Editorial

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PSA, PCA3 and the phi losophy of prostate cancer management

The fundamental role that laboratory medicine currently takes in the management of cancer patients [1] is probably more visible in prostate cancer than any other tumor [2]. In patients with prostate cancer, laboratory medicine plays not only a crucial role in the early diagnosis, but also has a major impact on subsequent phases of the management of the patient throughout the entire course of the disease. The advent of prostate specific antigen (PSA) testing has transformed the management of prostate cancer in such a fundamental way that we can now speak about the ‘pre-PSA era’ and the ‘PSA era’. Prostate cancer is one of the most common malignant tumors in men and therefore represents a major public health problem. Despite the unprecedented progress in the clinical management of patients with prostate cancer we have witnessed during the last decade that encompasses new approaches in surgical therapy, radiation therapy or systemic treatment, the advances in clinical management are still limping behind the potential of technological progress in laboratory medicine.

In clinical oncology, it is generally accepted that the patient outcome depends primarily on early diagnosis. However, randomized clinical trials of prostate cancer screening have been reported with conflicting results [3, 4]. In patients with early prostate cancer, overtreatment that results in unnecessary biopsies as well as in aggressive treatment being instituted in elderly patients who would otherwise experience an indolent course of disease remains a serious issue of concern. In fact, the recently reported Prostate Cancer Intervention versus Observation Trial (PIVOT) study that randomized patients with early prostate cancer to radical prostatectomy or observation failed to demonstrate a survival benefit of surgery [5]. Interestingly, a survival benefit was evident in a subgroup of patients with serum PSA above 10 ng/mL [5]. Although the therapeutic landscape of metastatic prostate cancer has changed in a fundamental manner during the last decade and new anticancer therapies significantly prolong patient survival, metastatic prostate cancer still remains an incurable disease. Hormonal therapy consisting of surgical or medical androgen deprivation remains the cornerstone of the treatment for metastatic prostate cancer. Despite the fact that cytotoxic chemotherapy has been used to treat the patients with metastatic prostate cancer progressing on androgen deprivation (castration-resistant prostate cancer) for decades, it was not until 2004 that two large prospective trials have demonstrated that administration of docetaxel actually prolongs survival [6, 7]. However, the duration of response to first-line chemotherapy is limited. Recently, two new agents, carboplatin, another taxane cytotoxic agent [8], and abiraterone [9], were shown in randomized clinical trials to prolong survival in patients with metastatic castration-resistant prostate cancer progressing after docetaxel. The administration of autologous mononuclear cells activated with tumor antigen (sipuleucel-T) has also been demonstrated to prolong survival in patients with metastatic castration-resistant prostate cancer [10].

Despite the widespread use of PSA measurement in clinical practice it is often difficult based on the PSA concentration to predict the presence of prostate cancer or the biological behavior of the tumor. PSA is a member of kallikrein and kallikrein-related peptidases (KLK) family of proteases that comprises 15 homologous single-chain proteins coded by genes clustered on the long arm of chromosome 19 that are involved in different physiological and pathological processes [11]. PSA (or KLK3) in the circulation is predominantly complexed with $\alpha_1$-antichymotrypsin, $\alpha_2$-macroglobulin or $\alpha_1$-protease inhibitor (complexed PSA). The unbound PSA is referred to as free PSA. Diagnostic information may be derived from comparing total PSA and free PSA, with free PSA constituting about 33% of total PSA, and a low free PSA/total PSA ratio indicating the presence of cancer. Moreover, free PSA comprises three forms called benign PSA, intact PSA and proPSA [12]. While benign PSA is expressed predominantly in the transitional zone and is associated with benign prostatic hyperplasia, proPSA is expressed in the peripheral zone and is associated with prostate cancer. Native proPSA that contains a seven amino acid N-terminal pro-leader peptide, [-7] proPSA, is truncated by proteolytic cleavage to [-4] proPSA, [-5] proPSA or [-2] proPSA, but most of proPSA is present as [-2] proPSA.
because this isoform cannot be cleaved further and accumulates in the serum. Another member of the KLK family, kallikrein-related peptidase 2 (KLK2) is also being increasingly used as a prostate cancer biomarker [13–15]. Compared to total PSA uncomplexed prostate KLKs (i.e., free PSA, intact PSA and KLK2) may perform better in distinguishing between benign and malignant lesions. It has been demonstrated that utilization of a panel of biomarkers that includes PSA forms and KLK2 could result in reduction of biopsy rates [16].

