
Comparison of detection methods for HPV status as a prognostic marker for loco-regional control after radiochemotherapy in patients with HNSCC

Eintragsart Zeitschriftenartikel

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Zusammenfassung OBJECTIVE: To compare six HPV detection methods in pre-treatment FFPE tumour samples from patients with locally advanced head and neck squamous cell carcinoma (HNSCC) who received postoperative (N=175) or primary (N=90) radiochemotherapy. MATERIALS AND METHODS: HPV analyses included detection of (i) HPV16 E6/E7 RNA, (ii) HPV16 DNA (PCR-based arrays, A-PCR), (iii) HPV DNA (GP5+/GP6+ qPCR, (GP-PCR)), (iv) p16 (immunohistochemistry, p16 IHC), (v) combining p16 IHC and the A-PCR result and (vi) combining p16

IHC and the GP-PCR result. Differences between HPV positive and negative subgroups were evaluated for the primary endpoint loco-regional control (LRC) using Cox regression. RESULTS: Correlation between the HPV detection methods was high (chi-squared test, $p < 0.001$). While p16 IHC analysis resulted in several false positive classifications, A-PCR, GP-PCR and the combination of p16 IHC and A-PCR or GP-PCR led to results comparable to RNA analysis. In both cohorts, Cox regression analyses revealed significantly prolonged LRC for patients with HPV positive tumours irrespective of the detection method. CONCLUSIONS: The most stringent classification was obtained by detection of HPV16 RNA, or combining p16 IHC with A-PCR or GP-PCR. This approach revealed the lowest rate of recurrence in patients with tumours classified as HPV positive and therefore appears most suited for patient stratification in HPV-based clinical studies.

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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

Eintragsart Zeitschriftenartikel

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Anhänge

- Volltext
-

HPV status, cancer stem cell marker expression, hypoxia gene signatures and tumour volume identify good prognosis subgroups in patients with HNSCC after primary radiochemotherapy: A multicentre retrospective study of the German Cancer Consortium Radiation Oncology Group (DKTK-ROG)

Eintragsart Zeitschriftenartikel

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Zusammenfassung OBJECTIVE: To investigate the impact of the tumour volume, HPV status, cancer stem cell (CSC) marker expression and hypoxia gene signatures, as potential markers of radiobiological mechanisms of radioresistance, in a contemporary cohort of patients with locally advanced head and neck squamous cell carcinoma (HNSCC), who received primary radiochemotherapy (RCTx). MATERIALS AND METHODS: For 158 patients with locally advanced HNSCC of the oral cavity, oropharynx or hypopharynx who were treated at six DTK partner sites, the impact of tumour volume, HPV DNA, p16 overexpression, p53 expression, CSC marker expression and hypoxia-associated gene signatures on outcome of primary RCTx was retrospectively analyzed. The primary endpoint of this study was loco-regional control (LRC). RESULTS: Univariate Cox regression revealed a significant impact of tumour volume, p16 overexpression, and SLC3A2 and CD44 protein expression on LRC. The tumour hypoxia classification showed a significant impact only for small tumours. In multivariate analyses an independent correlation of tumour volume, SLC3A2 expression, and the 15-gene hypoxia signature with LRC was identified (CD44 protein n/a because of no event in the CD44-negative group). Logistic modelling showed that inclusion of CD44 protein expression and p16 overexpression significantly improved the performance to predict LRC at 2years compared to the model with tumour volume alone. CONCLUSIONS: Tumour volume, HPV status, CSC marker expression and hypoxia gene signatures are potential prognostic biomarkers for patients with locally advanced HNSCC, who were treated by primary RCTx. The study also supports that the individual tumour volumes should generally be included in biomarker studies and that panels of biomarkers are superior to individual parameters.

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 Middle Aged Neoplastic Stem Cells/*metabolism Papillomaviridae/*isolation & purification Prognosis
 Radiation Tolerance/genetics Retrospective Studies Squamous Cell Carcinoma of Head and Neck Tumor
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 radiochemotherapy

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Linge, Annett Lohaus, Fabian Lock, Steffen Nowak, Alexander Gudziol, Volker Valentini, Chiara von
 Neubeck, Clare Jutz, Martin Tinhofer, Inge Budach, Volker Sak, Ali Stuschke, Martin Balermipas,
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 Pigorsch, Steffi Combs, Stephanie E Monnich, David Zips, Daniel Buchholz, Frank Aust, Daniela E
 Baretton, Gustavo B Thames, Howard D Dubrovskaja, Anna Alsner, Jan Overgaard, Jens Krause, Mechthild
 Baumann, Michael eng Multicenter Study Ireland Radiother Oncol. 2016 Dec;121(3):364-373. doi:
 10.1016/j.radonc.2016.11.008. Epub 2016 Nov 29.

