HPV and beyond—looking out for biomarkers for distinguishing the good prognosis from the bad prognosis group in locally advanced and clinically high risk HNSCC

Fabian Lohaus[1,2,3], Annett Linge[1,2,3], Michael Baumann[1,2,3,4]

[1]German Cancer Research Center (DKFZ), Heidelberg and German Cancer Consortium (DKTK) partner site Dresden, Dresden, Germany; [2]Department of Radiation Oncology, [3]OncoRay – National Center for Radiation Research in Oncology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität, Dresden, Germany; [4]Institute of Radiooncology, Helmholtz-Zentrum Dresden – Rossendorf, Dresden, Germany

Correspondence to: Prof. Dr. med. Michael Baumann. DKTK partner site Dresden, Department of Radiation Oncology and OncoRay - National Center for Radiation Research in Oncology, Medical Faculty and University Hospital Carl Gustav Carus, Technische Universität Dresden, Fetscherstraße 74, 01307 Dresden, Germany. Email: Michael.Baumann@uniklinikum-dresden.de.

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In their recent editorial Kimple and Harari (1) reviewed the current knowledge of the importance of HPV status of head and neck squamous cell carcinoma (HNSCC) for outcome of radiotherapy. The editorial summarized, among others, a retrospective multicenter study by the German Cancer Consortium Radiation Oncology Group (DKTK-ROG) which demonstrated significant prognostic value of the HPV status in patients with locally advanced HNSCC on the outcome of postoperative radiochemotherapy (PORT-C) (2). The overall aim of the DKTK-ROG head and neck program is to identify and validate biomarkers including biological and clinical parameters as well as imaging data for patient stratification in terms of individualization of radiotherapy by multimodal treatment. The study design includes retrospective explorative analyses in patients who received PORT-C or primary radiochemotherapy (RCT) for biomarker identification. The most promising biomarkers will then be validated in a prospective validation cohort, which is currently recruiting at all eight DKTK-ROG partner sites. Based on these results, interventional studies are under preparation. Biomarker analyses are being performed at all eight DKTK partner sites and are addressing different topics such as HPV status, hypoxia, cancer stem cells, tumor infiltrating lymphocytes, tumor volume, targeted next generation sequencing, transcriptomics and methylome analyses.

With a 2-year overall survival rate of about 83% in the retrospective PORT-C study, the patients treated at the DKTK-ROG sites seem to have a favorable prognosis compared to the two landmark studies of the RTOG (#9501) (63%) and EORTC (#22931) (75%) (3,4). This difference may be due to differences in staging (in the DKTK-ROG study staging was performed with contrast-enhanced MRI, CT or PET/CT) and the broad availability of intensity modulated radiotherapy (IMRT). However, also formal differences exist between these three studies, with the DKTK-ROG study evaluating contemporary retrospective data from a limited number of tertiary high volume centers, while the randomized RTOG and EORTC trials have prospectively accrued patients in a larger number of centers. This limits the validity of direct comparison of the survival data of these studies. It is also not straightforward to compare the PORT-C data reported by the DKTK-ROG with the outcome of studies testing primary RCT, as the patient cohorts submitted to these different treatment strategies may vary in important parameters, including stage and co-morbidity. Therefore it appears most rationale to compare the relative impact of biological stratification parameters on outcome separately in different trials.

Impact of HPV in non-oropharyngeal cancer

In our DKTK-ROG study, the HPV status was analyzed in patients with locally advanced HNSCC of the oral cavity, oropharynx and hypopharynx. However, 35 patients with

hypopharyngeal carcinoma were included in this study with five of them being HPV16 DNA positive. Because of this low number, we did not draw any conclusion of the impact of the HPV status in this tumor subsite. Kimple and Harari pointed out that in a study by Chung *et al*. (5), patients with p16-positive non-oropharyngeal cancer treated with different RCT schedules had a significantly better overall survival than patients with p16-negative tumors. Whether this applies also to patients in Germany and Europe needs to be addressed in larger studies, as today's HPV infection rate is lower in Germany than in North America.

Impact of HPV in primary RCT *vs.* PORT-C

In our retrospective DKTK-ROG PORT-C cohort, a very high locoregional tumor control rate was achieved in HPV16 DNA positive (oropharyngeal) tumors. If confirmed in our ongoing multicenter validation trial, this observation is of substantial importance for the design of future clinical studies. Local control rates close to 100% should allow to testing the value of dose de-escalation in HPV positive tumors without compromising locoregional control. This is in contrast to primary RCT of macroscopic tumors (e.g., RTOG0129, RTOG 0522, DAHANCA 5, DAHANCA 6, DAHANCA 7) where long term local control rates of HPV positive oropharyngeal cancers are in the range between 70% and 80%. Further clinical and biological parameters are needed in this situation to safely stratify patients to less or more aggressive treatments. This can for example be demonstrated in the primary RCT DKTK-ROG cohort, which shows that tumor volume, hypoxia and stem cell markers add significantly to the prognostic power of HPV (Lohaus, Linge, Löck, Baumann *et al*., to be submitted).

Beyond HPV infection

To further stratify patients with HPV negative tumors undergoing PORT-C, further biomarkers are currently under investigation. Recently, Balermpas *et al*. showed in the retrospective PORT-C cohort of the DKTK-ROG, the prognostic value of tumor-infiltrating CD8 positive lymphocytes on overall survival and local progression-free survival independent of the HPV status (6). In terms of potential treatment modulation, the question remains to be resolved whether HPV positive HNSCC are more radiosensitive *per se* or if the improved response is due to the immune response. Furthermore, targeted next generation sequencing in the retrospective DKTK PORT-C cohort revealed that loss-of-function alterations in tumor suppressor genes are related to an increased risk of loco-regional recurrence, distant metastases and death, mainly in HPV negative tumors (7). Also hypoxia and expression of cancer stem cell markers, independently of HPV, correlate with outcome of PORT-C (Linge *et al*., submitted for publication). Thus clinical applicable biomarkers beyond HPV are emerging which, if validated in our ongoing prospective trial, may significantly enhance our arsenal for stratification of patients for clinical trials and individualized treatment approaches, offering new opportunities on the avenue towards personalized precision radiation oncology in head and neck cancer.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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