timeframes, ranging from a minimum of 6-8 hours for small biopsies to a maximum of 24-72 hours for surgical specimens, also depending on sample size.[53,54]

Suboptimal tissue handling or processing may compromise diagnostic accuracy, forcing patients to undergo further invasive biopsy procedures, which may lead to diagnostic delays and increased costs. From a sustainability perspective, maximizing the diagnostic yield of each biopsy, preserving tissue for potential additional testing, and avoiding repeat biopsy procedures whenever possible can reduce the unnecessary consumption of resources while limiting the additional burden on patients and healthcare systems.

In the future, emerging technologies, including stain-free, fixation-free, and section-free platforms for three-dimensional histological analysis,[55] may offer new opportunities for tissue assessment. Although their potential application in routine diagnostic pathology, as well as their performance in relation to the type of biopsy and the amount of tissue, remains to be

defined, these innovative technologies will still require suitable tissue samples to avoid artifacts that could compromise diagnostic outcomes. The availability of adequate samples will continue to benefit ancillary investigations, microenvironment studies, and biobanking for future pathologic and therapeutic issues.

Availability of material for future investigations and biobanking

Residual tissue following a primary lymphoma diagnosis can serve as an important resource for future prognostic and predictive investigations, novel molecular characterization, and translational research. Typically, following an initial lymphoma diagnosis, further tissue-based analyses may be required to enable the use of personalized and innovative therapeutic approaches. This may include additional immunohistochemical analyses to detect surface antigens (such as CD30 or PD-L1), as well as a centralized review and specific tests to assess eligibility for participation in clinical trials. It is unlikely that, following the diagnostic characterization of CNB samples to establish a diagnosis of lymphoma, a sufficient amount of tissue will remain for further investigations, should these become necessary. The typically limited availability of tissue provided by CNB may, therefore, restrict access to emerging therapies, including clinical trials of which patients might otherwise be unaware. Clonotype-specific minimal residual disease testing may also require access to the primary tumor tissue.[9] As these needs increase, preserving sufficient residual tumor tissue in pathology archives is important to support patient management throughout the disease course.

Our understanding of lymphoproliferative disorders has advanced through pathological and molecular research, which depends on tissue availability and appropriate patient consent. These studies have contributed to the development of treatments that have improved outcomes for many patients with lymphoma. Research aims to characterize lymphoma heterogeneity, elucidate tumor biology, and identify novel therapeutic targets and predictors

of treatment response. As recently supported by Jaffe and Cook[9], approaches such as high-throughput DNA/RNA sequencing and spatially resolved transcriptomics require tumor tissue that CNB samples are unlikely to provide. Furthermore, some molecular studies and clinical trials may still require cryopreserved material, for which biobanking is advisable. Consequently, when the sample size allows and routine processing has been prioritized, a portion of the specimen should ideally be snap-frozen and stored at −80 °C. However, this may not be feasible when tissue availability is limited, particularly with CNB.

Finally, the increasing use of CNB in place of SEB may have implications for the future development of artificial intelligence (AI) algorithms for lymphoma diagnosis. To date, research has explored machine learning-based approaches that utilize images of samples obtained via SEB,[56] as well as tissue microarrays derived from such samples.[57] Currently, no AI-based diagnostic tool is yet ready for clinical use and there is no available data regarding the application of AI-algorithms developed using SEB specimens to samples obtained via CNB. Consequently, it is not possible to determine to what extent the quantity and representativeness of CNB tissue cores might affect the performance of such algorithms. Further studies are needed to assess how tissue sampling characteristics, including biopsy size, may affect the accuracy, robustness, and generalizability of AI-assisted diagnostic approaches.

Conclusions

Clinicians and pathologists should recognize SEB as the gold standard for the evaluation of lymph nodes in cases where a lymphoproliferative disorder is suspected, as well as for the accurate characterization and subtyping of lymphomas. Although CNB offers practical advantages, it carries an inherent risk of inconclusive and/or incorrect diagnoses, potentially leading to delayed diagnosis and/or inappropriate clinical management. Moreover, SEB

usually provides adequate tissue for biobanking and future diagnostic, therapeutic, and research needs, whereas CNB samples may be rapidly exhausted.

Given its clinical importance, SEB should be performed by experienced surgeons to minimize non-diagnostic sampling, particularly when lymph nodes are small (typically <1.5 cm) or potentially non-representative. Whenever feasible, SEB should be recommended to maximize diagnostic accuracy and guide appropriate treatment.