HPV16 DNA status is a strong prognosticator of loco-regional control after
 postoperative radiochemotherapy of locally advanced oropharyngeal carcinoma:
 results from a multicentre explorative study of the German Cancer Consortium
 Radiation Oncology Group (DKTK-ROG)

Eintragsart Zeitschriftenartikel

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Zusammenfassung **OBJECTIVE:** To investigate the impact of HPV status in patients with locally advanced head and neck squamous cell carcinoma (HNSCC), who received surgery and cisplatin-based postoperative radiochemotherapy. **MATERIALS AND METHODS:** For 221 patients with locally advanced squamous cell carcinoma of the hypopharynx, oropharynx or oral cavity treated at the 8 partner sites of the German Cancer Consortium, the impact of HPV DNA, p16 overexpression and p53 expression on outcome were retrospectively analysed. The primary endpoint was loco-regional tumour control; secondary endpoints were distant metastases and overall survival. **RESULTS:** In the total patient population, univariate analyses revealed a significant impact of HPV16 DNA positivity, p16 overexpression, p53 positivity and tumour site on loco-regional tumour control. Multivariate analysis stratified for tumour site showed that positive HPV 16 DNA status correlated with loco-regional tumour control in patients with oropharyngeal carcinoma ($p=0.02$) but not in the oral cavity carcinoma group. Multivariate evaluation of the secondary endpoints in the total population revealed a significant association of HPV16 DNA positivity with overall survival ($p<0.01$) but not with distant metastases. **CONCLUSIONS:** HPV16 DNA status appears to be a strong prognosticator of loco-regional tumour control after postoperative cisplatin-based radiochemotherapy of locally advanced oropharyngeal carcinoma and is now being explored in a prospective validation trial.

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Notizen:

Lohaus, Fabian Linge, Annett Tinhofer, Inge Budach, Volker Gkika, Eleni Stuschke, Martin Balermipas, Panagiotis Rodel, Claus Avlar, Melanie Grosu, Anca-Ligia Abdollahi, Amir Debus, Jurgen Bayer, Christine Belka, Claus Pigorsch, Steffi Combs, Stephanie E Monnich, David Zips, Daniel von Neubeck, Clare Baretton, Gustavo B Lock, Steffen Thames, Howard D Krause, Mechthild Baumann, Michael eng Multicenter Study Research Support, Non-U.S. Gov't Ireland Radiother Oncol. 2014 Dec;113(3):317-23. doi: 10.1016/j.radonc.2014.11.011. Epub 2014 Dec 2.

Anhänge

- Volltext

Independent validation of the prognostic value of cancer stem cell marker expression and hypoxia-induced gene expression for patients with locally advanced HNSCC after postoperative radiotherapy

Eintragsart Zeitschriftenartikel

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Zusammenfassung Objective: To validate the impact of HPV status, cancer stem cell (CSC) marker expression and tumour hypoxia status in patients with locally advanced head and neck squamous cell carcinoma (HNSCC), who received postoperative radiotherapy. The results of the exploration cohort have previously been reported by the German Cancer Consortium Radiation Oncology Group (DKTK-ROG; Lohaus et al., 2014;

Linge et al., 2016). Materials and methods: For 152 patients with locally advanced HNSCC the impact of HPV16 DNA status, CSC marker expression and hypoxia-associated gene signatures on outcome of postoperative radiotherapy were retrospectively analysed. Out of them, 40 patients received postoperative radiochemotherapy. Cox models presented in a previous study were validated using the concordance index as a performance measure. The primary endpoint of this study was loco-regional control. Results were compared to those previously reported by DTKK-ROG. Results: Loco-regional control, freedom from distant metastases and overall survival were inferior to the previously reported cohort. Despite of this, the prognostic value of the combination of HPV infection status, CSC marker expression (SLC3A2) and tumour hypoxia status could be validated in univariate analyses using an independent validation cohort. For multivariate models, the concordance index was between 0.58 and 0.69 in validation, indicating a good prognostic performance of the models. The inclusion of CD44 and the 15-gene hypoxia signature moderately improved the performance compared to a baseline model without CSC markers or hypoxia classifiers. Conclusions: The HPV status, CSC marker expression of CD44 and SLC3A2 as well as hypoxia status are potential prognostic biomarkers for patients with locally advanced HNSCC treated by postoperative radiotherapy.

