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An Overview on Cancer Diagnosis based on Antibody-Based Immune Techniques

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ABSTRACT

Cancer is known as a second-high fatal disease after cardiovascular disease in the world. Although many techniques have been investigated for the treatment of cancer, none of them satisfied completely. Investigation of a cancer diagnosis is the new pathway to cancer therapy. It has been known that cancer diagnosis at its early stage could help eradicate it in the patient's body. Among different techniques that have been investigated for cancer diagnosis in its early stages, immune assay techniques due to high sensitivity and selectivity have been comprised. This review investigates new immune assay techniques and their combination with others as a new cancer diagnosis method.

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Abbreviations

MRI, Magnetic resonance imaging; CT, Computed technology; PET, Positron emission tomography; IGs, Immunoglobulins; CA 125, Cancer antigen 125; CA19-9, Cancer antigen 19-9; MoAb, Monoclonal antibodies; PoAb, Polyclonal antibodies; PSA, Prostate-specific antigen; IL-6, Interleukin-6; IL-2, Interleukin-2; IL-11, Interleukin-11; IL-12, Interleukin-12; ERBB2, Erythroblastic oncogene B; TNC, Tenascin C; ESR1, Estrogen Receptor 1; ICAM-1, Intercellular Adhesion Molecule 1; MCP-1, Monocyte Chemoattractant Protein-1; AIP, Autoimmune pancreatitis; GC, Gastric cancer; TNF, Tumor necrosis factor; TGF-β, Transforming growth factor-β; MAPK, Mitogen-activated protein kinase; IFN γ, Interferon γ; THBS1, Thrombospondin 1; FGFR, Fibroblast growth factor receptors; HER2, Human epidermal growth factor receptor 2; K-RAS, Kirsten rat sarcoma virus; ERK, Extracellular signal-regulated kinase; PDA, Pancreatic ductal adenocarcinoma; AFP, α-Fetoprotein; SPR, Surface plasmon resonance; PTM, Protein post-translational modification; HAT, Histone acetyltransferases; BRCA1, Breast Cancer gene 1; KLK6, Kallikrein-related peptidase 6; FOS, Fiber-optic sensors; SWCNT, Single-wall carbon nanotube; QCM, Quartz crystal microbalance; scFv, Single-chain variable fragment; MUC, Multiple mucin; HRP, Horseradish peroxidase; PSMA, Prostate-specific membrane antigen; pf-4, Platelet factor 4; F-FDG, [fluorine]fluoro-D-glucose; AR-V7, Androgen-receptor splice variant 7; Urinary EVs, Urinary Extracellular Vesicles

Introduction

Cancer is the second leading cause of death in the world (1). Early detection represents one of the most promising approaches to reduce the growing cancer difficulty. One of the challenges consists of detecting tumors at early stages to make possible treatment before progression occurs (2-4). Many diagnostic techniques are available, but the survival rate remains low, and it has been seen patients die due to late diagnosis and advanced stage of the disease (5-7). What can be known as the ideal feature in diagnosing and treating cancer is recognition in the early stages, which is the main purpose of all techniques, and lots of researches have been set until today (8, 9). In about 20th century, cancer was known as a genetic disease, and thus diagnosis methods were formed based on this idea (10). In 2003, The completed human genome project marked a dramatic shift in understanding cancer and other diseases. After 13 years, researchers mapped the entire human genetic code, discovering that every human cell is packed with an estimated 20,000 to 30,000 genes (11). Researchers have used the discoveries to link dozens of diseases, such as Alzheimer's disease (12, 13) and inherited colon cancer (14), to specific genes. Identification of genetic variants could potentially assist with earlier diagnosis and thus more effective treatment.

Several techniques are using for a cancer diagnosis like ultrasound (15, 16), magnetic resonance imaging (MRI) (17, 18), X-ray computed technology (CT) (19, 20), biopsy (21, 22), and blood tests (23,24) for cancer biomarkers. Tumor markers are the proteins that have presented in the circulatory system, and their elevated levels can indicate the stage of cancer (25, 26). Immunoassay has been known as one of the uppermost analytical techniques widely used in clinical diagnoses and biochemical studies because of its incredibly high selectivity and sensitivity (27-29). In the following, we talked about antibodies in antibody-based immune assays, which have been used until now for cancer diagnosis.

Antibodies

Antibodies or immunoglobulins (IGs) are the principles of each immunoassay for cancer diagnosis. Antibodies are the protein produced by the immune system in response to any foreign things or unusual situations happening to the body (30). Each IGs has comprised of a specific antigenic determinate or epitope.