Nevertheless, we emphasize that SEB and CNB should be regarded as complementary rather than mutually exclusive approaches. CNB is preferred when SEB carries excessive surgical risk (very elderly patients and/or patients with poor performance status and/or comorbidities) or lesions are deep-seated or surgically inaccessible. Furthermore, an inappropriately long waiting time for SEB, when adjusted for disease severity, may itself justify CNB**.** However, in all cases, patients should be informed that CNB may not be conclusive and that subsequent SEB may be required. When CNB is performed, a large-gauge needle (at least 15 gauge) and multiple cores (at least 3–4) are strongly recommended.[31,43] Persistent diagnostic uncertainty should prompt pathologists to advocate for repeat biopsy, preferably SEB when feasible.

Finally, careful tissue handling and appropriate pre-analytical procedures remain essential to ensure both the quality and the sustainability of the histopathological diagnostic process.

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Source	Study Design	Case selection criteria	Diagnostic endpoints	Biopsy site	Type of CNB sampling	FC	Expert review/reference center review	N of specimens	Diagnostic yield of CNB	Number/% of pts with unsuccessful diagnosis by CNB	Fully diagnostic yield of SEB	Paired CNB/SEB (N of cases)	Concordance between CNB and SEB
Amador-Ortiz et al. 2011 [42]	Retrospective	Patients undergoing CNB for suspected lymphoma	Diagnosis established; definitive versus incomplete lymphoma diagnosis	Nodal	FNA and CNB	Yes	No	263 CNB/FNA 55 subsequent SEB	Diagnosis established: 237/263 (90.1%) Definitive lymphoma diagnosis: 193/263 (73.4%)	26/263 (9.9%) non diagnostic; 44/263 (16.7%) incomplete diagnosis	n.a.	38	Lymphoma diagnosis: 37/38 (97%); 1 false negative CNB
Burke et al 2011 [29]	Retrospective	Head and neck lymphadenopathies	Definitive lymphoma subtype diagnosis	Head and neck	US-CNB	No	No	83 CNB 104 SEB	67/83 (81%)	16/83 (19%)	103/104 (99%)	14	Not reported
Pruneri et al 2015 [41]	Retrospective	Patients undergoing CNB for suspected lymphoma	Diagnosis established; definitive lymphoma subtype diagnosis	Nodal/ Extranodal	US-CNB CT-CNB	No	No	390 CNB 36 SEB	Diagnosis established: 372/390 (95.4%); definitive lymphoma subtype diagnosis: 301/372 (80.9%)	18/390 (4.6%)	n.a.	36 selected cases	Lymphoma diagnosis: 24/36 (66.7%); 8 false negative and 4 false positive CNBs
Skelton et al. 2015 [19]	Retrospective	All cases of lymphoma diagnosed between 2008 and 2013	Fully diagnostic (subtyping/grading sufficient to initiate treatment); partially diagnostic, equivocal, or inadequate	Nodal/ Extranodal	US-CNB FNA	No	Yes	237 CNB 80 SEB 6 US-FNA	Fully diagnostic: 230/237 (97.0%)	Partially diagnostic, equivocal, inadequate: 7/237 (3.0%)	79/80 (98.8%)	7 SEB following non diagnostic CNB	Not applicable; 2 partially diagnostic CNB suspicious for HL confirmed by SEB

He Y et al. 2015 [44]	Retrospective	Patients undergoing CNB and/or SEB for suspected lymphoma	Lymphoma and lymphoma subtype diagnosis	Nodal/ Extranodal	US-CNB	No	No	110 CNB 98 SEB	Lymphoma diagnosis: 105/110 (95.5%); subtype diagnosis: 102/110 (92.7%)	8/110 (7.3%)	96/98 (97.9%)	8 SEB following non diagnostic CNB	Lymphoma diagnosis: 3/8 (37.5%); 4 false negative CNBs; 1 DLBCL diagnosed as carcinoma on CNB
Johl et al. 2016 [38]	Retrospective	Patients undergoing CNB and/or SEB for suspected lymphoma	Diagnosis established; lymphoma diagnosis	Nodal/ Extranodal	Image guided CNB	No	Academic reference center	229 CNB 1212 SEB	Diagnosis established: 210/229 (91.7%); lymphoma diagnosis 187/229 (81.7%).	19/229 (8.3%)	1,178/1,212 (97.2%)	n.a.	n.a.
Groneck et al. 2016 [28]	Retrospective	Lymphadenopathy or suspected lymphoma	Clinically conclusive diagnosis; lymphoma diagnosis	Nodal/ Extranodal	US-CNB	No	Yes	138 CNB 26 SEB 28 non-nodal biopsies	Clinically conclusive diagnosis: 121/132 (91.6%), including 76 lymphoma diagnoses, 65 of which clinically conclusive	11/132 (8.3%)	n.a.	26	n.a.; overall 7 false-negative and 2 false-positive CNBs
Allin et al. 2017 [36]	Retrospective	Cervical mass or Suspected Lymphoma	Full histological diagnosis via CNB; lymphoma and lymphoma subtype diagnosis	Head and Neck	CNB FNA	No	No	70 CNB	Full histological diagnosis: 63/70 (90.0%); including 19 lymphoma diagnoses, 18 of which with histological subtype	7/70 (10.0%)	n.a.	n.a.	n.a.
Kwon et al. 2018 [40]	Retrospective	Patients diagnosed with head and neck lymphoma	Definitive lymphoma diagnosis (subtyping/grading sufficient to initiate treatment)	Cervical lymph nodes	US-CNB	No	No	26 CNB 57 SEB	Definitive lymphoma diagnosis: 18/26 (69.2%)	8/26 (30.8%)	56/57 (98.2%)	8 SEB following non diagnostic CNB	n.a.

