MEDICAL UNIVERSITY OF VIENNA

Predictive modelling for prognostic stratification of head and neck cancer patients using multi-omics data

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Objective

The integration of data from multiple biological levels is vital for a holistic approach to personalized patient management. Machine learning (ML) serves as an ideal tool to reveal relevant patterns of these high-dimensional data and their association with clinical endpoints. In this study, we combined functional and anatomical in vivo imaging as well as genomic data to improve the prognostic stratification of patients with head and neck squamous cell carcinoma (HNSCC).

Patients and Methods

Seventy-seven (77) patients with HNSCC (Table 1 & 2) who underwent whole-exome sequencing (WES) and PET/CT imaging were included in the analysis. Of the 1,554,752 genetic alterations detected by WES, a total of 8 genetic targets was selected for further analysis using survival analysis ranking and validation with public data. Of the 892 radiomic features extracted from the PET/CT images, 109 were included in the subsequent analysis. Predictive modelling was performed using a statistical model and a crossvalidated random forest model with recursive feature elimination.

Results

Combined radio-genomic markers did outperform corresponding genomic and radiomic markers. By stratifying patients based on combined genomic markers in *MSH6* and *ERCC6* with a PET-based texture feature, the difference in mean overall survival between the two prognostic groups was improved by 20 and 13 months, respectively (p-values < 0.001). The three ML models using radiomics, genomics and combined features for each model, delivered accuracies of 0.70, 0.77 and 0.81, respectively for predicting treatment response.

Data	Feature Selection	Feature Number	Accuracy
Radiomics	KDE	10	0.67
Radiomics	RFECV	10	0.70
Genomics	None	8	0.77
Radiomics + Genomics	**RFECV**	**10**	**0.81**

Table 3: Performance comparison of multiple machine learning models with different feature types and feature numbers. The combined performance of the model using radiomics and genomics features (bold) was clearly superior compared to all single feature type models in a 10-fold Monte Carlo cross-validation procedure. Recursive feature elimination with internal cross-validation (RFECV) lead to better performances for the radiomics features compared to the KDE-based feature selection. For the genomics model, all eight alterations were included into the analysis.

Conclusion

Prognostic stratification of HNSCC patients based on genetic and imaging patterns is feasible with high accuracy levels when combining non-/imaging data using machine learning models. Our study provides a methodological template for the analysis of other cancers, while showcasing a data model for a potential decision support system and providing a seed point for further mechanistic research.
Furthermore, the approach can be extended by integrating further feature types into the analysis, such as data derived from histopathological images and blood parameters. When integrating the treatment type as an additional feature, the resulting predictive models might also be suiting for the development of a decision support system for providing clinicians with information on the most promising treatment types as shown in Figure 2.

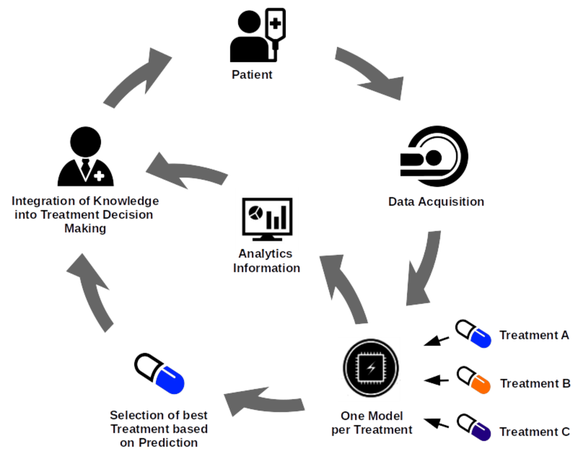

Figure 2: . Using prognostic models for guiding treatment decision making. When using the treatment type along with other acquired features as input of a predictive model, individual predictions can be performed for a given patient, each one corresponding to one treatment type. For the prediction suggesting the best prognosis, the corresponding treatment can be suggested to the clinician as most promising candidate. In addition, the clinician can be supplied with analytical information including how the given prediction was determined. This provides the clinician with the ability to estimate whether the model's decision-making procedure was reasonable and how to incorporate further information into the clinical workflow.

