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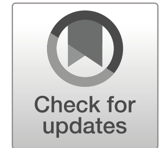
REVIEW ARTICLE



A practical approach to FISH testing for *MYC* rearrangements and brief review of *MYC* in aggressive B-cell lymphomas

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Abstract
Aggressive B-cell lymphomas, including the WHO diagnoses of diffuse large B-cell lymphoma, high-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements, high-grade B-cell lymphoma, not otherwise specified, and Burkitt lymphoma, together account for approximately 40% of B-cell non-Hodgkin lymphomas. Identification of *MYC*, *BCL2*, and *BCL6* rearrangements in these neoplasms is critical for diagnostic, prognostic, and therapeutic purposes. Herein, we address technical issues surrounding identification of these genetic abnormalities, discuss their diagnostic, prognostic, and therapeutic implications, and present an algorithm for use of interphase FISH in the work-up of aggressive B-cell lymphomas. To maximize sensitivity while still limiting cost, it is recommended that interphase FISH be performed in all B-cell lymphomas with large cell or high-grade morphology using both *IGH/MYC* dual-color dual-fusion (D-FISH) and *MYC* break-apart probes (BAP) as an initial probe set, followed by *BCL2* BAP (or *IGH/BCL2* D-FISH) and *BCL6* BAP if a *MYC* rearrangement is identified. In pediatric patients or aggressive B-cell lymphomas with Burkitt-like morphology, a complete analysis at the outset using BAP probes for *MYC*, *BCL2* (or *IGH/BCL2* D-FISH), and *BCL6* as well as D-FISH probes for *IGH/MYC*, *IGK/MYC*, and *IGL/MYC* is recommended.

Keywords Aggressive B-cell lymphoma · Diffuse large B-cell lymphoma · High grade B-cell lymphoma (HGBL) with *MYC* and *BCL2* and/or *BCL6* rearrangements · Burkitt lymphoma · FISH testing

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common lymphoma diagnosed in the United States and accounts for approximately 30–40% of all non-Hodgkin lymphomas [1]. Of cases morphologically classified as DLBCL, approximately 4–8% will be reclassified as the more aggressive entity designated "High-grade B-cell lymphoma (HGBL) with *MYC* and *BCL2* and/or *BCL6* rearrangements" per WHO 2017 criteria (DHL/THL, also referred to as "double-hit" or "triple-hit" lymphoma) [2, 3]. B-cell lymphomas with high-grade morphology, while less common overall, also frequently possess *MYC* and *BCL2* and/or *BCL6* rearrangements and are thus often reclassified as DHL/THL. The identification of an isolated *MYC* rearrangement (*MYC*-R) in B-cell lymphomas with large cell or high-grade morphology ("single hit lymphoma" SHL) may also confer a poorer prognosis, although this area is still controversial. Burkitt lymphoma nearly always possesses a *MYC*/immunoglobulin (IG) gene fusion, and although it typically has a uniform morphology and immunophenotype, its features may overlap with other aggressive B-cell lymphomas. As therapeutic regimens vary depending on the specific diagnosis, it is critical to establish the correct diagnosis for prognostic and therapeutic purposes.

Several methods have been used to detect gene rearrangements, including conventional cytogenetics, PCR, mate pair sequencing, and fluorescence in situ hybridization (FISH). However, conventional cytogenetics requires fresh tissue and may be hindered by the difficulty in obtaining suitable metaphases, PCR has low sensitivity, and mate-pair sequencing requires fresh or frozen tissue and at present is not widely available clinically. Interphase FISH, in contrast, has excellent sensitivity and specificity, is widely available, and it may be

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performed on formalin-fixed, paraffin-embedded (FFPE) material, including archival specimens and those with limited tissue [4–6]. Limitations of FISH often relate to specimen quality and processing prior to evaluation. For example, FISH testing performed on decalcified specimens, such as bone marrow trephine biopsies or bone-based lesions, may have limited success depending on the decalcifying agent used [7]. Additionally, approximately 20% of DLBCL cases have tumor necrosis at diagnosis [8], which may preclude accurate FISH testing on small biopsies.

