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Mini-Review

Non-Invasive and Minimally Invasive Diagnosis of Cancers- Current Status and Caveats

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Abstract

Early detection is key to the success of anti-cancer therapies. Invasive detection methods would be ill-favored in asymptomatic individuals and there is hence a need for use of non-invasive imaging technologies or minimally invasive detection of circulating tumor features in the blood for early detection of cancers.

Introduction

The inability of existing chemotherapeutics, radiotherapy and even immunotherapy to attain complete remission of later stage metastatic disease, shows that detection of cancers before the onset of metastatic spread is critical, so that the disease can be surgically resected entirely and /or irradiated, and relapse can be prevented. Biopsy is a robust detection method that is used in cases where macroscopic lesions are present. However, being an invasive technique, it is not apt for early detection. Early detection of cancer is limited by the availability of markers that can be detected by non-invasive or minimally invasive methods. Recent literature in the field of early cancer diagnosis has been promising but there is a need to fully understand the currently available diagnostics and to convince the scientific community about the importance of investing time and resources in this field that advocates for nipping cancer in the bud [1-3].

Non-Invasive Diagnosis of Solid Tumors

Anatomical Imaging

Mammography, for detection of breast cancer is an approved non-invasive detection method for breast cancer and can routine mammography can detect early stage tumors that can be successfully removed which followed radiotherapy can provide complete remission. However, many women avoid routine mammography due to the immense physical uneasiness involved in the imaging methodology. Radionuclide and optical imaging techniques are other age-old methods of cancer detection. The major caveats of using X-rays or ultrasound for imaging is that, the sensitivity of the assay is limited to palpable/visible tumors. This frequently corresponds to late-stage aggressive disease that may not be manageable by existing treatment modalities. These techniques are unable to detect the pre-invasive lesions which are further obscured by the basement membranes [4]. Positron emission tomography (PET), magnetic resonance imaging (MRI), single-photon emission computed tomography (SPECT) significantly improved the detection limits of imaging techniques and are used till date. The low sensitivity of detection however precludes these techniques from use in early cancer detection.

Molecular Imaging

Molecular imaging employing bioluminescence and fluorescence techniques holds promise for the detection of micrometastases if probed using a specific protein/metabolite. Tumor hypoxia can be efficiently detected using molecular imaging techniques with dyes that send out fluorescent signals in hypoxic regions. This however would be useful only in tumors large enough to have a hypoxic core [5]. Recently, Bhatnagar *et al.*, discovered a low cost, advanced application of this technique by orally administering and intravitally imaging a near infra-red agent/dye. This foregoes the need to use radionuclides and oral administration of the dyeing agent is the methodology that would accrue maximum compliance from patients [2].

Detecting Cancer in the Blood

Detection of Circulating Proteins and Genetic Material

Interest in the field of minimally invasive cancer diagnostics spiked after Stamey *et al.*, found that the prostate-specific antigen (PSA) could be used as a marker for prostate adenocarcinoma [6]. PSA detection is the only approved method till date for diagnosis of cancer from blood. However, PSA is elevated in inflammatory conditions as well as case of an enlarged prostate. Conversely, obesity and certain urinary conditions can lower PSA levels. Hence, the robustness of the test to detect prostate cancer is still debatable. The other approved detection tests such as colonoscopy (for colon cancer detection) and PAP smear analysis (for cervical cancer detection) are both invasive methods. Recently, as discussed below, there have been several research studies that have reported the use of circulating cell-free DNA (cfDNA), RNA and micro RNA (miRNA) in the blood as methods for the detection of several cancers.

In the last 2 decades, immense time and effort has been invested in identifying diagnostic biomarkers by analyzing circulating, extracellular miRNAs. A total of about 26 different tumor types have been studied and

miRNA panels for diagnosis/prognosis have been developed. However, there has been a lack of consistency between multiple studies for panels associated with the same type of cancer [7]. There are several problems associated with using extracellular miRNA for cancer detection, not the least of which is that miRNA levels in serum and plasma are very low, recovery is cumbersome and hence data collected with them is unreliable and often non-reproducible. Also, hemolysis of RBCs that releases the miRNAs is a random, non-regulated event. Another caveat is that circulating miRNA is frequently seen associated with several proteins. To address the problem of low recovery of extracellular miRNA, a recent study by Ma *et al.*, reported in 2016, isolated miRNAs from peripheral blood mononucleated cells (PBMCs) of non-small cell lung carcinoma patients and found significant differences in miRNA profiles between Stage 1 patients and cancer-free smokers [8]. The rationale behind this was that dysfunction of the PBMCs is an early event in cancer in both cancer immune evasion and immunogenicity.