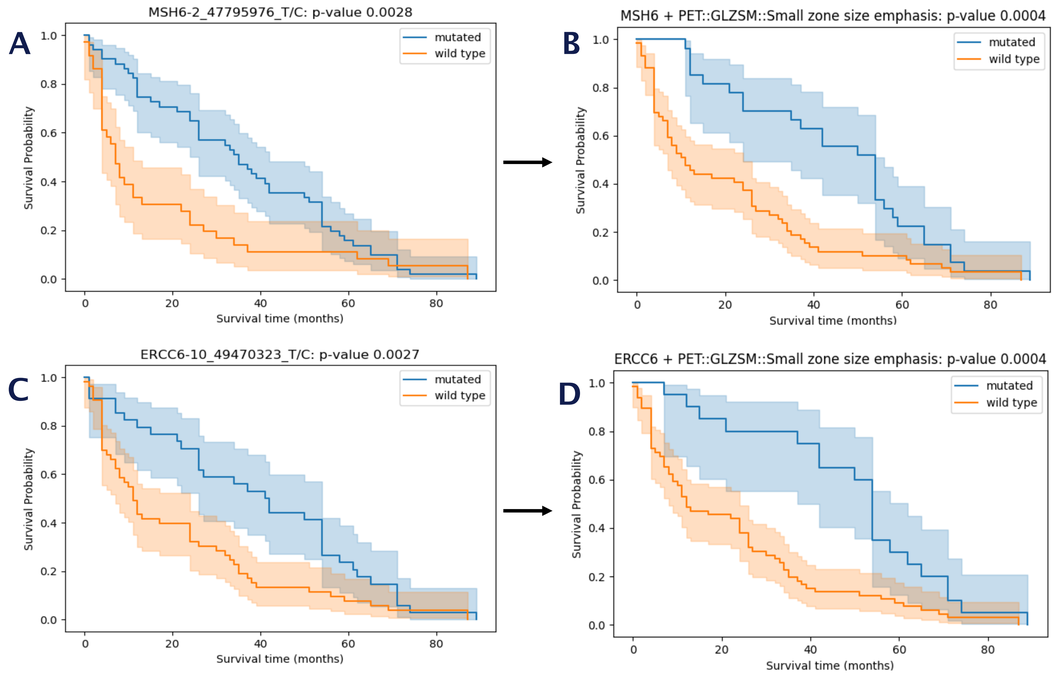

Figure 1: Improvement of prognostic stratification by combining the identified genomic markers in *MSH6* and *ERCC6* combined with a PET-based heterogeneity marker. Kaplan Meier curves on the left demonstrate the prognostic stratification of the HNSCC patients depending on whether the DNA damage response genes *MSH6* (A) and *ERCC6* (C) are mutated or not. On the right, the stratification of MSH6 (C) and ERCC6 (D) have been extended depending on whether the PET-based grey-level zone size matrix (GLZSM) feature, small zone size emphasis, has been above its median value over all patients. By combining radiomic and genomic markers, the difference between the median overall survival time (m.o.s.) has been increased from 26 to 46 months (*MSH6*) and from 30 to 43 months (*ERCC6*).

Characteristics	Absolute frequency	Relative frequency (%)
Age, mean ± SD [years]	66.2 ± 11.0	
Gender		
Male	57	74.0
Female	20	26.0
Tumour location		
Oral Cavity	46	59.7
Oropharynx	16	20.8
Hypopharynx	8	10.4
Larynx	6	7.8
Unknown primary site	1	1.3
Clinical disease stage		
Unknown	2	2.6
I	5	6.6
II	4	5.3
III	7	9.2
IV A	56	74.0
IV B	1	1.3
IV C	3	4.0

Characteristics	Absolute frequency	Relative Frequency (%)
Single treatment		
Radiotherapy	14	18.2
Chemotherapy	8	10.4
Surgery	17	22.1
Combination treatment		
Radiochemotherapy (RCT)	13	16.9
Targeted therapy (Cetuximab)	1	1.3
Cetuximab + chemotherapy	3	3.9
Radioimmunotherapy (RIT)	7	9.1
Immunotherapy	1	1.3
Best supportive care	13	16.9

Table 1 & 2: Characteristics of the HNSCC cohort. In accordance with the overall population, the cohort included more male than female HNSCC patients (52 vs. 20). For more than hald of the tumors, the main site of origin was the oral cavity (46) followed by the oropharynx (16). The cohort consisted mostly of late-stage patients (60 in stage IV). The patients had all been treated, 39 of which received single treatments while the remaining 38 received a combination of treatments.