Herein, we address the use of interphase FISH and propose an algorithm to aid in diagnosis of aggressive B-cell lymphomas, including the WHO diagnoses of DLBCL, DHL/THL, high-grade B-cell lymphoma, not otherwise specified (HGBL-NOS), and Burkitt lymphoma (BL). We also discuss the current challenges faced by pathologists and clinicians regarding interpretation of immunohistochemical (IHC) and cytogenetic findings in these cases. Beyond the scope of this paper are B-cell lymphomas such as plasmablastic lymphoma, blastoid mantle cell lymphoma, and others which may show *MYC*-R but remain within their respective diagnostic classifications. Also not discussed here are the gene expression profiles and/or mutational burden of these neoplasms. In this manuscript, concurrent *MYC* and *BCL2* rearrangements, concurrent *MYC* and *BCL6* rearrangements, and concurrent *MYC*, *BCL2*, and *BCL6* rearrangements are referred to as *MYC/BCL2*, *MYC/BCL6*, and *MYC/BCL2/BCL6*, respectively.

Fish probe selection for the identification of *MYC*, *BCL2*, and *BCL6* rearrangements

Several commercial FISH probe strategies used to test for *MYC*-R are available. The most commonly utilized FISH probes include *IGH*/*MYC* dual-color dual-fusion (D-FISH) and *MYC* break-apart probes (BAP). Due to the complex nature of rearrangements involving *MYC* at 8q24, false negatives may occur with either modality alone [9–13]. In one study, false negative rates (i.e., "normal" results, with no evidence of a *MYC*-R using a *MYC* BAP probe and no evidence of *IGH/MYC* fusion nor additional *MYC* signals compared to centromere 8 using an *IGH/MYC* D-FISH probe) were 4.1% and 22.1% using probes for *MYC* BAP and *IGH/MYC* D-FISH alone, respectively [12]. Furthermore, only about 45% of *MYC*-rearranged cases harbor *IGH/MYC* fusion, and thus, additional false negatives may occur in the setting of non-*IGH* partners. *MYC* BAP probes often fail to detect distal telomeric *MYC* translocation events, while *IGH/MYC* D-FISH probes may yield false negative results due to cryptic insertional mechanisms. There is also varying sensitivity among commercially available *MYC* BAP probes depending on extent of breakpoint region coverage, with some probes lacking distal 5′*MYC* or 3′*MYC* gene coverage [11]. Therefore, to maximize sensitivity and minimize turnaround time, it is recommended that both *IGH/MYC* D-FISH and *MYC* BAP probes be performed concurrently, with the caveat that cases with non-*IGH/MYC* fusions that are falsely negative by *MYC* BAP, will not be detected. Detection of these cases would require fresh/frozen tissue and sophisticated mate pair/whole genome sequencing methods that are not readily available for routine clinical use. An alternate approach in which *MYC* BAP is performed initially, with reflex to *IGH/MYC* D-FISH only if *MYC* BAP is negative, is also valid. The latter approach is less costly but would lengthen the turnaround time. In discordant cases, characterization of exact breakpoints may be determined by other genomic technologies such as next-generation sequencing.

To identify rearrangements of *BCL2* and *BCL6* by FISH, BAP probes rather than D-FISH probes are recommended. *BCL6* is known to have numerous translocation partners, including immunoglobulin genes and multiple non-immunoglobulin genes [14]. *BCL2* is almost always rearranged with *IGH* [15], although *BCL2* rearrangements to *IGK* and *IGL* have been described [13, 16]. Advantages of using *BCL2* BAP include ease of interpretation in FFPE as well as distinction of gains of gene regions on chromosome 18 from *BCL2* rearrangements to non-*IGH* genes. However, false negative results using *BCL2* BAP have been reported [13], although data remain limited. Therefore, for labs which offer only *IGH/BCL2* D-FISH or prefer this method, *IGH/BCL2* D-FISH remains an acceptable alternative to BAP.

MYC gene deregulation and tumorigenesis

The *MYC* proto-oncogene encodes the Myc protein, which is a nuclear transcription factor involved in multiple cellular functions including proliferation and apoptosis. Deregulation of *MYC* (e.g., via a translocation event) is a key factor in the pathogenesis of Burkitt lymphoma and many other lymphomas and malignancies [17]. The current understanding is that isolated *MYC* deregulation is not in itself tumorigenic as its increased apoptotic function keeps cellular proliferation in check. However, once *MYC* deregulation is coupled with another molecular event, such as *TP53* mutations in Burkitt lymphoma, or *BCL2*/*BCL6* rearrangements upregulating anti-apoptosis in DHL/THL, then tumorigenesis may occur [17, 18].

