Clinical relevance of genetic tumor progression scores

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Introduction Human tumors are often associated with typical tumor-specific chromosomal alterations that accumulate over time. Relating tumor progression to the occurrence of such alterations can help in the identification of cancer genes and in cancer diagnosis. Prediction of time until death or time until relapse after surgery is important for the treatment of cancer patients. Traditional biostatistics research considers clinical and histological measurements like tumor stage, tumor volume, or lymph node status, as prognostic factors. The identification of genetic markers that better reflect tumor biology is eminent.

Material and Methods We have introduced a new genetic prognostic marker, the so-called genetic progression score (GPS) that estimates the progression of a tumor based on oncogenetic trees mixture models [1]. The new probabilistic model class of trees mixture models is used to describe evolutionary processes [2]. In these models, progression is characterized by the ordered accumulation of permanent genetic changes. In every tree edges are weighted with the conditional probability of the child event given that the parent event has occurred. The GPS is derived from a tree model by replacing conditional probabilities with expected waiting times, based on the assumption of independent Poisson processes on the tree edges. The GPS directly estimates the age of a tumor up to a scaling.

Results For different types of tumors, we have investigated the correlation of the GPS with clinically relevant parameters. Using Cox regression models we demonstrated that the GPS is a medically relevant prognostic factor that can be used to discriminate between patient subgroups with different expected clinical outcome.

1) We analyzed the prognostic value of the GPS for relapse of prostate cancer patients. Cox proportional hazard models were fitted to observed times until PSA (prostate specific antigen) relapse following radical prostatectomy. GPS was calculated from CGH (comparative genomic hybridization) measurements. For prostate cancer, the Gleason score reflecting the histological pattern of tumor growth is a common grading system with high predictive value. In practice, many tumors are scored with an average value of 7. Restricting to patients with such a score only, we showed that the GPS can be used to further identify subgroups with different prognosis. This shows that the GPS can improve diagnostics even after adjusting for traditional markers.

2) We analyzed survival times of glioblastoma patients. The genetic events of interest were chromosome aberrations measured by loss of heterozygosity (LOH) on the p-arm or q-arm of single chromosomes. GPS was shown to better discriminate between short and long survival times than single chromosomal aberrations or the total sum of aberrations in a tumor. Fitting multivariate Cox regression models we showed that the GPS is prognostic also after adjustment for age, a critical factor for the expected survival time in glioblastomas.

3) We analyzed the time to recurrence for meningioma patients. This tumor is a usually benign brain cancer, the most frequent tumor of neuroectodermal origin in humans. Most of the tumors show either monosomy 22 or a diploid karyotype. Progression of meningiomas is known to be correlated with increasing hypodiploidy and structural aberration (loss of the short arm of chromosome 1) showing characteristic clonal evolutions. This a priori knowledge is also reflected in the estimated oncogenetic trees mixture model. The GPS was used to quantify cytogenetic progression. It was shown that GPS is significantly correlated with tumor recurrence, with the location of the tumor, and with the WHO grade. Even within subgroups defined by the same WHO grade, the GPS can be used to further discriminate between patients with different expected time to recurrence.

Discussion With oncogenetic trees mixture models the most likely order of cytogenetic aberrations in human tumors can be estimated. The estimated mixture models can be used to assign a genetic progression score to single tumors. It has been demonstrated that for a variety of different human cancers the GPS allows a more precise assessment of progression than classical clinical markers.

Literature

[1] Rahnenführer J, Beerenwinkel N, Schulz WA, Hartmann C, von Deimling A, Wullich B, Lengauer T. Estimating cancer survival and clinical outcome based on genetic tumor progression scores. Bioinformatics 2005; 21(10):2438-46.

[2] Beerenwinkel N, Rahnenführer J, Däumer M, Hoffmann D, Kaiser R, Selbig J, Lengauer T. Learning multiple evolutionary pathways from cross-sectional data. Journal of Computational Biology 2005; 12(6):584-98.