Genomic DNA sequencing methods have extensively been employed recently to detect cell free circulating DNA (cfDNA). The high-throughput methods are now in use to analyze the 'cancer signals' in the blood at early stages (asymptomatic) of the disease. The main hurdles to developing clinical detection methods involving cfDNA are the need for sensitivity as early stage disease has fewer circulating 'cancer signals' and the need for a large number of control patients who do not present the disease in order to discern the somatic mutations that are exclusive to cancer patients [1,3]. There are several methods that are being pursued to fill these lacunae. GRAIL, a company that was recently started with the aim to develop cfDNA based methods for early detection of cancers has embarked on a >10,000 subject study to develop a library of all the mutations observed in the cfDNA of cancer patients [3]. This study will also involve sequencing with larger coverage of different areas of the genomic DNA. Another method that has been studied is whole-exome sequencing to reduce potential error by observing trends exclusively in the coding regions of DNA [9]. This method seems to correlate well with tumor biopsy gene signatures in more metastatic disease in this study and hence may not be a method of choice for early cancer detection. Several studies have attempted to identify a serum biomarker panel of antigen that can be used for diagnosis. Patz *et al.*, successfully designed a panel of four serum proteins, Carcinoembryonic antigen, retinol binding protein, α 1-antitrypsin, and squamous cell carcinoma antigen that could detect lung cancers with 89.3% sensitivity and 84.7% specificity [10]. However, combined analyses of serum proteins and circulating genetic material holds the most potential as the same test could be used for the detection of an array of cancers.

CancerSEEK, a recently reported method that analyzes circulating proteins as well as mutations in circulating DNA to successfully detect early-stage, surgically resectable tumors of the ovary, stomach, pancreas, esophagus and liver can also localize the tumor to a specific tissue [1]. This test helps overcome the problem of protein-associated, circulating genetic material by analyzing the presence of ctDNA using 61 robust amplicons followed by elevations of 8 antigens that are upregulated in several cancer types namely, cancer antigen 125 (CA-125), carcinoembryonic antigen (CEA), cancer antigen 19-9 (CA19-9), prolactin (PRL), hepatocyte growth factor (HGF), osteopontin (OPN), myeloperoxidase (MPO), and tissue inhibitor of metalloproteinases 1 (TIMP-1). This technique shows 69-98% specificity in detecting early stage cancers of the ovary, liver, stomach, pancreas, and esophagus.

Detection of Metabolites

A newer approach to early detection is the analysis of cancer-associated metabolites in the blood. The concept of using metabolomics for early disease diagnosis was succinctly described in 2008 by Gowda *et al.*, for detection of diabetes, cancers, inborn errors of metabolism and cardiovascular diseases [11]. This concept did not make headway in the field of cancer diagnosis using patient blood/ urine/ other tissue. However, a decade later, a report shows promising *in vivo* data using the method of biomedical tattoos for detecting hypercalcemia associated with cancer [12]. This excellently designed study opens new avenues for the use of altered blood metabolites for early cancer detection.

Outstanding Questions

Detection of 'cancer signals' in the form of antigens, genetic materials and metabolites in the blood has tremendous potential for improvement to be applicable to a broader spectrum of cancers. There is a dearth of effective, specific therapy for aggressive cancers such as triple negative breast cancers and these cancers have poor prognosis. None of the minimally invasive methods till date have been able to address this class of cancers where the only effective method of management is early detection. Is there potential in the future to use differences in sweat and urine proteome or metabolome to detect cancers in asymptomatic individuals? Another intriguing aspect that can be probed and developed into a non-invasive diagnostic is the differences in microbiome between patients and control subjects. Figure 1 gives a comprehensive view of the currently available early detection techniques as well as the new methods that could potentially be applied for early cancer detection in the near future.

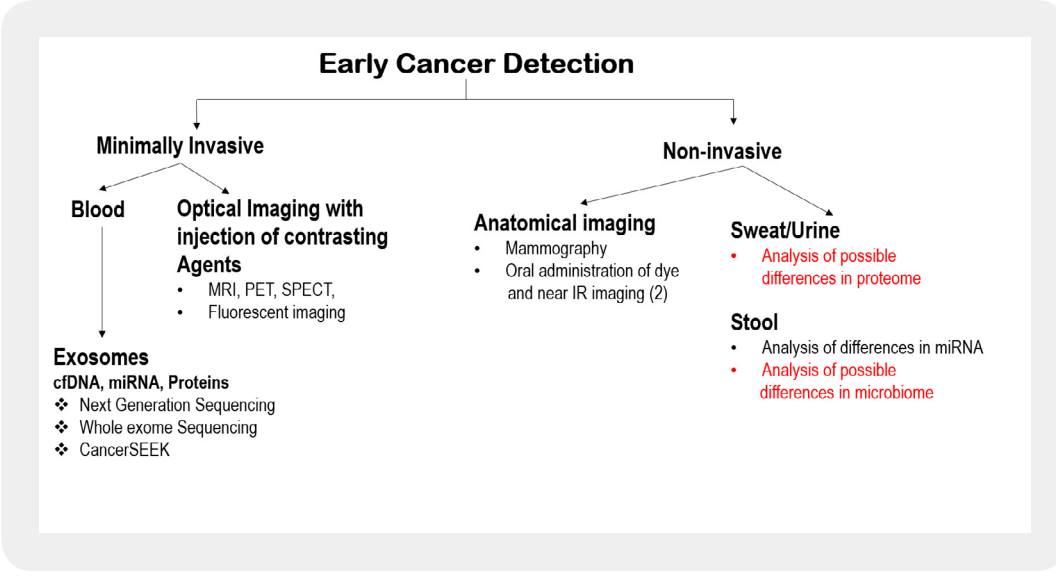

Figure 1: *This figure gives a comprehensive view of the early detection techniques that are currently in various stages of development*

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