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Telomere maintenance and dysfunction predict recurrence in paediatric ependymoma

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Abstract

We have recently described the enzymatic subunit of telomerase (hTERT) as an important prognostic marker for paediatric ependymoma. Because of the lack of good, representative pre-clinical models for ependymoma, we took advantage of our large cohort of ependymoma patients, some with multiple recurrences, to investigate telomere biology in these tumours. Our cohort consisted of 133 ependymomas from 83 paediatric patients and included 31 patients with recurrences. Clinical outcome was measured as overall survival, progression-free survival and response to therapy. In all 133 tumours, hTERT expression correlated with proliferative markers, including MIB-1 index ($P < 0.0001$) and mitotic index ($P = 0.005$), as well as overall tumour grade ($P = 0.001$), but not with other markers of anaplasia. There was no correlation between telomere length and hTERT expression or survival. Surprisingly, prior radiation or chemotherapy neither induced sustained DNA damage nor affected telomere maintenance in recurrent tumours. There was an inverse correlation between hTERT expression and telomere dysfunction as measured by γ H2AX expression ($P = 0.016$). Combining γ H2AX and hTERT expressions could segregate tumours into three different survival groups (log rank, $P < 0.0001$) such that those patients whose tumours expressed hTERT and showed no evidence of DNA damage had the worst outcome. This study emphasises the importance of telomere biology as a prognostic tool and telomerase inhibition as a therapeutic target for paediatric ependymoma. Furthermore, we have demonstrated that analysing tumours as they progress *in vivo* is a viable approach to studying tumour biology in humans.