Cohen et al. 2021 [31]	Retrospective	Suspected and/or relapsed lymphoma	Definitive histological diagnosis	Nodal/ Extranodal	US-CNB PET-CT CNB	No	No	554 CNB	510/554 (92.1%) definitive diagnoses	44/554 (7.9%) non definitive diagnosis, 38 requiring 2nd biopsy	n.a.	n.a.	n.a.
Chatani et al. 2020 [33]	Retrospective	Suspected and/or relapsed lymphoma	Full diagnosis with lymphoma subtyping	Nodal/ Extranodal	US-CNB CT-CNB	No	No	263 CNB 108 SEB	Full lymphoma diagnosis: 234/263 (89.0%)	29/263 (11%); 4 partial diagnoses and 25 failures	101/108 (93.5%)	12 non diagnostic CNBs followed by SEB	n.a.
Assaf et al. 2020 [43]	Retrospective	Suspected lymphoma	Full diagnosis with lymphoma subtyping	Nodal/ Extranodal	CNB	Yes	No	210 CNB 163 SEB	Complete lymphoma diagnosis: 166/210 (79.0%)	44/210 (21.0%)	159/163 (97.5%)	9 non diagnostic CNBs followed by SEB	n.a.
Ingersoll et al. 2019 [39]	Retrospective	Suspected and/or relapsed lymphoma	Definitive lymphoma diagnosis and classification via FNA/CNB	Nodal/ Extranodal	FNA and CNB	Yes	No	152 FNA/CNB 28 SEB	Definitive lymphoma diagnosis: 124/152 (81.6%)	28/152 (18.4%)	n.a.	28 CNBs requiring subsequent SEB	23/28 (82%; lymphoma histotype diagnosis)
Wilczynski et al 2020 [37]	Retrospective	Patients with lymphadenopathies suspicious for malignancies	Established diagnosis; Lymphoma diagnosis sensitivity	Nodal	US-CNB	No	Yes	793 CNB 85 SEB	Established diagnosis: 782/793 (98.6%) Lymphoma diagnosis sensitivity: 238/245 (97.2%)	40/793 (5%) not correctly diagnosed (29 false negative; 11 inadequate)	n.a.	85 selected cases	75/85 (88.2%; malignancy and/or lymphoma diagnosis)
Syrykh et al. 2022 [8]	Retrospective, multicenter nationwide study	Newly diagnosed or suspected lymphoma submitted for expert pathological review before treatment.	Definitive WHO-classified lymphoma diagnosis; nondefinitive diagnosis; inadequate material; referral–expert diagnostic concordance; diagnostic changes after expert review;	Nodal	CNB	n.a.	Yes, systematic through French Lymphopath network	10,285 CNB 22000 SEB	9,497/10,285 (92.3%) definitive WHO-classified lymphoma diagnosis after expert review	788/10.285 (7.7%): 606 (5.9%) nondefinitive diagnoses and 182 (1.8%) without diagnosis due to inadequate material	21,584/22,000 (98.1%) definitive diagnoses after expert review	125 SEB following non-definitive diagnosis after expert review on CNB	24/125 (19.2%) initial CNB diagnostic suspicions confirmed by SEB

