ELSEVIER

Critical Reviews in Oncology/Hematology 93 (2015) 103–115

CRITICAL REVIEWS IN
Oncology
Hematology
Incorporating Geriatric Oncology

www.elsevier.com/locate/critrevonc

Evaluation of serum-based cancer biomarkers: A brief review from a clinical and computational viewpoint

Sohiya Yotsukura *, Hiroshi Mamitsuka

Bioinformatics Center, Institute of Chemical Research, Kyoto University, Gokasho, Uji 611-0011, Japan

Accepted 1 October 2014

Contents

Abstract

Biomarkers are vital to detect diseases in various clinical stages. A variety of cancer serum biomarkers are already known, while for more accurate cancer-type detection, there required more rigorous evaluation manners, especially computational evaluation measures, for biomarkers. In this review, we first show three typical pitfalls in finding biomarkers and their examples, after briefly presenting standard five clinical biomarker screening phases by National Cancer Institute. We then introduce current computational biomarker evaluation measures, including current, standard methods with their intrinsic features. We further show an up-to-date list of existing cancer serum biomarkers,

Abbreviations: PSA, prostate-specific antigen; TP, true positive; FP, false positive; TPR, true positive rate; FN, false negative; FNR, false negative rate; FPR, false positive rate; ROC, receiver operating characteristic; AUC, area under the curve; DOR, diagnostic odds ratio; ROMA, Risk of Ovarian Cancer Malignancy Algorithm; cfDNA, cell-free DNA; IDI, integrated discrimination improvement; NRI, net reclassification improvement; EPCA-2, early prostate cancer antigen-2.

* Corresponding author. Tel.: +81 774 38 3038; fax: +81 774 38 3037.
E-mail address: yotsus@kuicr.kyoto-u.ac.jp (S. Yotsukura).

http://dx.doi.org/10.1016/j.critrevonc.2014.10.002

pointing out several issues, being caused by the limitations of current biomarker evaluation approaches. Finally we discuss the current attempts to develop new, statistically robust, computational serum-based biomarker measures in terms of specificity to each of various cancer types.

Keywords: Serum biomarkers; Quantitative assessment; Computational evaluation; Predictive values; Likelihood ratios; Receiver operating characteristic curve; Diagnostic odds ratio

1. Introduction

Biomarkers are believed to increase the accuracy of diagnosis to precisely characterize the disease in a diagnostic or prognostic level. Biomarkers predict the response of the patient, helping to guide a more tailored treatment for the patient. Serum biomarkers are more appealing due to their simplicity of obtaining the blood samples. There are several serum cancer biomarkers, which are routinely used in clinical oncology, e.g. prostate specific antigen (PSA) for prostate cancer and cancer antigen (CA)-125 for ovarian cancer. However, their applications have significant limitations, because of low specificity, i.e. small probability of samples with no biomarkers in all non-diseased samples. In fact, the issue of specificity has become much more acute, since more than 30% or higher circulatory PSA level patients have to go for extensive testing and treatment, indicating its lack of specificity of prostate tumor detection [1]. In summary, lack of specific serum biomarkers has impeded the change in morbidity and mortality in cancer patients.

The traditional "a priori" approach for biomarker development needs a well-established biological procedure, being subjected to two-step clinical validation: (1) simple test with a high level of quality control, and (2) planned statistical prospective evaluations within the validation pilot studies to prove an established clinical impact [2]. Contrarily, more recently "a posteriori" approaches evaluate the clinical rationale of a "biological indicator" through a systematic discovery of various screening tools (e.g. microarray, bioinformatics, High-throughput DNA sequencing). These biological instruments are "black boxes", meaning that a clinical usage can be discovered through research pilot studies. Computational approaches give possible candidates for detecting certain diseases, by "sensitivity" and "specificity", within a patient population, but the proper quantification of a single biomarker in serum is limited to the evaluation technicalities. Therefore this review will focus on the latter approach since the recent technologies provide a plethora of potential candidates which are in proper need of evaluation.

Over the past twenty years, biomarkers have shown significant promise in the mechanism of how it will transform a patient's treatment. Therefore, biomarker research has been aimed towards the development of personalized targeted therapy. Despite the recent technological advancements, there are still relatively few biomarkers that are in routine clinical use today [3]. With a growing number of complex genomic tests for biomarker signatures becoming commercially available, the promise of personalized medicine is fast becoming a reality. Much attention has to be placed on the reason why the promising biomarkers and the biomarkers signatures entering the clinic is a long road ahead [4].

2. Biomarker discovery validation: Three pitfalls

In this section, we first briefly show the most widely accepted guideline for evaluation and validation of biomarkers (Diagram 1): "Early Detection Research Network (EDRN)" developed by National Cancer Institute [5]. We then explain typical pitfalls and their examples of clinical biomarker evaluation failures, mainly caused by poor experimental design and inappropriate choice of the diagnostic assay.

Phase I of EDRN is the discovery of biomarkers through knowledge—based gene selection, gene expression profiling or protein profiling by setting the platform to rank and select the biomarkers via their characteristics. Most biomarker candidates are obtained from organized and characterized cohort studies, tissue banks or clinical trials with active follow-ups. Phase II establishes a clear indication of the biomarker's intended use in clinic by checking the validity, portability and reproducibility of these biomarker assays in various samples amongst various laboratories and clinics. The sensitivity and the specificity determined during this stage, which assess the quality of the biomarker, in the designated assay for clinical usage. Phase III evaluates the sensitivity and the specificity of the biomarker in various other diseases, to see its potential predictive value to ascertain the disease occurrence. Phase IV assesses the sensitivity and the specificity on prospective cohorts [6], identifying the false negative samples by evaluating the extent and characteristics of the disease at the time of detection. This process estimates the false referral rate and evaluates the diagnostic features of the biomarker, e.g. the definition, stage, grade of the tumor types. Phase V evaluates the overall benefits and the risks of performing the new biomarker diagnostic test in a controlled screened population.

In 2011, there were 7720 publications on biomarkers usage, but only 407 of these were actually patented [7]. Surprisingly, from these 407 patented biomarkers, none have obtained FDA approval. This fact reflects how many studies report the discovery of different potential biomarkers, but most of them do not meet the criteria of high sensitivity and specificity, necessary to enter into the clinical setting. Moreover, there is a shortage of quality specimens for the validation studies. This subsequently pushes the biomarker