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Short Communication

Cancer: Diagnosis, Staging, and Complication

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Introduction

Cancer is one of the biggest causes of death, with more than 10 million mortalities annually, as reported in GLOBOCAN 2020 [1]. The most common types of cancer, according to WHO, are lung, breast, rectum, colon, and prostate cancers [2]. The essential characteristics of cancer are interlaced with an altered cancer-cell intrinsic metabolism, that maybe be the reason or an after-effect [3].

As alarming as the disease is, its prioritized diagnosis and subsequent staging are likewise challenging, since to produce valid and certain results lucratively, not a single tool, but a combination of diagnostic methods is required. These are critically dependent on the location of the organ we are examining for cancer. Subsequently, early diagnosis holds a better chance of treating tumors with minimal consequences and greater implications for survival. Therefore, programs targeting cancer diagnosis should be framed to reduce delays in detection and improve precision in therapy followed by supportive care [2]. In the current article, we firstly discuss the existing cancer diagnostic and staging tools that are continuously evolving, like imaging techniques, biopsy, and biomarkers, and secondly the emerging perspective tools for diagnosis specifically nanotechnology, breath testing (an extension of biomarkers), CRISPR/Cas systemic development, and bioinformatics (machine learning). The article further discusses complications associated with developing novel techniques and their shortcomings.

Diagnosis and staging of cancer

With the invention of the imaging technique, clinical examination has revolutionized. It is, undoubtedly, the most prominently used cancer diagnostic tool. It broadly includes MR (Magnetic Resonance), CT (Computed Tomography), X-ray, endoscopy (such as a colonoscopy), and PET (Positron Emission Tomography). These techniques, in addition to detection, also assist in determining the stage of cancer, whose knowledge is essential for therapy. Some imaging techniques are specifically used for a particular type of cancer. We see that DCE (Dynamic Contrast-enhanced) MRI and PET/CT are dominantly used to image tumors and associated lesions of prostate cancer [4]. Meanwhile, multi-parametric MRI delineates the stages of prostate cancer viz. localized tumor- restricted to the primary organ, regional tumor- spread of the tumor to the neighboring tissues, distant tumor- the malignancy spread to the faraway region, and unknown [4,5].

The study of the diagnosis of cancer at early stages is crucial since it can provide an appropriate evaluation of tumors, and corresponding treatments thereby increasing survival chances, as observed in the case of breast cancer. It is the most frequently diagnosed cancer in women worldwide, with 2.3 million cases annually [6]. After screening via physical examination, breast cancer, according to current trends, is mainly diagnosed through mammography or its advanced method, Digital Breast Tomosynthesis (DBT), and other secondary imaging techniques like optical imaging [7]. It is staged, according to Tumour-Node-Metastasis (TNM) system, demarcating stages 0 to 4. Presently, prognostic and anatomical staging are combined for better evaluation, which merges receptor status (cancer cell-specific), tumor grading (low, intermediate, and high-grade), and genomic testing (for screening presymptomatic cases), to generate a reliable report of the disease [7].

Another considerably researched and used diagnostic tool is cancer biomarkers. They comprise nucleic acids (DNA, RNA, miRNA, lncRNA), metabolites, proteins (intracellular, surface receptors, or extracellular) cytogenetic entities, genes (usually polymorphisms are analyzed), and circulating tumor cells (CTCs). These are either causative of tumor growth or produced as a product of abnormal cancerous cells, and thus are indicative of the presence of a tumor [8]. Moreover, different phases of cancer demonstrate and express different biomarkers, that once identified and validated, can facilitate cancer staging. For instance, early-stage lung cancer can be detected via the presence of ctDNA (cell-free tumor DNA) from liquid biopsies. There are other genetic markers for lung cancer as well such as mutations in tumor suppressor genes, like p16, TP53, and RB, which are accordingly screened via PCR and microsatellite analysis [9]. Taking the example of pancreatic cancer, which is extremely difficult to diagnose at early stages, there is extensive research done to identify suitable biomarkers. One such reliable and substantiated biomarker is carbohydrate antigen (CA) 19-9, with a sensitivity of 79-81% and specificity of 82-90%. However, asymptomatic patients have a low predictive value [10]. Regardless of the limitations, it is worthwhile to mention that biomarkers of various cancers have been identified and are under study, and hold vast potential for early detection of cancer.