Prognostic implications of *MYC* rearrangements

High-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements

DHL/THL was established as a diagnostic category in the 2017 revision of the World Health Organization (WHO) classification of lymphoid neoplasms because of its poor prognosis. These lymphomas are defined by the presence of *MYC*-R

with an additional rearrangement in either *BCL2*, *BCL6*, or both and have a morphologic appearance that can vary from DLBCL-like (large cell) to intermediate between Burkitt lymphoma and DLBCL (high-grade) to blastoid [19]. DHL/THL often presents with advanced disease stage, and involvement of bone marrow and extranodal sites such as central nervous system is common. Median overall survival is less than 2 years, and DHL/THL has significantly poorer overall and progression-free survival than DLBCL [20–26]. However, some patients survive long term, with 5-year overall survival rates up to 49% [23].

Within the category of DHL/THL, the presence of high-grade cytologic features may confer a particularly poor survival [23, 27], and thus, the WHO recommends noting the morphologic appearance in all DHL/THL [19]. No significant survival differences between HGBL with *MYC/BCL2* and HGBL with *MYC/BCL2/BCL6* have been elucidated [24, 28, 29]. Some groups have observed improved survival in HGBL with *MYC/BCL6* [23, 30, 31], but this remains controversial. Another contentious issue is the prognostic implications of *MYC* translocation partners. In DHL/THL, approximately 45% of *MYC* rearrangements involve *IGH* [t(8;14)(q24;q32)], and about 15% involve *IGL* (22q11.2) or *IGK* (2p11.2) [23]. In the remaining 40% of cases, *MYC* is translocated to a variety of non-immunoglobulin partners (non-IG-*MYC*), including, but not limited to, *BCAS2*, *BCL6*, *BCL11A*, *IKZF1*, *IMMP2L*, *IRF4*, and *PAX5* [32, 33]. Some groups have demonstrated that DHL/THL with IG-*MYC* fusion have a poor prognosis, while those with non-IG-*MYC* fusion have a survival pattern similar to non-*MYC*-R DLBCL [24, 27, 30, 34]. However, other researchers have shown equally poor outcomes for DHL/THL patients regardless of IG-*MYC* versus non-IG-*MYC* fusion status [23, 35]. Resolution of this controversy is hampered by variation in cohort size and lack of uniformity regarding morphology, de novo versus transformed disease, and treatment regimens.

MYC-R in the absence of *BCL2* and *BCL6* rearrangements

The three morphologic variants of aggressive B cell lymphomas (Burkitt-like, high-grade, and large cell) may all harbor *MYC*-R in the absence of *BCL2* and *BCL6* gene rearrangements. Most cases with Burkitt-like morphology, characteristic immunophenotypic features, and IG-*MYC* fusion are diagnosed as Burkitt lymphoma, particularly in pediatric patients [19, 36]. However, as rare cases of pediatric DHL/THL have been described [37], and as DHL/THL may have Burkitt-like morphology, it is critical to evaluate for rearrangements involving *MYC*, *BCL2*, and *BCL6* in every case of aggressive B-cell lymphoma in children and/or with Burkitt-like morphology to establish the correct diagnosis. Furthermore, pediatric patients with pathologic features suspicious for Burkitt lymphoma who lack *MYC*-R may carry a diagnosis of Burkitt-like lymphoma with 11q aberration, and chromosomal microarray analysis to investigate this possibility may be indicated [38]. In laboratories where chromosomal microarray is unavailable, FISH studies using probes specific to the regions of interest may have appropriate sensitivity; however, data are limited and additional confirmatory studies may be needed [39].

High-grade B-cell lymphoma, not otherwise specified (HGBL-NOS), per 2017 WHO criteria, is an aggressive B-cell lymphoma with high-grade morphology that lacks the cytogenetic features of DHL/THL, although it may have an isolated *MYC*-R (20–35% of cases) [40]. Aggressive B-cell lymphomas with large cell morphology may also have as isolated *MYC*-R (4% of cases) [3] and are still diagnosed as DLBCL, NOS. These two categories together have been colloquially referred to as "single hit lymphomas" (SHL). The prognostic significance of SHL is controversial. Data are limited regarding the prognostic significance of isolated *MYC*-R in HGBL-NOS due to small cohort sizes [19, 40, 41]. Regarding large cell morphology, a recent large retrospective study by Rosenwald et al. [24] showed that DLBCL patients with *MYC*-R have a statistically similar progression-free survival and overall survival to non-*MYC*-R DLBCL. This is in contrast to several other smaller cohorts showing that patients with SHL may have a poor prognosis similar to DHL/THL [30, 42–46].