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Anhänge

- Volltext

Independent validation of tumour volume, cancer stem cell markers and hypoxia-associated gene expressions for HNSCC after primary radiochemotherapy

Eintragsart Zeitschriftenartikel

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Zusammenfassung Objective: To independently validate the impact of tumour volume, p16 status, cancer stem cell (CSC) marker expression and hypoxia-associated gene signatures as potential prognostic biomarkers for patients with locally advanced head and neck squamous cell carcinoma (HNSCC), who underwent primary radiotherapy or radiochemotherapy (RCTx). These markers have previously been reported in a study of the German Cancer Consortium Radiation Oncology Group (DKTK-ROG) (Linge et al., 2016). Materials and methods: In this retrospective monocentric study, 92 patients with locally advanced HNSCC were included. Univariable and multivariable logistic regressions and Cox models presented in the study of the DKTK-ROG were validated using the area under the curve (AUC) and the concordance index (ci), respectively. The primary endpoint of this study was loco-regional tumour control (LRC) after primary RCTx. Results: Although both cohorts significantly differed in the proportion of the tumour subsites, the parameters tumour volume, p16 status and N stage could be validated regarding LRC and overall survival (OS) using multivariable Cox regression (LRC ci: 0.59, OS ci: 0.63). These models were slightly improved by combination with the putative CSC marker CD44 (LRC ci: 0.61, OS ci: 0.69). The logistic regression model for 2-year LRC based on tumour volume, p16 status and CD44 protein was validated with an AUC of 0.64. The patient stratification based on hypoxia-associated gene signatures status was similar to the original study but without significant differences in LRC and OS. Conclusions: In this validation study, the inclusion of the putative CSC marker CD44 slightly improved the prognostic performance of the baseline parameters tumour volume, p16 status and N stage. No improvement was observed when including expressions of the hypoxia-associated gene signatures. Prospective validation on a larger cohort is warranted to assess the clinical relevance of these markers.

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Anhänge

- Volltext

Low Cancer Stem Cell Marker Expression and Low Hypoxia Identify Good Prognosis Subgroups in HPV(-) HNSCC after Postoperative Radiochemotherapy: A Multicenter Study of the DKTK-ROG

Eintragsart Zeitschriftenartikel

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Zusammenfassung PURPOSE: To investigate the impact of hypoxia-induced gene expression and cancer stem cell (CSC) marker expression on outcome of postoperative cisplatin-based radiochemotherapy (PORT-C) in patients with locally advanced head and neck squamous cell carcinoma (HNSCC). EXPERIMENTAL DESIGN: Expression of the CSC markers CD44, MET, and SLC3A2, and hypoxia gene signatures were analyzed in the resected primary tumors using RT-PCR and nanoString technology in a multicenter retrospective cohort of 195 patients. CD44 protein expression was further analyzed in tissue microarrays. Primary endpoint was locoregional tumor control. RESULTS: Univariate analysis showed that hypoxia-induced gene expression was significantly associated with a high risk of locoregional recurrence using the 15-gene signature ($P = 0.010$) or the 26-gene signature ($P = 0.002$). In multivariate analyses, in patients with HPV16 DNA-negative but not with HPV16 DNA-positive tumors the effect of hypoxia-induced genes on locoregional control was apparent (15-gene signature: HR 4.54, $P = 0.006$; 26-gene signature: HR 10.27, $P = 0.024$). Furthermore, MET, SLC3A2, CD44, and CD44 protein showed an association with locoregional tumor control in multivariate analyses (MET: HR 3.71, $P = 0.016$; SLC3A2: HR 8.54, $P = 0.037$; CD44: HR 3.36, $P = 0.054$; CD44 protein n/a because of no event in the CD44-negative group) in the HPV16 DNA-negative subgroup. CONCLUSIONS: We have shown for the first time that high hypoxia-induced gene expression and high CSC marker expression levels correlate with tumor recurrence after PORT-C in patients with HPV16 DNA-negative

HNSCC. After validation in a currently ongoing prospective trial, these parameters may help to further stratify patients for individualized treatment de-escalation or intensification strategies. Clin Cancer Res; 22(11); 2639-49. (c)2016 AACR.

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Anhänge

- Volltext