Although an antigen may have many different epitopes that react with several different IGs, a unique IG joins with only one epitope. This epitope (and the antibody's combining site for it) has a size of about five to seven amino acids (31). This feature makes it to be used in a cancer diagnosis. Anticancer antibodies are widely used for cancer diagnosis in immunohistochemistry and immune assays to detect tumor associate antigens. There are two different antibodies; monoclonal antibodies (MoAb) and polyclonal antibodies (PoAb). Both of these antibodies have similar structures and functions. MoAb and PoAb are different based on their first principle, production, and specificity. The difference between these two antibodies is based on the clonally of the cells that produce them. MAbs are produced by a single clone, while PoAbs are produced by numerous clones together. However, problems such as lack of adequate specify have limited the use of these antibodies for diagnoses (32, 33).

Antibody-based microarrays

In the 1980s microarray technique was introduced. This technique on cancer diagnosis was based on genome detection. This technique is separated into four branches; microarray DNA, microarray protein, antibody-based microarray, and microarray carbohydrate (34-37).

The mechanism of this technique is based on the binding or hybridization of the sample with the template that developed over time, and its usage has been changed. Antibody-based microarray is one of the microarray techniques used today to detect specific biomarkers with high sensitivity. Rapid diagnostic speed and cost-efficiency are the two main benefits of this technique. In addition, the microarray is a non-invasive procedure, and it is highlighted in a study by Karen et al., which has demonstrated higher levels of serum protein in the patient plasma of cancer patients compared to control samples (37, 38).

Biomarkers are the proteins that increase or decrease their amount in serum, may cause the presence of disease. A drawback of protein biomarkers is a lack of specificity, and also they could be suggestive for more than one disease (39).

Serum prostate-specific antigen (PSA) is a protein that is elevated in some benign prostate diseases as well as prostate cancer (40), or interleukin 6 (IL-6), is also a protein biomarker which, if overexpressed in the serum of patients, could be known as inflammation of the prostate (41), lung (42), multiple myeloma (43) and renal cell cancer (44). Thus, single cancer biomarkers are often not unique to specific cancer. However, the detection of some biomarkers together could be more specific for one disease, specifically for cancer disease. Antibody-based microarray has the ability to concurrently detect multiple particular biomarkers and target specific cancers using a panel of biomarkers (34, 36).

In 2003 miller et al. (45) developed a practical strategy for serum protein profiling using antibody-based microarray. They compare the specific biomarkers of the patients' serum with the control one. The result shows that biomarkers can be detected with the help of the microarray technique, which can be used as one of the cancer diagnosis techniques. Other studies show the further advantage of utilizing antibody microarray for early-stage diagnosis. Pancreatic cancer is an aggressive disease with a poor prognosis which delay in diagnosis caused a high fatality. CA125 and CA19-9 are the specific biomarkers for pancreatic cancers which cannot be detected unless in advanced stages; however, the high sensitivity technique which has acquired through antibody-based microarray has caused these markers to be used before any crucial progression occurs (46, 47). by investigation of 3 groups of patients with early-stage pancreatic cancer, chronic cancer, autoimmune pancreatitis (AIP), and control patients, Wingren et al. has identified a panel for 148 patients with microarray technique. This panel contains 25 protein targets biomarkers such as IL-2, IL-11, IL-12, and tumor necrosis factor (TNF), distinguishing pancreatic cancer from healthy controls. These 25 biomarkers have shown high sensitivity in pancreatic cancer diagnosis (AUC 88%) (46). In a recent study, researchers have found three proteins of ERBB2, TNC, and ESR1 for pancreatic ductal adenocarcinoma (PDA), which increases the AUC from 0.86 to 0.97. By employing this technique, CA19-9 plays an essential role in early cancer diagnosis (34, 35, 46).

The mechanism of tumor progression can be understood much easier with antibody-based microarray. Gastric cancer (GC) is the gravest among many solid tumor cancers. Puig-Costa et al.; find more than 100 biomarkers associated with GC, including 120 cytokines, 43 antigenic factors, 41 growth factors, 40 inflammatory factors, and ten metalloproteinases, by using antibodies microarrays (48). ICAM-1 and MCP-1 are other markers related to high inflammatory response and tumor development in GC that find with this technique. In 2017, Quan et al. (49) introduced novel diagnostic and predictive biomarkers by evaluation of released cytokines from tumor microenvironment or cancer cells, based on considering inflammation as the characteristic feature of the development and progression of GC. Also, they found some cytokines such as TGF-β, TNF, and mitogen-activated protein kinase (MAPK) signaling pathway, acting as a useful biomarker for early-stage cancer diagnosis.

