P – 054 Predicting HER2 status in esophagogastric cancer: Development and validation of an easy-to-use nomogram

L Fornaro[1], A Parnofiello[2], C Ugolini[3], N Cardarelli[4], G De Maglio[5], I Pecora[6], F Crivelli[7], S Catanese[8], G Cardellino[9], G Musettini[8], N Pella[9], G Pasquini[10], S Pizzolitto[5], F Salani[11], M Clerico[7], G Fontanini[12], G Fasola[13], D Maurizio[4], C Vivaldi[8], F Montagnani[7]

[1]U.O. Oncologia Medica 2, Azienda Ospedaliero-Universitaria Pisana, Istituto Toscano Tumori, Pisa, Italy, [2]Department of Oncology, Azienda Sanitaria Universitaria Integrata di Udine, Udine, Italy, [3]Department of Laboratory Medicine, Section of Pathology, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy, [4]Department of Oncology, San Bortolo General Hospital, AULSS8 East District, Vicenza, Italy, [5]University Hospital Udine, Udine, Italy, [6]Azienda Ospedaliero Universitaria Pisana, Pisa, Italy, [7]Department of Oncology, Azienda Sanitaria Locale di Biella, Biella, Italy, [8]Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy, [9]Department of Oncology, Azienda Sanitaria Universitaria Integrata S. Maria della Misericordia, Udine, Italy, [10]Department of Oncology, University Hospital, Pisa, Italy, [11]Unit of Oncology 2, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy, [12]Department of Surgical, Medical, Molecular Pathology and Critical Area, University of Pisa, Pisa, Italy, [13]University Hospital Santa Maria della Misericordia, Udine, Italy

Introduction: HER2 currently represents the only available predictive biomarker in advanced esophagogastric cancer. Trastuzumab plus chemotherapy is the standard of care in tumors carrying HER2 protein overexpression by immunohistochemistry (IHC) or gene amplification by in situ hybridization (ISH). However, heterogeneity in protein expression, lack of adequate tumor samples for analyses and the need for rapid target assessment for patient management underline the need for a pre-test screening tool in order to anticipate the probability of carrying a HER2-positive disease.

Methods: The clinical and pathological data from 695 consecutive esophagogastric carcinomas analyzed at three different Institutions were collected. HER2 positivity was defined as IHC score of 3+ or 2+ with a positive ISH. 411 cases from one Institution were used to build a multivariate logistic regression model able to predict HER2 positivity. Both backwards and forward method were used to build multiple models. Collinearity was evaluated with Fisher's test, t-test and ANOVA, depending on the nature of the covariates, and Variance Inflation Factor (VIF). Final model was selected considering statistical significance of the covariates, clinical plausibility and global fit and it was used to develop a nomogram. Validation and calibration were performed on an external series of 284 patients treated at other two Institutions. C-index, visual inspection of the calibration plot, Brier score and Spiegelhalter z-test were used to assess the performance of the nomogram. 95% confidence intervals (CIs) of C-index were calculated with bootstrap method.

Results: 119 cases (17%) showed HER2 positivity in the development cohort. After univariate analyses and adjustment of collinearity, four variables were introduced in the final model: tumor grading (G1 vs. G2 vs. G3) ($p = 0.0018$), Lauren's histotype (intestinal vs. diffuse) ($p = 0.044$), type and adequacy of pathological material (surgical specimen vs. $\geq$5 biopsy samples vs. <5 biopsy samples) ($p = 0.19$) and site of sampling (primary cancer vs. metastasis) ($p = 0.034$). Tumor grading was associated to the greatest number of points, followed by site of sampling, Lauren's histotype and type of pathologic material. Visual inspection of the calibration plot revealed a very good overlap between predicted and observed probabilities, with a Brier score of 0.048 and a statistically significant Spiegelhalter z-test ($p < 0.0001$). C-index resulted in 0.84 (95%CI 0.75-0.93).

Conclusion: We developed a simple nomogram based on four immediately and always available pathological characteristics able to accurately predict the probability of HER2 positivity in esophagogastric cancer. This could be useful to minimize HER2 test heterogeneity and prompts re-biopsy in those cases of inadequate material but an anticipated high probability of HER2 positive status. A visual format of the nomogram will be presented.