In daily clinical practice, we often see different worlds clashing. The progress in understanding the molecular basis of malignant transformation and tumor progression is usually much faster compared to the pace with which this knowledge is implemented into the clinical practice. The introduction of discoveries regarding the pathogenesis and laboratory diagnosis into the treatment of malignant disorders is usually even slower. Thus, because of differences in the speed of discovery of molecular mechanisms of cancer, diagnostic technologies and new treatments, these three parts of the universe are inevitably destined to clash. The recent story of sarcosine originally reported to represent a promising biomarker of prostate cancer, but not confirmed by subsequent studies is just one example of these turbulences [17]. Five papers in the current issue of Clinical Chemistry and Laboratory Medicine describe different aspects of this clash [18–22].

The PSA concentrations between 2 and 10 ng/mL constitute a diagnostic ‘gray zone’ as patients with PSA values within this interval may harbor prostate cancer or may have only a benign pathology [23]. Different approaches have been used to improve the diagnostic accuracy of PSA measurements. Serial PSA measurements or association of PSA concentrations with other parameters introduced the concepts of PSA velocity, PSA density, or PSA doubling time. In addition, the measurements of different molecular forms of PSA mentioned above have been used. The data obtained by measuring prostate KLKs or subforms have also been combined to form derivative tests that are based on calculation of indices. Although the term derivative may evoke some distrust, in laboratory medicine, in contrast to the financial world, derivative tests are based on solid scientific foundations and are useful in aiding diagnosis. In the current issue of Clinical Chemistry and Laboratory Medicine, Filella and Gimenez [18] present a systematic review and meta-analysis focusing on the utilization of [-2] proPSA and one such derivative test, the prostate health index (phi) in the detection of prostate cancer. [-2] proPSA is assessed as a percentage of [-2] proPSA to free PSA (%[-2] proPSA), and phi is calculated from [-2] proPSA, free PSA and total PSA using the formula

\[ ([\text{phi}] = \frac{\text{[-2] proPSA/free PSA}}{\text{total PSA}} \times 100) \]

Across the studies reviewed in the meta-analysis, the sensitivity of both %[-2] proPSA and phi was around 90%, with specificity ranging mostly between 20% and 40%, with phi showing similar or slightly better results compared to %[-2] proPSA [18]. It has been demonstrated that despite costs associated with the procedure, the utilization of %[-2] proPSA or phi is cost-effective and reduces the global costs. In addition, the data indicate that higher levels of %[-2] proPSA or phi are associated with the aggressiveness of prostate cancer, and the utilization of these tests may help in the crucial, but difficult clinical decision between radical therapy and active surveillance.

In addition to the review on [-2] proPSA and phi by Filella and Gimenez [18], other papers in the current issue of Clinical Chemistry and Laboratory Medicine illustrate the philosophy behind tumor marker utilization in the management of prostate cancer as well as other tumors. Two papers address different methodological issues of PSA determination. In a letter, Fischer et al. [19] report on the lack of concordance of the results of measurements using two assays for total PSA determination. These results confirming that the total PSA assays are not exchangeable and will have potentially serious implications for the clinical practice. PSA concentrations that are determined serially to detect disease recurrence are fundamental to the point that a sustained rise is called the ‘biochemical relapse’ with important implications for patient management. Therefore, the discrepancies in serial PSA concentrations caused by different assays may affect therapeutic decisions.