MYC and BCL2 protein expression by immunohistochemistry in *MYC*-R

Not all large B cell lymphomas with *MYC*-R, including DHL/THLs, have poor survival [22], and several groups have tried to identify factors that are associated with better survival. Only about 80% of DHL/THL express both MYC and BCL2 protein ("double-expressers"; DEL), even though the vast majority possess both *MYC* and *BCL2* rearrangements. The remaining 20% of DHL/THL may have a more favorable outcome, although data are limited [27, 47, 48]. *MYC*-R may only confer a worse prognosis if MYC expression is also increased [45, 46], and conversely, elevated MYC protein expression may confer a poor prognosis regardless of *MYC*-R status [49–52]. Others have found that *MYC*-R is only significant if also accompanied by BCL2 protein overexpression [47, 53]. It has been proposed that in cases both with and without *MYC*-R, the degree of MYC and BCL2 protein expression is proportional to clinical risk [54].

Treatment implications of *MYC*-R

Historically, patients with *MYC*-rearranged aggressive B cell lymphomas do poorly with standard dose R-CHOP chemotherapy or R-CHOP-like regimens. Patients who can tolerate it

may benefit from more intensive induction regimens [22, 55]. More aggressive induction regimens are typically used in patients with DHL/THL [22, 23, 56], although this remains an area of clinical uncertainty. While data from single arm studies and observational studies suggests that patients with *MYC*-R DLBCL and DHL/THL that receive more aggressive regimens such as dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab (EPOCH-R) may trend towards similar overall survival to those with non-*MYC*-R DLBCL [23, 57], there are no definite randomized studies proving that intensified chemotherapy is indeed superior to standard R-CHOP used in DLBCL. Newer targeted therapies, such as the anti-*BCL2* venetoclax, may prove to be an effective option [55, 58], and a randomized study sponsored by the National Cancer Institute is ongoing (NCT03984448). As yet, targeted therapies which directly inhibit *MYC* are elusive [59, 60]. Autologous stem cell transplants have been attempted in patients with relapsed or refractory DHL/THL with poor results, but remain an option [48]. Early results of chimeric antigen T cell receptor (CART) therapy have shown promising results in relapse/refectory setting [61] and will likely lead to development of post induction chemotherapy consolidative approaches in high-risk patients.

When to perform FISH for *MYC*, *BCL2*, and *BCL6* rearrangements

Recommended: perform FISH on every aggressive B cell lymphoma

Because of the prognostic and therapeutic implications of DHL/THL, all new aggressive B cell lymphoma diagnoses should be accompanied by appropriate FISH testing to rule out DHL/THL when biopsy tissue quantity and quality permit. One important argument for testing all DLBCL specimens is that DHL/THL with DLBCL morphology is uniquely defined by genetics. Considering that DLBCL is the most common lymphoma in the United States, cost and turnaround time issues will understandably arise in certain practices which lack the resources and capability of performing these assays. For those that cannot manage this approach, or when small specimen size precludes full workup, selective FISH strategies are also outlined below.

Proposed algorithms for the order of FISH testing

An algorithmic approach for performing interphase FISH testing in B cell lymphomas with large cell or high-grade morphology is presented in Fig. 1. Since all DHL/THL possess a rearrangement of *MYC* by definition and isolated *MYC*-R (SHL) may have prognostic significance, all cases are tested for a *MYC* rearrangement, using both BAP and *IGH*/*MYC* D-FISH probes to minimize false negative results; both are performed simultaneously to minimize turnaround time. This is followed by testing for both *BCL2* and *BCL6* translocations if *MYC* is rearranged. A similar algorithmic approach is recommended as essential diagnostic testing for DLBCL per the NCCN Guidelines Version 1.2020 [62]. However, depending on clinical practice, resources, and/or laboratory workflow, some practices may choose to test for rearrangements of *MYC*, *BCL2*, and *BCL6* at once to expedite diagnosis of DHL/THL, although this will often result in unnecessary testing for *BCL2* and *BCL6* rearrangements.