The cost-effectiveness and high sensitivity of this technique led to the use in a different cancer diagnosis area. In bladder cancer, it was understood that 50 to 70 percent of cancers could recur after standard transurethral resection. Srinivasan et al. (50) have found 20 proteins to track the tumor progression with a sensitivity of 80% and specificity of 100%. They showed that some signaling factors such as IFNG, TNF-α, and THBS1 were expressed less. The abundance of the inhibitor MAPK3 (also known as ERK1) was higher, while SMAD2, SMAD3, and SMAD4 were significantly underrepresented in patients with bladder cancer. They reported that TGF-β signaling pathway inhibitors might reduce bladder cancer recurrence.

Miller et al. (45) compared two microarray methods; antibody-based microarray and hydrogel bed. They have reported that antibody-based microarray facilitates marker discovery and enables to find of the relationships between proteins. Thus, in an experiment, both data sets could help examine multiple markers that may increase the statistical significance of a diagnosis.

PTM and its function in Cancer Diagnosis

Protein post-translational modification (PTMs) means the covalent and generally enzymatic modification of proteins for protein biosynthesis. PTMs are very important in order to form a mature protein product. These modifications include phosphorylation, acetylation and methylation (51, 52). Phosphorylation, acetylation, and glycosylation can modify the cell surface receptors such as receptor tyrosine kinases and G-protein coupled receptors. These receptors are able to activate signaling pathways and change normal cellular function, which is directly contributed to tumorigenesis.

Hence detection of PTM can provide useful information about the epigenetic regulation of cellular processes. Until recent advances in antibody microarray technology, the study of PTMs and their role in cancer diagnosis and prognosis had been minimal.

In tumorigenesis, genetic alternation happens in signaling molecules which causes the over-activation of cell surface receptors, which can affect the downstream in the signaling pathway. For instance, in breast cancer, membrane receptors like HER2 and FGFR and the intracellular signaling components provide the K-RAS and ERK kinases that could joint and cascade some abnormal signaling (53, 54). It causes cells to alter signaling, leading to neoplastic growth. Recent investigations have shown that genetic alterations, such as somatic or germline mutations, modulate protein kinases' functional activity (including multiple receptor tyrosine kinases and phosphatases in the genome), which has a practical impact at the proteome level (55).

Another PTM modification is acetylation, which has a rule in regulating numerous Onco-proteins which are involved in tumorigenesis and cancer progression. Lysine N-acetylation has a straight role in regulates the function of histone and non-histone proteins. Histone acetyltransferases (HATs) are dysregulated because of numerous genetic or epigenetic alterations. In general, HATs act as tumor suppressors and control normal cell growth, cell cycle, and oncogenes. However, whenever abnormal acetylation happens could activate malignant proteins and trigger tumorigenesis. Detection of this abnormal acetylation could be helpful in cancer diagnosis in its early stage. Also, acetylation has the potential to work as a prognostic biomarker to monitor cancer treatment. Researchers found that histone deacetylase inhibitors and acetylation modulators indicate promising results in treating some forms of cancers in epigenetic therapy (56, 57).

Another PTMs is glycosylation that is involved in neoplastic transformation. Abnormal alternation in glycosylation can lead to tumor aggression and tumor microenvironment heterogeneity. Also, N-linked glycosylation is involved in metastasis and cancer progression. The Discovery of the N-linked glycosylation has opened a new sight for cancer diagnosis, especially in breast and ovarian cancer. The glycosylation plays an essential role in regulating BRCA1 in breast cancer and CA125 and KLK6, which are known today as qualified biomarkers in early cancer diagnosis.

A comparative proteomic analysis of three breast cancer cell lines (MCF-7, MDA-MB-453, and MDA-MB-468) has identified three N-linked glycosylated membrane proteins, namely galectin-3 binding protein, lysosome-associated membrane glycoprotein 1, and oxygen-regulated protein, can be used as a diagnostic marker in breast cancer (58).

Proteomic microarray facelifted the PTM detection that makes this immune technique more popular among the other ones. Nevertheless, despite its advances and advantages (e.g., quality controls, specificity, functionality, and/or reproducibility), this technique is not sufficient individually. It requires the input of other diagnostic techniques to complete validation.

