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Using tumor growth modeling and informed neural networks as early predictive clinical endpoints.

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Background: Immunotherapy has significantly improved cancer treatment outcomes but presents unique challenges in assessing response due to complex tumor kinetics. Traditional efficacy criteria like RECIST 1.1 often fail to capture these complexities. Tumor growth modeling (TGM) offers a complementary approach that can capture more in-depth the longitudinal dynamics of tumor size. This study evaluates the utility of TGM with informed neural networks in predicting response and durability. **Methods:** We analyzed 116 patients with non-small cell lung cancer (NSCLC). Early phase was characterized as up to two follow-up timepoints. Response was defined as complete or partial response (CR/PR) before progressive disease (PD); durable response as early response without PD in the late phase; non-durable response as early response with PD during the late phase. A novel Gompertz model was fitted to early phase tumor burden (SODs) using two follow-up timepoints. Growth rate at each timepoint and parameters A, B, and M, capturing depth of response, speed of response, and long-term growth modulation, respectively, were derived then feeded into neural network. SOD(t) = SOD_0 e^(Ae^(-Bt)+Mt) A binary classification model using a neural network was developed to predict response outcomes. Input features were standardized and reduced using Principal Component Analysis (PCA). The neural network, consisted of four fully connected layers with batch normalization, ReLU activation, dropout (rate 0.5), and sigmoid activation. Binary Cross-Entropy Loss and Adam optimizer were used. Performance was evaluated using AUC, accuracy, sensitivity and specificity. Time-to-event analysis employed Cox models and Log rank tests with subgroup (using medians as cutoffs) of derived parameters from one follow-up timepoint model fit. **Results:** No significant differences in SODs were observed between responders and non-responders (p-value $\geq$ 0.05). However, all model parameters (GR, A, B, and M) showed significant differences between the groups: GR (p-value $<$ 0.001), A (p-value $<$ 0.001), B (p-value $<$ 0.001), and M (p-value $<$ 0.05). Test set model predictions demonstrated robust performance on: Responder vs. non-responder: AUC = 0.94, accuracy = 85.7%, sensitivity = 80.0%, specificity = 87.5%. Durable vs. non-durable response: AUC = 0.91, accuracy = 80.9%, sensitivity = 81.3%, specificity = 80.0%. Patients with high A values exhibited a significantly shorter time to response (HR = 11.6, 95% CI: [6.44, 20.93], p-value $<$ 0.0001). At 23 weeks, 79% of high-A patients responded compared to 6% of low-A patients. Similarly, patients with high B had a hazard ratio of 4.65 (95% CI: [2.77, 7.81], p-value $<$ 0.0001). Notably, SODs and growth rate were not discriminative at this level. **Conclusions:** Our findings suggest that early tumor growth parameters, may serve as predictive clinical endpoints for response and long-term outcomes. Research Sponsor: None.