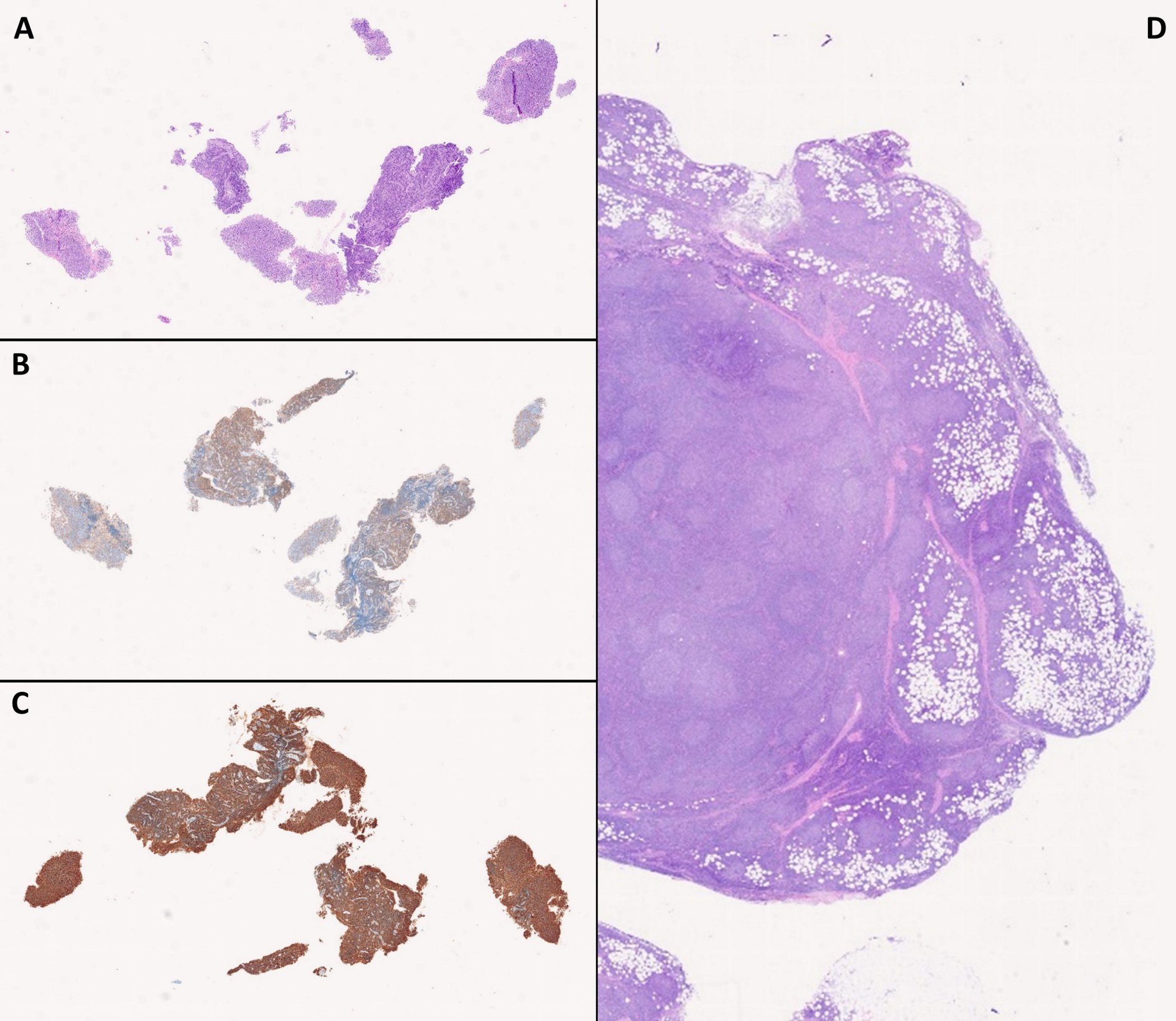
			comparison of sequential CNB and SEB										
Picardi et al. 2023 [30]	Retrospective, multicenter	Untreated patients with suspected lymphoma	Established diagnosis; lymphoma subtype diagnosis	Nodal	US-CNB	No	Yes	1000 CNB 100 SEB selected cases	Established diagnosis: 970/1000 (97%) Lymphoma subtype diagnosis: 800/830 (96.4%)	30/100 (30%) inconclusive diagnosis	n.a.	100 selected SEB, 30 following inconclusive CNB	Not applicable; 30 inconclusive CNBs diagnosed as lymphoma by subsequent SEB; results of the other 70 excisions were used for confirmation

Table 1. Characteristics and diagnostic yields of the major published studies evaluating CNB and SEB for lymphoma diagnosis.

CT: computed tomography; CNB: core needle biopsy; FC: flow cytometry; FNA: fine needle aspiration; PET: positron emission tomography; SEB: surgical excision biopsy; US: ultrasonography.

Figure Legend

Figure 1. Comparison of CNB and SEB samples from the same lymph node in a patient with follicular lymphoma. A) CNB specimens with tissue fragmentation and artifactual changes; nodal architecture cannot be assessed (HE, 2x). B) CD3 immunostaining documents the presence of T lymphocytes (4x). C) CD20 immunostaining shows a prevalence of B lymphocytes (4x). D) SEB specimen shows a lymphoid proliferation with follicular growth pattern and infiltration of perinodal adipose tissue, consistent with follicular lymphoma (HE, 2x).


A
B
C
D