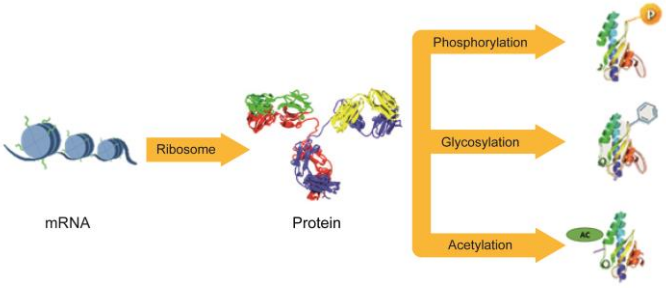

Figure 1. Mechanism of PTM. PTM, Protein post-translational modification.

Antibody-based Immunosensors

Biosensors are devices that can detect the concentration of a biological analyte such as a biomolecule, a biological structure, or a microorganism enzyme, antibodies, antigens, and nucleic acid, which could interact and bind with specific analytic. Its operation is based on the combination of the physicochemical detector and biological component (52). In this method, Immunosensors are like biosensors that act based on the interactions between an antibody and an antigen on a transducer surface (Figure 3). Antibodies and antigens bind together with great strength; then, they are immobilized on a transducer and detect each other. The specificity of antibody-antigen interaction leads to an increase in the sensitivity of these techniques as well.

Immunosensors have been divided into the three-part 1- Electrochemical 2- Optical, 3- Piezoelectric immunosensors (electrochemical quartz crystal microbalance). Immunosensors can be either direct or indirect, which means they can operate directly via the Ab/Ag interaction or indirectly with a further label, such as an enzyme or fluorescent molecule, to be detected whether a binding event has occurred (59).

Using nanoparticles such as carbon nanotubes has developed efficiency in body fluids' biomarker detection (65).

Piezoelectric immunosensor operation is based on the conversion of physical or mechanical changes into electrical energy and vice versa. The quartz crystal microbalance (QCM) is the commonest piezoelectric sensor. When antibody or antigen is immobilized on

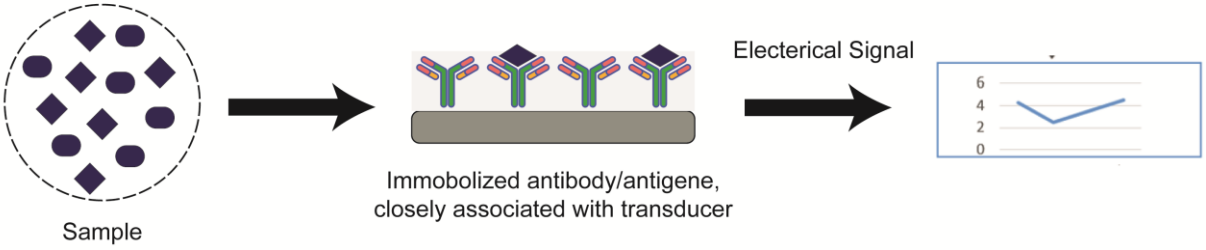

Figure 2. Schematic representation of antibody-based immounosensors

Electrochemical immunosensors performance work in the way of measuring an electrical signal produced on an electrochemical transductor. Immunosensors electrochemical detection is a portable, simple, and automated detection technique that does not require handling by a person. Immunosensors consist of several essential parts with a crucial role. The electrode surface is one of the most important parts. An electrode surface can be modified with different conducting materials such as gold nanoparticles (60), carbon nanotubes (61), nanofibers, or any conductive polymers (62, 63) to provide high sensitivity in detection. This conductive electrode has stayed on immobilization platforms where bio receptors are set on. The following important part is bioreceptors, antibodies, or aptamers on the surface, where the modified electrodes exist. The mechanism of this immunosensor is based on the interactions between the immobilized bioreceptors and proteins inside the sample. Which is like antibody-antigen or aptamer-antigen labeled with an enzyme, create measurable signals. pH, buffers, temperature, the concentration of nanostructures, monomers, and incubation times with aptamers, tumor markers, and antibodies should be considered as essential parameters that need to be modified for a reasonable results (52, 64, 65).

