

79.6. Hodgkin and Non-Hodgkin Lymphomas: Peripheral T-cell Lymphoma

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Emerging Prognostic Factors for Clinical Care

Recently, a molecular classifier developed from paraffin-embedded tissue significantly improved the prognostic stratification of patients with PTCL. Particularly, it enhanced the distinction between ALK-negative ALCL and PTCL NOS, especially some cases of CD30+ PTCL NOS with uncertain morphology, and discriminated some cases of T-follicular helper (Tfh) PTCL NOS from AITL; thus, it may serve as an additional tool in the diagnostic workup of nodal PTCL.¹

ALCL, ALK⁻. ALCL, ALK-negative (ALK⁻) was a provisional entity in the WHO 2008 classification; however, in the upcoming revision, ALCL, ALK⁻ is no longer provisional. Although this PTCL subtype shares morphologic and immunophenotypic features with ALCL, ALK⁺, including CD30 expression, it characteristically lacks *ALK* translocations. ALCL, ALK⁻ occurs in older individuals and has a poorer prognosis compared with ALCL, ALK⁺.²

Next-generation sequencing analysis identified a recurrent balanced translocation, t(6;7)(p25.3;q32.3), in ALCL ALK⁻. Mutually exclusive rearrangements of *DUSP22* and *TP63* are seen in 30% and 8%, respectively, of ALCL, ALK⁻.³ ALK⁻ ALCL harboring a *DUSP22* rearrangement had a 5-year OS indistinguishable from that of ALK⁺ ALCL (5-year OS of 90% for *DUSP22*⁺ ALK⁻ ALCL vs. 85% for ALK⁺ ALCL). Conversely, *TP63*-rearranged cases (8%) had a 5-year OS of only 17%. Based on these data, the authors suggested that all ALK⁻ ALCLs undergo FISH testing for rearrangements involving *DUSP22* or *TP63*. If a *TP63* rearrangement is present, they advocate that the pathology report indicate that an ALK⁻ ALCL with *TP63* rearrangement is associated with poor prognosis. If a *TP63* rearrangement is absent and a *DUSP22* rearrangement is present, the recommended designation is ALK⁻ ALCL with *DUSP22* rearrangement. However, FISH testing for these lesions is not routinely available; therefore, this prognostic marker is considered an emerging factor.

AITL. In AITL, high expression of several gene expression signatures associated with the tumor microenvironment are significantly associated with outcome. A combined prognostic score predicted survival in an independent cohort ($p = .004$).⁴ However, this assay is not clinically available. Next-generation sequencing and targeted sequencing have found that mutations in *RHOA* and the epigenetic regulators TET2, IDH2, and DNMT3A occur frequently in AITL and PTCL NOS with Tfh-like features.⁵⁻⁷ Recent studies show that specific inhibition of IDH mutants with targeted agents can reverse the

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abnormal methylation due to the mutation, and these drugs have been efficacious in preclinical and phase I clinical studies.

Factor	Definition	Clinical significance	Level of Evidence
<i>DUSP22</i> in ALK-negative ALCL	Rearrangement present in ALK-negative ALCL	Excellent outcomes equivalent to ALK-positive ALCL	I

Risk Assessment Models

Risk assessment models and prognostic tools play an important role in cancer medicine because they provide a mechanism to integrate disparate data elements into a process that leads to decreased prognostic heterogeneity. Such processes are useful for (1) identifying and characterizing important prognostic factors, (2) improving prognostic predictions for individual patients, and (3) designing, conducting, and analyzing clinical trials.⁸ The most common type of prognostic tool is a prognostic calculator that provides time-specific outcome (e.g., 5-year OS) probability predictions for individual patients based on their demographic, clinical, and tumor characteristics. The prognostic nomogram developed by Yang et al⁹ is an example of a risk calculator. Another type of prognostic tool is a prognostic classifier that places patients into ordered prognostic risk classes (either directly or based on cutoffs for individual probability estimates). The remaining tools referenced in this chapter (e.g., IPI, MIPI, FLIPI, and CLL-IPI) are prognostic classifiers. The AJCC Precision Medicine Core (PMC) developed and published criteria for critical evaluation of prognostic calculators,¹⁰ which are presented and discussed in Chapter 4. The prognostic nomogram developed by Yang et al⁹ meets all but one of the AJCC PMC criteria because it lacks discussion of how missing data were treated.

Recommendations for Clinical Trial Stratification

The authors have not provided any recommendations for clinical trial stratification at this time.

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