Emerging diagnostic technologies

Needless to say, despite there being a plethora of existing diagnostic techniques, there is a necessity and scope for development, given the impact of cancer as a disease globally. Hence, we try to further investigate the emerging techniques. Diagnostic nanotechnology has the competence for early detection of cancer with the help of nanoscale materials; quantum dots, gold particles, etc. They assist in recognizing cancer biomarkers (mostly protein biomarkers) with high sensitivity [11]. Presently, clinical trials are run on several nanotechnology-based diagnoses of cancer, for instance, c-dots labeled with fluorescent cRGDY have been under study to visualize and map cancerous lymph nodes [12].

Another interesting method under research is breath testing for the detection and quantification of volatile organic or inorganic compounds, which are specifically produced by the body hosting cancerous tissues. The results are subjected to a comparative study with healthy individuals' breath [13]. More than the simplicity of use, it is non-invasive and can detect cancer at early stages. However, it is limited by a lack of research to ascertain standard samples and ideal equipment for detection and quantification.

Moving on to advancing gene-editing technology, we note another diagnostic tool, CRISPR technology, which has emerged as one of the techniques for screening cancer-related genes. One such CRISPR-based diagnostic system is SHERLOCK, which can detect mutant genes. CRISPR has been extensively used to supplement the biomarkers library related to cancer, generate cancer models (through knockout genes), and assist in gene diagnosis. Thus, they provide better knowledge and approaches to screen, identify and treat cancerous cells at the genomic level. However, they face certain challenges, which include the need for safe and targeted delivery of CRISPR/Cas systems in the body without inducing any immune response, increasing target efficiency to lessen off-target effects, and overcoming the cost barriers [14]. In addition to above mentioned potential diagnostic tools, there is a computerized approach or machine learning, wherein benchmark datasets (a databank of previously diagnosed and verified cancer imaging results) are employed for trained and comparative analysis of MR or CT/PET imaging reports of patients and determine if the tumor is malignant or benign [15]. Computational tools, with their applicability and incorporation of -omics data can be used to characterize and verify unidentified biomarkers [16]. Bioinformatic tools thereby have greatly eased research with accessible biodata of promising biomarkers and tumor images along with verified analytical evidence [17]. Nevertheless, there is an enormous number of studies performed to improvise prevailing diagnosis approaches. The scientific world regularly witnesses growing research on either a new technique to validate a theory or a supplement to the existing one.

Complications in the diagnosis of cancer

With cancer being a highly complex disease, a single technique may fail to accurately diagnose it. Accounting for the prevalence of cancer, diagnostic tools are undergoing relentless and commendable advancements to reduce any complications and inaccuracies in results. This requires developing analytical assays that generate robust and reliable signals for cancer detection (since overdiagnosis adversely affects the treatment) and also ensure the elimination of any background signal that might give a false-positive cancer diagnosis [8]. One of the biggest challenges is to develop a tool that is non-invasive, cost-efficient, and gives a spot-on diagnosis. Cancer, involving metastasis, makes it difficult to just focus on one organ and pinpoint its site of growth. Circulating tumor cells (CTCs) in the bloodstream can lodge in any organ that could harbor their uncontrolled growth. This creates a problem for staging cancer. Also, accessibility to diagnosis and thereafter treatment is not widespread. A study shows that inability to access diagnostic tools for breast cancer in rural areas results in a delay in diagnosis and led to poor treatment of the same [7]. This becomes hurdled by the requirement of operative specialists for cancer diagnosis modalities, like MRI or PET/CT. The state of development of a region is a big determinant of its healthcare amenities.

Another complication is the patient's mental well-being. Getting diagnosed with cancer is never good news, and is often taken as a death sentence. Studies show that stress disturbs the body's homeostasis. This greatly impairs an individual's willingness to get it screened and diagnosed and may entail the effectiveness of the therapy [18].

Moreover, despite being successfully developed for diagnosis, the clinical relevance of biomarkers is deficient, given the complicated interactions between probe and target, leading to low specificity or less sensitivity. Furthermore, it usually takes time for their thorough investigation, which involves analysis of their pattern of interference in the normal metabolic process and expression in the presence of abnormal tissue/cells [8].

All these complications are hampering our diagnosis of cancer, yet offer an opportunity to create the finest and more accessible detection techniques. Future does hold a prospect of more efficient diagnostic tools with minimal to no complications, and researchers all over the world are tirelessly working to achieve it.

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