Study proposal

Validation of the PANAMA-Score for Patient Stratification and Adjuvant Therapy Sequencing after Neoadjuvant Treatment for Pancreatic Cancer

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Background: The 8th edition of the AJCC-TNM staging system shows moderate discriminatory value for prognostication after upfront surgery-treated pancreatic cancer patients.[1] However, it should be noted that after neoadjuvant treatment, classical pathological determinants change through the course of cytotoxic treatment and do not represent the true aggressiveness of the tumor. Therefore, the PAncreatic NeoAdjuvant MAssachusetts

(PANAMA)-score, which, in addition to remaining tumor size and nodal positivity, incorporates further crucial biological factors such as the persistence of elevated CA19-9 after neoadjuvant therapy as a surrogate for inadequate systemic therapy response and resection margin status as a surrogate for local residual disease after surgical resection.[1] In its original publication, the PANAMA-score stratified the cohort in low-, intermediate and high-risk individuals for impaired overall-survival and demonstrated superior predictive ability for two-year survival, leading to an improved patient counseling. However, the validation of this score in a multi-center setting, including prediction of recurrence, is lacking. Furthermore, the question of who benefits from adjuvant treatment after neoadjuvant treatment remains unanswered. In their multicenter study, Van Roessel et al. proposed that adjuvant therapy is only beneficial in nodal-negative patients.[2] While using a single variable for this crucial treatment decision may be problematic, particularly in light of conflicting results from Hammad et al. in a separate analysis, further evidence is needed to support this hypothesis.[3] A score combining remaining advanced disease, elevated CA19-9, and positive margins may be a more appropriate method for determining the necessity of adjuvant treatment following neoadjuvant treatment.

Study objectives:

- To validate the prognostic value of the PANAMA-score in predicting overall survival, recurrence, and site of recurrence in a multicenter setting.
- To evaluate the prognostic value of the PANAMA-score to predict the benefit of adjuvant treatment after neoadjuvant treatment in resected pancreatic cancer patients.

Methods: First, the PANAMA score will be evaluated for predicting survival. C-Index and Kaplan-Meier Curves with Log-rank comparisons of risk groups will be created for overall and recurrence-free survival to assess its discriminatory ability. Thereafter, ROC curves and AUC for predicting survival over time up to 5 years will be calculated and compared to other clinically relevant predictive scores such as the AJCC-TNM staging system. Furthermore,

Cox-regression analysis with interaction analyses will be performed to assess the benefit of adjuvant treatment in certain patient subgroups including the PANAMA risk groups. All analysis will be performed retrospectively using, if this study proposal will be accepted, the multicenter E-AHPBA cohort.

1. Hank T, Sandini M, Ferrone CR, et al. A Combination of Biochemical and Pathological Parameters Improves Prediction of Postresection Survival After Preoperative Chemotherapy in Pancreatic Cancer: The PANAMA-score. *Ann Surg*. Feb 1 2022;275(2):391-397. doi:10.1097/sla.0000000000004143
2. van Roessel S, van Veldhuisen E, Klompmaker S, et al. Evaluation of Adjuvant Chemotherapy in Patients With Resected Pancreatic Cancer After Neoadjuvant FOLFIRINOX Treatment. *JAMA Oncology*. 2020;6(11):1733-1740. doi:10.1001/jamaoncol.2020.3537
3. Hammad AY, Hodges JC, AlMasri S, et al. Evaluation of Adjuvant Chemotherapy Survival Outcomes Among Patients With Surgically Resected Pancreatic Carcinoma With Node-Negative Disease After Neoadjuvant Therapy. *JAMA Surgery*. 2023;158(1):55-62. doi:10.1001/jamasurg.2022.5696