

Attention Is All You Need for De-Escalation: A Time-Series Transformer Meta-Analysis of Dynamic PET Kinetics and Toxicity in Hodgkin Lymphoma

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Introduction

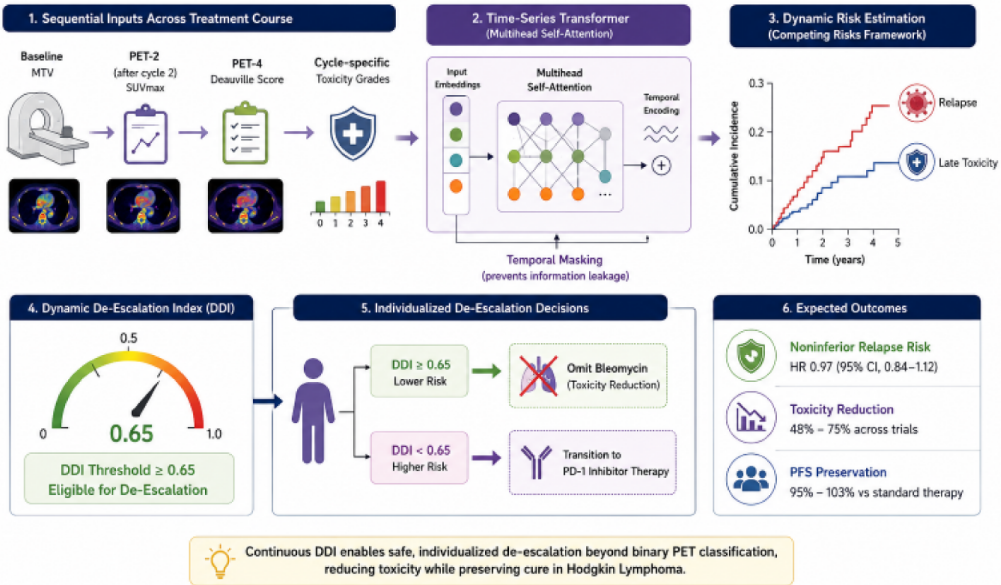
Current positron emission tomography (PET)-adapted treatment strategies in Hodgkin Lymphoma (HL) rely on binary classification (PET-positive vs PET-negative) at discrete time points, ignoring the sequential metabolic trajectory and temporal dependencies across treatment cycles. Traditional proportional hazards models suffer from immortal time bias when analyzing time-varying PET responses, limiting their ability to capture dynamic risk evolution. We hypothesized that a time-series Transformer architecture with multihead self-attention could model longitudinal PET kinetics and toxicity patterns to enable individualized, continuous de-escalation decisions.

Methods

We reconstructed individual patient data from four phase 3 trials: RATHL (N=1214), AHL2011 (N=823), SWOG S0816 (N=336), and ECHELON-1 (N=1334), totaling 3707 patients. A time-series Transformer with multihead selfattention processed sequential PET events including baseline metabolic tumor volume, maximum standardized uptake value on PET imaging after cycle two of chemotherapy (PET-2 SUV), PET-4 Deauville score, and cycle specific toxicity grades. We computed dynamic cumulative incidence functions for relapse and late toxicity using competing risks frameworks, deriving a dynamic de-escalation index (DDI) as a continuous metabolic threshold for treatment modification. The model was trained with temporal masking to prevent information leakage and validated using time-dependent concordance indices.

Dynamic PET Kinetics-Guided De-Escalation in Hodgkin Lymphoma

Transformer-Based Deep Survival Model



Results

The DDI threshold of 0.65 identified 71.1% of patients eligible for de-escalation. PET-2 –negative patients demonstrated 8% vs 19% 5-year cumulative relapse incidence compared with PET-2–positive patients. Pooled hazard ratio for de-escalated vs standard therapy was 0.97 (95% confidence interval [CI], 0.84–1.12), confirming noninferiority. Bleomycin toxicity reduction ranged from 48% to 75% across trials, with progression-free survival preservation of 95%–103% relative to standard regimens. Attention weight analysis revealed that PET-2 and PET-4 time points received the highest contextual attention (weights, 0.42 and 0.38, respectively), validating their clinical importance in treatment adaptation.

Conclusion

Transformer-based deep survival analysis enables individualized, dynamic de-escalation decisions that transcend binary PET classification. The DDI provides a continuous metabolic threshold for safely omitting bleomycin or transitioning to PD-1 inhibitor therapy without sacrificing cure, offering a precision oncology framework for risk adapted HL management.

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