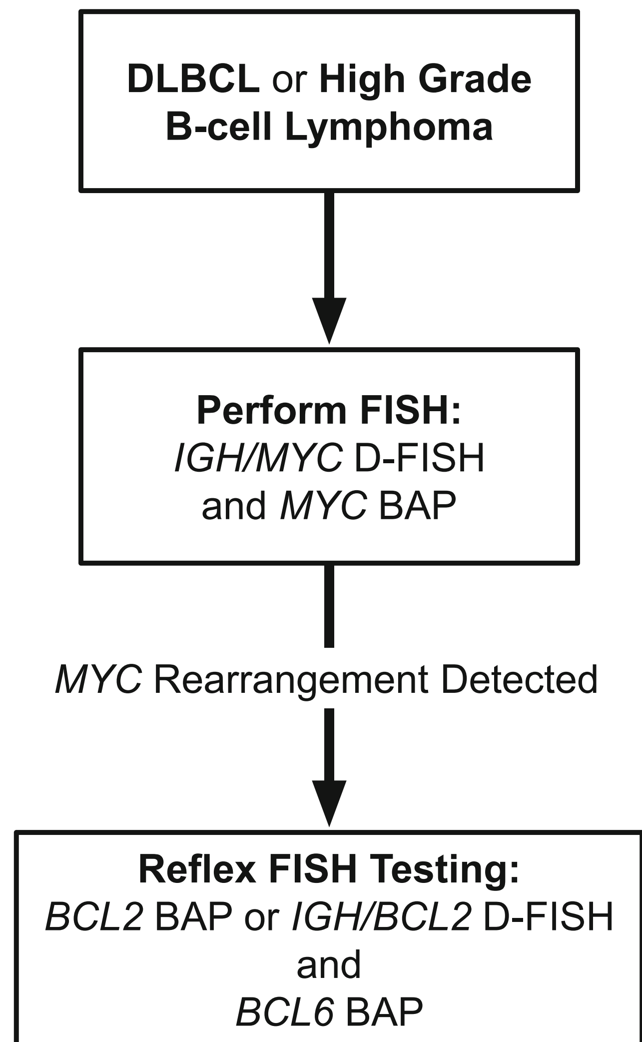

Fig. 1 Algorithm for performing interphase FISH in B-cell lymphomas with large cell or high grade morphology

In cases with classic Burkitt morphology or in pediatric populations where Burkitt lymphoma remains high in the differential diagnosis even without classic morphology, a modified algorithmic approach is proposed (Fig. 2). In these cases, testing using BAP probes for *MYC*, *BCL2*, and *BCL6*, as well as D-FISH probes for *IGH*/*MYC*, *IGL*/*MYC*, and *IGK*/*MYC*, is performed simultaneously. This expedites the analysis, which is especially important in Burkitt lymphoma given its highly aggressive biology. It also evaluates for all IG/*MYC*

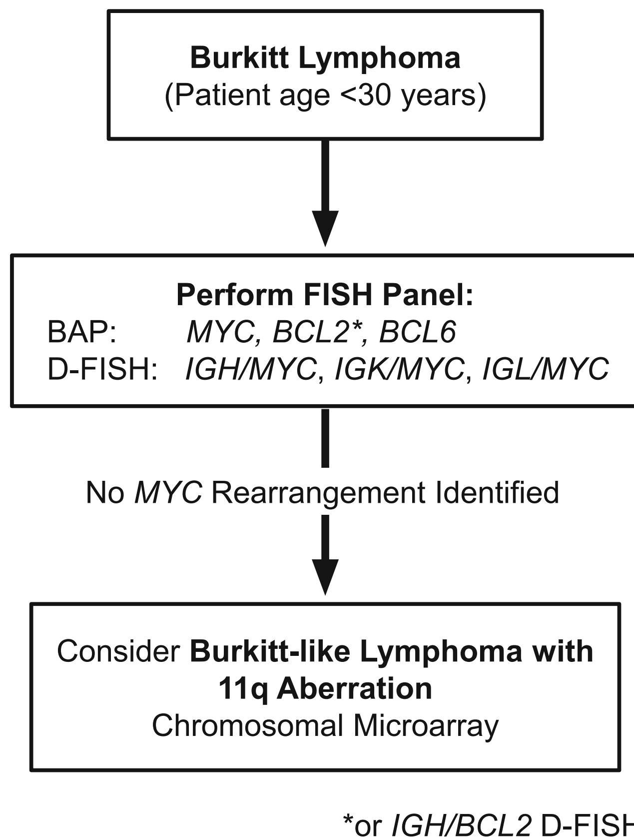

Fig. 2 Algorithm for performing interphase FISH in B-cell lymphomas with Burkitt morphology or in pediatric patients

combinations, as non-IG/*MYC* rearrangements are extremely rare in Burkitt lymphoma. Finally, it excludes the unlikely possibility of DHL/THL [19].