Another paper focuses on a methodological issue with wide repercussions for clinical practice, the quality of control materials for PSA measurement [20]. In clinical practice the serum PSA concentrations may span across six orders of magnitude. The authors demonstrate that most of the commercially available control materials are composed only of free PSA or contained between 50% and 75% of free PSA. Adding to the discordance between different PSA assays, the commercially available control materials mostly contain irrelevant quantities of free PSA that may again significantly affect the test results.

Notwithstanding the important methodological issues mentioned above [19, 20], the most important problem of PSA measurement is the lack of specificity. The prostate cancer antigen 3 (PCA3) has been suggested as a specific biomarker of prostate cancer. PCA3 is a non-coding RNA that is highly expressed in prostate cancer, but with no expression or only low expression in non-cancerous tissues. Neves et al. [21] examined PCA3 expression using reverse transcription polymerase chain reaction in
peripheral blood and prostate tissue. While PCA3 detection in peripheral blood had 94% specificity and 32% sensitivity, the diagnostic performance increased when positivity in either peripheral blood or prostate tissue was considered.

Increased serum concentrations of some tumor biomarkers may be encountered in patients affected with non-neoplastic disorders [24]. Turgutalp et al. [22] examined the concentrations of tumor biomarkers in patients with proteinuria associated with primary glomerular disease or diabetic nephropathy, and no accompanying malignant tumor. While, compared to healthy controls, the concentrations of carbohydrate antigen (CA) 125, CA15–3 and CA19–9 were increased in patients with proteinuria, the concentrations of total PSA, free PSA, α-fetoprotein and carcinoembryonic antigen were lower in these patients. Thus, proteinuria has to be added to a growing list of ‘benign’ conditions that may affect the concentrations of circulating tumor markers. Importantly, the concentrations of some tumor biomarkers, notably total and free PSA were decreased in proteinuric subjects, adding to the complexity regarding the interpretation of PSA concentrations.

As stated above, the role of laboratory medicine in the management of prostate cancer is in many respects exceptional. The papers in the present issue of Clinical Chemistry and Laboratory Medicine focus mostly just on one aspect of biomarker determination, i.e., early detection and diagnosis. However, an equally important issue is that of utilization of biomarkers for the follow-up of patients and assessment of response to therapy. New drugs are being tested in patients with advanced, mostly metastatic tumors, and in the majority of malignancies radiological criteria are used to determine the response to the treatment. Epithelial ovarian carcinoma is another example of a tumor that is managed by a multimodality approach relying on determination of tumor biomarkers both in the diagnostic setting and in the patient follow-up when the disease course and/or the response to therapy can be assessed by the serial measurement of biomarkers as the assessment of peritoneal spread may be difficult by imaging studies [25, 26]. Similarly, most patients with metastatic prostate cancer present with bone metastases that are not evaluable by standard radiological studies, and serial measurement of PSA is commonly used to evaluate the response in these patients. However, the interpretation of changes in serial PSA concentrations during therapy remains a complex issue. The changes of PSA concentrations in patients treated with hormonal manipulations may reflect not only the reduction of the tumor mass, but also result from a direct effect of hormonal therapy as the expression of PSA is under the control of androgen receptor [27]. Thus, the decrease of PSA concentration is usually less dramatic after cytotoxic chemotherapy compared to hormonal treatment, but the change of PSA concentration is an established surrogate endpoint in patients with castration-resistant prostate cancer treated with docetaxel [28]. However, the interpretation of changes of serial PSA concentrations is compounded by the surge phenomena characterized by a rise of PSA concentrations with a subsequent decline. Gonadotropin-releasing hormone agonists commonly used as an alternative to surgical castration in the treatment of prostate cancer such as goserelin could elicit, due to the agonist activity the utilization of these drugs, a disease flare phenomenon that may be accompanied by a transient surge of PSA concentration. Similarly, a PSA surge that could last for up to 2 months has been described in patients treated with cytotoxic agents [29, 30]. Unlike gonadotropin-releasing hormone agonists or chemotherapy, the administration of gonadotropin-releasing hormone antagonists is not associated with the surge or flare phenomena. In a recent paper, Ulmert et al. studied the kinetics of PSA and KLK2 in prostate cancer patients treated with the gonadotropin-releasing hormone antagonist degarelix and observed an exponential decline of serum PSA and KLK2 concentrations [31]. The decrease of concentrations of free PSA, intact PSA and KLK2 was significantly faster compared to complexed PSA and total PSA indicating that the uncomplexed prostatic KLKs may allow an earlier estimation of response to systemic therapy [31].

