MINI REVIEW

UROLOGICAL ONCOLOGY

Sniffing out prostate cancer: a new clinical opportunity

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Prostate cancer (PCa) is the fifth most frequent cancer in the world and the second most diagnosed non-cutaneous cancer in men in the United States [1]. Currently, the evaluation of serum prostate-specific antigen (PSA) levels has reduced PCa mortality, but has also led to unnecessary biopsies, over-detection and – treatment [2]. Although transrectal ultrasound-guided prostate biopsy sampling originally consisted of a small number of random biopsies, a systematic, numerical, and anatomical strategy is currently applied. However, the efficiency of this diagnostic test is mainly limited by patient tolerance and morbidity. In case of clinical suspicion of a PCa or elevated serum PSA levels, a prostate biopsy is the most widely used approach to confirm PCa. Unfortunately, exclusion of PCa is not feasible by means of biopsy and the negative rate remains consistently high [3]. It has been reported that the repetition of a prostate biopsy in patients with persistently elevated serum PSA levels after initial negative biopsy provides a detection rate of PCa from 10 to 20%, but patients have a higher risk of complications besides the psychological and health-care costs [4]. Recently, a prospective European Prostate Cancer Detection study investigated a total of 1,051 men with serum PSA levels between 4 and 10 ng/ml who underwent transrectal ultrasound guided sextant biopsy and 2 additional transition zone biopsies [5]. All patients in whom biopsy samples were negative for PCa underwent the second biopsy after 6 weeks. If also negative, biopsies 3 and even 4 were performed at 8-week intervals. It has been found that cancer detection rates on biopsies 1, 2, 3 and 4 were 22%, 10%, 5% and 4%, respectively [5]. Incorporating a painful diagnostic procedure as a routine practice is not only unwarranted but can also be considered unethical, particularly when it is performed in a predominantly older age group of patients harboring a low-grade, clinically insignificant disease that does not need aggressive management or treatment at all [6]. The majority of patients diagnosed with the disease have a relatively indolent form of PCa that is unlikely to invade beyond the local tissue environment [7]. It is indubitable that in the management of PCa, the major challenge remains to distinguish between men who need definite treatment and those who have a latent disease. Therefore, the management of PCa can be significantly improved by introducing more reliable serum, urine and tissue biomarkers for early detection, prognosis and monitoring of treatment response. From all PSA-based markers, the Food and Drugs Administration (FDA)-approved Prostate Health Index (phi) selectively recognize clinically-significant PCa and might be useful as part of a multifarious strategy to reduce prostate biopsies and over-diagnosis [8]. PCa gene 3 (PCA3) has been proven helpful in the detection and management of early PCa, although additional biomarkers may be promising

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means to determine further prognosis of patients with PCa [9]. It is now recognized that the detection and identification of volatile compounds is fundamental to the successful undertaking of various clinical diagnoses and novel scientific progress [8, 10]. It is also accepted that the macromolecules in urine represent intermediate products or end products of various metabolic pathways, and that these compounds contain structural motifs, which release a particular odor. Biological olfactory systems are characterized by a superior ability to not only detect thousands of distinct volatile olfactory compounds (VOCs) but also to discriminate between them [11]. The most well-known and widely applied biological receptor is the canine, *Canis lupus var. familiaris* [11]. As is widely ascertained, the primary advantages associated with the use of rigorously trained canines include their olfactory sensitivity that allows them to recognize and discriminate between target and non-target molecules even at low concentrations, and their scent-to-source capabilities that allow them to pinpoint areas of highest concentration. Urinary VOC patterns in cancer patients are different from the patterns in urine samples from healthy subjects, although the differences depend on cancer types [12]. In 2008, Gordon et al. published the manuscript entitled "The use of canines in the detection of human cancers" aimed to determine whether canines could be trained to identify patients with cancer by sniffing urine obtained from a patient with breast or PCa among samples obtained from healthy volunteers [13]. Unfortunately, the study did not yield success but offered valuable warning in the form of mistakes, with the hope that other investigators will benefit from them. They stated: "The use of canines in the detection of bombs, drugs, and other tasks evolved over time. With further studies, there is no reason why this should not be the case with dogs screening for human cancer." Cornù et al. show that dogs can be trained to detect PCa by smelling urine with a significant success rate [14]. The dog correctly recognized cancer samples in 30 of 33 cases. Of the three cases wrongly classified as cancer, one patient was re-biopsied and a PCa was diagnosed. The sensitivity and specificity were both 91%. The present research suggests that PCa gives a peculiar odor signature to urine. Recently, Taverna et al. established the diagnostic accuracy, in term of sensitivity and specificity at which a rigorously trained canine olfactory system can recognize prostate cancer-specific VOCs in urine samples [15]. Two, three-year old female German Shepherd Explosive Detection Dogs were trained to identify PCa-specific VOCs in urine samples and tested on 902 subjects (362 with PCa ranging from very-low risk to metastatic and 540 healthy, affected by non-neoplastic diseases or non-PCa control participants). The urine samples from both groups were blinded and analyzed by both dogs, and the sensitivity and specificity of each dog's efficiency was assessed. The first dog achieved a sensitivity of 100% and a specificity of 98%. The second dog reached 98.6% specificity, 97.6% sensitivity [15]. No relationship was detected between the dogs' efficiency to recognize the presence of cancer and the clinical or pathological stage of the cancer, prostate or tumor volume [15]. Furthermore, different therapeutics that patients were assuming did not interfere with the results. Interestingly, both dogs also correctly identified all patients with synchronous PCa who had other neoplastic diseases of different histologic origin. Although previous researchers have described heterogeneity in the performance of canines between and within studies investigating the ability of dogs to detect cancer, the study first reports that a rigorously trained dog is capable of detecting VOCs specific to PCa in the urine of patients with the disease. Although chemical sensors have been improved, the efficacy of these "detection technologies" still remains imperfect, and animals continue to appear more sensitive than man-made systems. It is indubitable that discovery of tumor-specific molecular targets is required to improve detection and efficient treatment of PCa at earlier stages. Unanswered questions remains, such as what does the dog smell? Further studies should be designed to investigate whether a single odor or a mixture of PCa-specific VOCs are recognized by the dogs. Another question is: "How could a dog that detects PCa-specific VOCs be used in daily practice?". The potential predictive power of this method needs to be investigated in the future by studying patients with negative biopsies, elevated PSA serum value and an adequate follow-up. At the same time, a proper follow-up of patients who underwent radical prostatectomy will indicate whether the dogs positively recognized the samples before or after the biochemical recurrence. Although further studies will be necessary to investigate the potential predictive value of using this procedure for recognizing PCa, the dog's olfactory system represents the most employed scent-detector "device" and might have the potential to offer a noninvasive alternative to PSA sampling and prostate biopsy for detecting PCa [16].

CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

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