Optical immunosensors are light- sensitive kinds of immunosensor techniques that are modified upon binding of a specific antigen. In this technique, an optical sensor uses light for stimulation. It can then detect alterations in the power of light as it passes through or refracts from a sampling system related to Ab/Ag binding. Optical immunosensors include surface plasmon resonance (SPR) based sensors, fiber-optic sensors (FOS), and various fluorescence-based sensors.

the crystal surface, their bonding will be measured electrically. New development in this technique increased its popularity. In 2017, Su et al. (66) have developed a new biosensor based on the piezoelectric ceramic to detect cancer biomarkers. The new one has two piezoelectric resonators in order to decrease the environmental influence such as temperature. This device has shown high sensitivity and faster detection of PSA and α-Fetoprotein (AFP) as a cancer marker.

The performance of any immunosensor is mainly dependent on the type of antibody and the associated antibody approach used to determine the sensor. Antibodies play a vital role in delineating the sensitivity and specificity of an immunosensor. The immobilization strategy used with the antibody or biorecognition ligand is a necessary parameter in immunosensor sensitivity (67). Several studies have been shown the enhancement in antigen-binding activity by oriented antibody immobilization on a sensor surface. Since recombinant antibody fragments have a small size, they are more stable and can be easily changed genetically to have highly oriented immobilization on the sensor surface. They were more popular to be used in this technique. Recombinant antibodies show significant additional promise for generating antibody-based sensors with many novel applications in cancer diagnostics. In 2016 Spain et al. (68) have developed a sensitive electrochemical immunosensor that use recombinant scFv as a receptor on electrocatalytic platinum nanoparticle to detect PSA in a serum sample. This device detected a high PSA concentration without the need for any other techniques such as PCR or NASBA amplification. Arkan et al. (69) have investigated the detection of HER2 in serum samples of patients with breast cancer. They have used gold as a Nanoparticle and discovered that by increasing the concentration of the HER2 antigen, detection is increased in serum samples of patients with breast cancer.

Carbon nanomaterials, because of their excellent electrical and mechanical properties, is one of the eminent materials that can enhance the sensitivity of the immunosensors. The combination of carbon nanomaterials into biosensor platforms is now widespread in biosensor design. Nowadays, Carbon nanomaterials are widely used as nanotubes (single-walled (SWCNT) and multiple-walled (MWCNT)), graphene, and carbon quantum-dots (QD) that emerging as novel materials for sensor construction in the field of breast and ovarian cancers immunology and cancer research (70).

Mucins are large glycoproteins. They have a crucial role in protecting and lubricating the surface of epithelial tissues like mammary glands, female reproductive tracts, kidneys, lungs, pancreas, and gall bladder. They also play a role in cell differentiation, cell adhesion, and signaling processes (71). The normal amount of mucin is present in the body, but its overproduction has been seen in the blood in ovarian cancer. Therefore, measuring this marker in the blood can help in the rapid diagnosis of cancer. Cristea et al. (72) have shown the development of a diagnostic device based on the optical and electrochemical principles for detecting the levels of multiple mucin (MUC) type biomarkers in the serum samples of patients. Combining SPR technique and electrochemical techniques have improved the obtained transducer's sensitivity and reliability. They have shown that the combination of these methods is more accurate than separate ones. Using carbon nanotubes makes this method more popular. As an electrode surface, it has excellent properties such as a large surface area, high conductivity, and easy chemical modification for use in electrochemical immunosensors. Rusling et al. (73) have developed nanostructured electrodes including densely packed films of SWCNT sections (forest) which are ultrasensitive in detecting PSA to increase the sensitivity. They have also identified attaching the tracer antibody to these carbon nanotubes with multiple HRP labels, giving a DL of 4pg mL−1 for PSA spiked into undiluted calf serum, would enhance the sensitivity. A 4-electrode SWCNT forest array for detection of multiple protein biomarkers (PSA, PSMA, IL-6, and platelet factor 4 (pf-4)) has investigated patient's serum samples. The results were positive, and the accuracy of protein biomarkers detection was evaluated by ELISA. Due to achieving larger immobilized antibodies in SWCNT forests more than usual immunosensors, a more significant enhancement in sensitivity has been seen in mentioned immunosensors. These results indicate that multiply-labeled detection probes have been used with electrode surface modification to increase their ability to capture a high-density antibody in immunosensors.

Comparing these techniques under similar experimental conditions to Rustling's group in the detection of IL-6 has revealed that the AuNP modified platform yielded a three-fold better detection limit than an SWCNT-based method (73).