Despite the progress outlined above and the fact that in the spectrum of different malignant disorders the prostate cancer is the tumor in which the utilization of biomarkers is probably most advanced, there is still room for further research. The utilization of PSA in prostate cancer may seem to have reached its limits and we may need to progress beyond PSA, but we are, certainly, still very far from entering a ‘post-PSA era’ [2]. For example, although prostate cancer is one of the few tumors in which immunotherapy is now an established treatment modality [10], little is known about the prognostic or predictive significance of immunologic or inflammatory parameters in patients with this tumor. Partly due to a relative lack of other biomarkers, laboratory parameters associated with inflammatory and immune response have been studied across the range of other malignancies. Immune response is disturbed in patients with advanced cancer, and alterations of laboratory parameters, e.g., decreased circulating CD4+ T-lymphocyte counts [32] or decreased lymphocyte proliferation [33], can be detected. However, in patients with different primary tumors the presence
of lymphocytes infiltrating the tumor tissue, the tumor-infiltrating lymphocytes, has been shown to represent an independent prognostic factor [34], or predict response to treatment [35]. The phenotype and function of leukocyte populations, including lymphocytes and monocytes/macrophages in the tumor microenvironment have been also studied in the malignant ascites [36, 37] and used to assess the response to therapy [38]. Apart from the analysis of immune cells, molecular biomarkers of host response have been also extensively studied. One such molecule associated with systemic response of the host to neoplasia is neopterin. Neopterin, a pteridine compound that is produced from guanosine triphosphate by macrophages activated with interferon-γ and that can be determined in serum or urine using immunoassay or high-performance liquid chromatography [39, 40], has been studied in-depth in patients with advanced cancer of different primary locations [41]. While elevated neopterin concentrations are observed in disorders including acute myocardial infarction [42, 43], infections, autoimmune disorders [44] or malignant tumors [41, 45], and, therefore, high neopterin concentrations are non-diagnostic, neopterin represents a biomarker indicating poor prognosis across a spectrum of different primary tumors [41, 45]. Of note, neopterin concentrations increase after administration of systemic chemotherapy [46]. For example, in patients with epithelial ovarian carcinoma both the presence of tumor-infiltrating lymphocytes as well as neopterin concentrations have been shown to represent independent prognostic markers [34, 41]. Moreover, neopterin is also a biomarker of the risk of cardiovascular events [47, 48] that in patients with prostate cancer represent the main competitive cause of morbidity and mortality. However, the information on neopterin in patients with prostate cancer is limited [49]. Thus, similarly to the utilization of prostatic KLKs serving as a paradigm for the integration of biomarkers into the strategy of management for other tumors, the experience with biomarkers related to the host response in patients with other tumors could lead to a more thorough study regarding the potential use of biomarkers associated with the host response in prostate cancer.

In conclusion, the determination of circulating biomarkers either alone or as part of derivate tests such as phi represents one of the cornerstones of the current philosophy of prostate cancer management. The use of biomarkers in prostate cancer may serve as a paradigm for the integration of biomarkers into the strategy of management for other tumors, both common and rare.

Conflict of interest statement

Author’s conflict of interest disclosure: The author stated that there are no conflicts of interest regarding the publication of this article.

Research funding: None declared.

Employment or leadership: None declared.

Honorarium: None declared.

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23. Melichar B. PSA, PCA3 and the phi losophy of prostate cancer management


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