Commentary

A new prognostic hypoxia biomarker consisting of imaging and gene-based data

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In the research article of EBioMedicine [1], Fjeldbo and colleagues developed a combined biomarker based on hypoxic fraction from dynamic contrast enhanced (DCE)-MRI imaging and genetic data of cervical cancer. They were able to predict the response to radiochemotherapy of these patients. The patients were divided into groups less or more hypoxic, based on a previously defined cut-off for the gene-based biomarkers (6 hypoxia-related genes) [2]. In the same group of 41 patients, a cut-off for the imaging biomarker was newly assessed by analyzing DCE-MRI data and using $A_{\text{inh}}$-images as parameter for the hypoxic fraction. In the next step these cut-offs were validated in 77 patients and subsequently a combined hypoxic biomarker was generated. The combination of the biomarkers revealed the same hypoxic status in 75% of the 118 patients. Therefore, besides the more and less hypoxic group, a third group with different hypoxia status was constituted.

The authors suspected at a first glance these contradictory results of both measurements to be based on the fact that only a small part of the tumor (biopsy of the distal part of the cervical carcinoma) can be examined in a biopsy, while the MRI technique shows the whole picture of intratumour heterogeneity. However, the variance analysis could not confirm this hypothesis, both biomarkers were robust against intratumoural heterogeneity. It is interesting to note that in the case of expected heterogeneity of a tumor, the hypoxia status in the biopsy was representative for the entire tumor. A possible explanation could be that the gene-based biomarker detects persistent changes in the genome and thus even a small sample can be representative for that.

The clinical endpoint of the trial was progression-free survival (PFS). Fjeldbo et al. show that higher tumor hypoxia is associated with a worse PFS. Both biomarkers alone could predict PFS, but the combination of both enabled a better prediction than one biomarker alone. The multivariate analysis identified the combined hypoxic biomarker and the tumor stage independently as prognostic factors for patients with cervical carcinoma.

These data show the potential for clinical use of the combined image- and genetic biomarker as a prognostic parameter for patients with cervical carcinoma, even though both markers are enough to measure the same resistance factor. While the gene array biomarker has already been validated [2], the DCE-MRI biomarker still needs proof of transferability to another patient cohort [3]. In order to apply the biomarker combination in clinical routine, the following step would then be an interventional trial with a treatment modification based on the prognosis given by the biomarkers. In the long term, an establishment in other tumor entities would also be desirable.

From a biological and clinical point of view, it is known from previous studies that tumor hypoxia significantly influences tumor progression and resistance to chemo- and radiotherapy and is associated with a worse outcome of the patients [4–6]. Hypoxia changes the tumor microenvironment and influences a variety of signaling pathways in tumor cells. As a result, hypoxia targeted therapy is an interesting approach for an individualised cancer treatment and could also be an intervention for the above-mentioned trial. Several studies have already investigated hypoxic-cell sensitizers like nimorazole in head–and neck cancers [7] or molecular targeting using small molecules, the modulation of hypoxia-dependent signaling pathways, e.g. VEGF inhibition or gene targeting (HIF-1α) [8, 9]. In a prospective randomized study, Di Silvestro and colleagues investigated the additional administration of tirapazamine, a drug that is activated under hypoxic conditions, in addition to standard radiochemotherapy with cisplatin in locally advanced cervical carcinomas. However, no advantage for local control, progression-free and overall survival could be determined by a combination treatment [10]. Therefore, further investigations, possibly the identification of new hypoxia targets are desirable to improve the prognosis of these patients.

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Declaration of Competing Interests

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