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Revisiting the correlation of *c-Kit* mutation status and treatment decisions in canine mast cell tumors

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Background: Mast cell tumors (MCTs) are the most frequent skin tumors in dogs, with an incidence of 16-21 % of all tumors. Mutations in the proto-oncogene *c-Kit*, which encodes for the transmembrane stem cell factor receptor on the mast cells surface, induce constitutive receptor activation (Willmann et al. 2021).

Objective: Up to 50 % of canine MCTs exhibit internal tandem duplications (ITDs) in either exon 8 or 11 promoting cell growth and survival. We aimed to establish an indication for the treatment with tyrosine kinase inhibitors, based on the *c-Kit* mutation status of the canine MCT patients.

Materials and Methods: In 43 histopathologically confirmed MCT dogs, the *c-Kit* exons 8, 9, 11, 13, 14 and 17 were investigated by isolating genomic DNA from remnant diagnostic material, PCR amplification and subsequent sequence comparisons to healthy and malignant reference material (Gregory-Bryson et al. 2010; Marconato et al. 2014; Gentilini et al. 2015; Paquay 2017; Hammer et al. 2022).

Results: For exon 8, no ITD was found, and only two patients showed ITDs in exon 11. For the latter exon, additional eight dogs exhibited the same silent mutation, not been detected in the reference material. Interestingly, in one patient, the high-grade (Kiupel)/grade III (Patnaik) tumor stage did correlate with an amino acid exchange V563D (T>A[1688]). This driving mutation in human gastrointestinal stromal tumors could therefore also be an activating mutation in canine mast cell tumors (Paquay 2017; Hammer et al. 2022).

Conclusions: For *c-Kit* mutation analysis, a time- and cost-efficient work routine was established. The low ITD frequency in exon 11 together with the absence of other known mutations in the remaining exons suggest that the *c-Kit* mutation status alone is not sufficient to make treatment decisions (Hammer et al. 2022).

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