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EDITORIAL COMMENT

Radiology in the lead: towards radiological profiling for precision medicine in glioblastoma patients? Editorial comment on *Glioblastoma patients with a moderate vascular profile benefit the most from MGMT methylation*

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Primary brain tumors, most commonly of glial origin, are responsible for a high disease burden and loss of healthy life years. Glioblastoma (GBM), being the most malignant and most frequently occurring subtype, has a median survival of only 14.6 months [1]. This devastating number has changed little over the past two decades. The last significant step forward for GBM patients came with the incorporation of temozolomide (TMZ) chemotherapy in standard treatment protocol, increasing the median overall survival with 2.5 months when compared to radiotherapy alone [1]. A need for novel treatment strategies for GBM patients clearly remains.

The paradigm shift of "one fits all" to "all fit one" associated with precision medicine has therefore in recent years also emerged in neuro-oncological treatment schemes. After all, it is rather peculiar to implement homogeneous treatment protocols for such a heterogeneous population. Molecular markers and genetic profiles now play a pivotal role in the management of GBM [2]. For instance, as suggested by an upcoming guideline update, certain molecular parameters such as TERT promoter mutation, EGFR gene amplification, or chromosome 7 gain define GBM even if histologically the tumor is suggestive of a lower grade tumor [3]. Thus, current and future guidelines emphasize the heterogeneity and interpatient variability of GBM.

Currently, one of the most widely accepted molecular markers for prognostication and treatment decision-making in GBM is O6-methylguanine-DNA methyltransferase (MGMT) methylation status. MGMT-methylated tumors are more susceptible to alkylating chemotherapeutic agents such as TMZ, leading to an improved prognosis. As a result, current guidelines suggest the addition of TMZ complementing radiotherapy for elderly patients (> 70 years) with MGMT-methylated GBM only [4].

Published in this issue, a study by Fuster-Garcia and colleagues, however, has found that the prognostic impact of MGMT methylation might be influenced by the tumor's vascularity [5]. In their multicenter retrospective study among 96 GBM patients, the authors have demonstrated that there is a beneficial effect of MGMT methylation in tumors with moderately vascular status only. Only a non-significant trend was found for patients with highly vascularized MGMT-methylated GBM. These results are indicative of certain subpopulations of MGMT-methylated GBM that are more susceptible to treatment than others. The authors correctly claim that not considering such information could potentially induce bias in future clinical studies.

For the abovementioned study, the authors used an open online segmentation service (ONCOhabitats) to identify different regions within the tumor based on conventional anatomical sequences as well as perfusion MRI. These regions (habitats) were identified, by fusing anatomical information of the tumor (the contrast-enhancing tumor bulk and peritumoral edema) with the perfusion data, leading to moderately vascularized and highly vascularized tumor habitats.

The habitat approach is drawn from the idea that GBM is not a homogenous entity but a rather heterogeneous tumor. Habitat approaches based on advanced MRI sequences such as perfusion or diffusion have been successfully applied by other studies [6, 7]. Certain habitats experience more aggressive features such as high perfusion and low diffusion, suggestive of a highly vascularized and cellular tumor component. Presence of such

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aggressive tumor habitats have been shown to have a negative impact on survival [8] and treatment response [9]. In addition, certain habitats have been suggested to play a role in resistance to chemotherapy and radiotherapy and thus might in part be responsible for treatment failure [10]. Identification of such tumor habitats and thus radiological "profiling" of the individual tumor could potentially guide subsequent treatment in addition to molecular biomarkers.

To conclude, certain biomarkers such as MGMT methylation status have been given a more prominent role in the management of GBM patients over recent years. However, as Fuster-Garcia and colleagues have demonstrated, in addition to this interpatient heterogeneity, intratumor heterogeneity also plays an important role in GBM. When moving towards a precision medicine approach, such information should indeed be considered, both in future clinical studies but also in the multidisciplinary management of GBM patients. Perhaps the radiologist should be in the lead to allow personalized treatment?

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