Alternative: selective FISH strategies to predict *MYC*-R

Several studies have investigated the value of cell of origin (COO) testing to predict for DHL/THL, relying on the fact that approximately 85% of DHL/THL possess a *BCL2* rearrangement and essentially all DHL/THL with *BCL2* rearrangements are of germinal center B cell (GCB) phenotype [3, 23]. Furthermore, DHL/THL with *BCL2* rearrangements have been most firmly established to have an aggressive clinical course and thus could potentially benefit most from more aggressive therapy. Since approximately 50% of DLBCL are of GCB phenotype [3], a laboratory could potentially cut the number of cases requiring FISH testing in half by using an IHC algorithm with appropriate specificity and sensitivity, such as the Hans or Choi algorithm, or a digital gene expression profiling assay such as Lymph2Cx to identify cases of GCB phenotype; however, each of these algorithms shows varying degrees of specificity, sensitivity, and reproducibility [63–66]. Performing FISH on only this cohort would detect 99% of DHL/THL with *MYC/BCL2* or *MYC/BCL2/BCL6*. However, this strategy would miss about half of DHL/THL with *MYC/BCL6* and about half of SHL, or about 25% of *MYC*-R cases overall [3].

It has also been proposed that coexpression of MYC and BCL2 proteins by IHC could be used to screen for DHL/THL, relying on the concept that gene rearrangements should result in increased expression of the corresponding protein in most cases. However, there are multiple problems with this approach. Firstly, assessing the percentage of tumor cells that express nuclear MYC protein by IHC has proven to be poorly reproducible among pathologists, particularly when MYC expression is near the 40% cutoff for positivity [67, 68]. MYC protein expression can vary throughout the tumor, shows significant variability in intensity of expression, and is affected by specific lab protocols and tissue fixation. Secondly, MYC protein expression status is a poor predictor of *MYC*-R, as there is no identified threshold for MYC IHC positivity that will predict *MYC*-R [3]. For example, using an IHC threshold of ≥ 40%, which was initially established for prognostic purposes and not to screen for *MYC* rearrangements, only 40% of DLBCLs that express MYC show *MYC*-R [3, 69]. Conversely, MYC protein is expressed in only about 80% of *MYC*-R cases. Scott et al. [3] outlined the percentage of DHL/THL cases that would be missed in aggressive B-cell lymphomas with large cell morphology if FISH testing was performed selectively depending on DEL ± COO status. If only DEL were investigated, one would expect to miss approximately 25% of DHL/THL, but would reduce testing to about 34% of DLBCL. If FISH investigation were further limited to DELs of GCB phenotype, FISH testing would be reduced to about 15% of all cases without any further decrease in sensitivity. In light of the poor sensitivity coupled with the difficulty in interpreting MYC expression by IHC reliably, this approach is not recommended.

Other factors such as age, IPI score, or disease stage are not good predictors of *MYC* rearrangement status [70]. Although most DHL/THL arise in older individuals, FISH testing for *MYC*, *BCL2*, and *BCL6* gene rearrangements must be performed on all aggressive B-cell lymphomas arising in pediatric patients to exclude both Burkitt lymphoma and DHL/THL. Histologic appearance is not a good predictor of *MYC*-R status, as only a subset of aggressive BCL with high-grade features (33–58%) [40, 50] or large cell features (12%) [3] will possess a *MYC*-R. Ki-67 proliferation index as estimated by IHC is also a poor predictor of *MYC*-R status [47, 70]. Lack of LMO2 protein expression by IHC may predict for *MYC*-R in CD10-positive DLBCL [71], but additional studies are needed to verify this finding.

Conclusions

Identification of *MYC*, *BCL2*, and *BCL6* translocations in aggressive B-cell lymphomas, in conjunction with clinical,

morphologic, and immunophenotypic features, is important for diagnostic, prognostic, and therapeutic purposes. Because most DHL/THL and some SHL have poor prognoses and may warrant more aggressive treatment, identification of *MYC* rearrangements ± *BCL2* and *BCL6* rearrangements is critical. To maximize sensitivity while still limiting cost, it is recommended that interphase FISH be performed in all B-cell lymphomas with large cell or high-grade morphology using both *IGH/MYC* D-FISH and *MYC* BAP probes as an initial probe set, followed by *BCL2* BAP (or *IGH/BCL2* D-FISH) and *BCL6* BAP probes if a *MYC* rearrangement is identified. In pediatric patients or aggressive B-cell lymphomas with Burkitt-like morphology, a complete analysis at the outset using BAP probes for *MYC*, *BCL2* (or *IGH/BCL2* D-FISH), and *BCL6* as well as D-FISH probes for *IGH*/*MYC*, *IGK*/*MYC*, and *IGL*/*MYC* is recommended.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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