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Abstract

Time dependence of critical deletions as prognostic factor for relapse-free survival (RFS) in localised GIST. A Spanish Group for Sarcoma Research (GEIS) study

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Background: Deletions involving KIT Ty557-Lys558 were related with a statistically significant worse RFS in localized and completely resected GIST patients, as it was published with a median follow-up of 44 months (*J Clin Oncol* 23: 6190–6198, 2005). The prognostic significance of such critical mutations for RFS over time as well as its relationship with the more recent prognostic index is unknown. **Methods:** To evaluate the time dependence of prognostic factors for RFS, a series of 162 localized GIST patients has been updated. The relative risk for recurrence was analyzed univariately and multivariately for the various prognostic factors, using the Cox proportional hazards model, over the entire follow-up period and over the intervals 0–4 years and > 4 years. The factors assessed were as follows: tumor location, size, mitotic rate per 50 HPF, cellularity, mitotic rate and size risk categories (Fletcher risk, FRC), mitoses-size and location risk categories (Miettinen risk, MRC) (*Semin Diagn Pathol* 23: 70–83, 2006), deletions involving KIT 557–558 codons (critical mutations) and no deletion type mutation within exon 11 of KIT gene. **Results:** Median age was 63 years. There were 93 gastric, 63 small intestinal and 6 with another primary site. Mutations were detected in 100 patients (DHLP analyses performed in wild type cases yielded 4 additional mutations). The median follow-up was 85 months. There were 49 relapses and 15 patients died without recurrence. On univariate analyses: mitoses, size, location, cellularity, FRC, MRC and critical mutation were found to be correlated with a poor RFS for the entire follow-up and for the first 4 years of follow-up. The multivariate analyses revealed that MRC (RR 11.1; CI 2.6–46.5 for the high-risk category, and RR 6.8; CI 1.8–25.9 for the moderate-risk) and critical mutations (RR 3.0; CI 1.6–5.8) were independent prognostic factors for RFS. Beyond 4 years of follow-up: mitotic count, tumor size, FRC, MRC and no deletion type mutations showed prognostic relevance for RFS. **Conclusions:** Critical mutation is time-dependent prognostic factor as its

influence is limited to the first 4 years after complete surgery and shows independent prognostic relevance, along with MRC, for RFS in localized GIST.