



A New Era in the Management of Tumors in Dogs Based on Liquid Biopsy

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Commentary

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Introduction

The naturally occurring high-grade invasive transitional cell carcinoma or canine invasive urothelial carcinoma localized in bladder can be successfully treated surgically, however, at time of your diagnosis, it may present itself at an advanced stage, and distant metastases occur in 50% of cases. The urothelial carcinoma has a poor prognosis due to its muscle-invasive nature and high degree of metastases to regional lymph nodes or distant organs [1], despite the availability of intensive multimodal therapies, including surgery, chemotherapy, radiation therapy, and palliative laser ablation [2].

The diagnostic gold standard of this tumor is the histopathological evaluation by biopsy. However, because the invasive nature of biopsy, risk of anesthesia and high cost of procedures, its diagnosis becomes limited [3,4].

Through the complete sequencing of the tumor transcriptome in dogs, a mutation in the BRAF gene was identified (V595E) [5] similar to BRAF mutation (V600E) in human's tumors [6]. The mutation harbors a single nucleotide variant at genomic position 8296284 on chromosome 16 of *Canis familiaris* (CFA16), which results in the substitution of valine for glutamic acid at codon 595 of canine BRAF. The BRAF V595E mutation can be found in transitional cell carcinoma and in different types of canine cancer such as urothelial carcinoma, prostatic carcinoma, lung carcinoma, oral squamous cell carcinoma, melanoma, melanocytoma, glioma and peripheral nerve sheath tumor [7].

This discovery stimulated the development of new approaches for detecting and treating cancer in dogs involving the BRAF and RAF/MEK/ERK signaling [5,8].

The urothelial carcinoma has a 21-fold increased risk associated with certain breeds of dogs such as Scottish Terriers and 3.0- to 6.5-fold increased risk in Eskimo dogs, Shetland Sheepdogs, West Highland White Terriers, Beagles, Samoyeds, Keeshonds in comparison with mixed breeds [9], and BRAF mutation research tests were sensitive in 73% of cases in breed dogs such as Terrier, and being screening for BRAF V595E mutation in this breed recommended [10].

For the molecular diagnosis of urothelial carcinoma in lower urinary tract and prostatic carcinoma in dogs, new strategies are being developed, such as the digital droplet PCR assay (ddPCR) with 83% sensitivity for the detection of canine BRAF V595E mutation from urine samples [7], because the V595E mutation is absent in approximately 20% of these tumor types [5], and the Sanger sequencing technique requires a fraction of 10 to 20% of mutated allele for reliable detection [11].

The introduction of liquid biopsy tests in veterinary medicine allowed the detection of genomic alterations in tumor cell-free DNA fragments in urine [5,12] and plasma [13] facilitating cancer detection by non-invasive methods. In the liquid biopsy, different biological fluids (blood, urine, cerebrospinal fluid and other secretions) can be used, that can be obtained by minimally invasive or non-invasive methods where obtention of a tissue sample for traditional histological analysis can be risky or difficult [13-15].

The liquid biopsy has numerous advantages such as the implementation of screening for early detection in patients without signs of cancer, because certain breeds are more predisposed [4]; assistance in diagnosis of dogs with clinical suspect of cancer [9]; identification of mutation for

targeted treatment selection [16,17], as seen in targeted genomic alterations in humans with ortholog in canine genome [5,18,19]; detection of minimal residual disease after interventions with curative purpose, as seen in human breast cancer [20]; monitoring in real time the response to treatment [21]; and monitoring of cancer recurrence [22].

However, the adoption of high complexity molecular tests by veterinary diagnostic medicine laboratories in different parts of the world, particularly in developing countries, presents problems due to the absence of governmental regulatory supervision, can be marketed with problems such as low sensitivity and specificity in diagnosis [23], with some veterinary diagnostic laboratories little concerned with the reliability of the results, aiming only the sale of a new diagnostic modality [24].

Discussion

The development of liquid biopsy tests for dogs based in mutational analysis has the potential to revolutionize the detection and management of different types of cancer in pets. The liquid biopsy in the veterinary medicine can be provides the opportunity of detecting, analyzing and monitoring cancer evolution and response to treatment in various body liquids such as blood or urine instead of a fragment of cancer tissue. However, further studies will be needed for the full adoption of liquid biopsy in the clinical workflow in veterinary medicine.

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