Many immunosensors have been investigated, and they are accepted as biomarker detection devices. Electrochemical and optical biosensors, because of their high sensitivity, relatively easy fabricating, easy operating procedures, and the potential to be miniaturized, are known as an attraction for multiple biomarker detection in a non-invasive way for early-stage cancer diagnosis methods.

Imaging and Immunodiagnostics Collaboration on Cancer diagnosis

It is known that unusual genomic alteration in nucleic acid levels and chromatin, causes overexpression of proteins which are responsible for cell function. These proteins might make a pattern that is relevant to malignant progression. Recent studies have seen significant changes in nucleic acid expression that have occurred in patients with end-stage cancer. Therefore, identifying the potential use of nucleic acids would be very useful for cancer screening and monitoring. Some biomarkers such as EGFR, P53, cell regulatory protein Bcl-29, and cell division cycle protein CDK-110 are overexpressed in specific cancers. The detection and evaluation of these nuclear biomarkers (nucleic acids and proteins) will help to clarify the signaling pathways in tumorigenesis and thus improve early-stage cancer diagnosis (74).

Imaging is a technique that is utilized to diagnosing and investigating the progression or improvement of the disease. Distinguishing malignant cells from normal cells is the main principle of imaging in cancer diagnosis. The imaging technique has six subdivisions for assessing diseases: CT, MRI, PET, US, SPECT, and visual detectors. Only four of these techniques, due to their three-dimensional imaging feature, can help detect cancer cells. The imaging technique shows poor ability to detect small tumor cells, so cancer diagnosis requires designing and modifying or combining them with new techniques for rapid, sensitive, and high selectivity detection (74, 75). Nevertheless, most recent studies have focused on incorporating imaging and other immunodiagnostic assays for maximum accuracy and effectiveness.

Molecular imaging is a novel technique that enhances the diagnostic and therapeutic approaches for cancer treatment. Ultrasonography (US), CT, MRI, and PET were the traditional techniques used for solid tumors. The disadvantage of these techniques is that they weren't accurate enough to detect the biochemical or molecular stage of neoplastic cells. The Molecular Imaging technique, because of the inducible "smart" molecular MRI probes, makes the imaging process of the tumor before and after the surgical removal easier, without renewing the probe to evaluate surgical accuracy. Moreover, these smart MR/Optical imaging probes have the ability to detect small tumors. Most of the new methods that have been investigated today have the dual-labeling of molecular MR probes with fluorescent dyes to facilitate the detection of cancerous tissue. (76).

Although in imaging methods, techniques such as US, CT, and MRI are prevalent and useful in bone and tissue imaging; however, they could not delineate the detection of solid tumors (77). Molecular imaging techniques vastly improve cancer diagnosis by displaying entirely new possibilities for early detection and effective cancer treatment that are crucial to conquer the disease successfully. As mentioned before, the development of a non-invasive method for therapy or diagnosis is the most critical factor in any disease; molecular imaging is defined as a non-invasive method of imaging for monitoring cellular and sub-cellular occurrences. Molecular imaging operation is on the distinctive molecular properties of malignant cells. In this technique, imaging probes detect and highlight the specific characteristics in each malignant cell, in the environs of the extracellular matrix, and cells in the vicinity (such as fibroblast, T cells, dendritic, macrophages, or endothelial cells). Therefore, this feature makes tumor detection easier, while traditional imaging techniques such as US, CT, and MRI do not have this ability. Recent studies have shown the high efficiency of molecular imaging for carcinogenesis detection at a much earlier time. This technique can detect alterations on the cellular level, and they are targeted as soon as they occur. Signaling changes in glucose metabolism of malignant cells occurs early in carcinogenesis, and molecular imaging can detect it easily.

PET imaging with F-FDG is another technique for cancer detection; however, they have a limited ability to detect malignant cells compared to molecular imaging.

Hence, an ideal imaging modality is developing more specific molecular imaging probes without radiation exposure and detection without the need for invasive procedures like biopsies or surgery. Ultimately, molecular imaging may be able to determine the best treatment.

The combination of imaging and immunodiagnostics can provide efficient techniques to improve cancer diagnoses and could allow for cost-effective personal treatment approaches for patients. Molecular imaging techniques, PET, and other techniques are continuously advancing to create effective non-invasive techniques for cancer diagnosis (74, 75, 77).

Non-invasive cancer diagnosis method based on Urinalysis

Non-invasive therapies are the most considerable approach against disease, and stem cell researches is a remarkable example of them with exciting results that can improve healthcare(78-80). There are different sources for the stem cells, such as bone marrow or adipose tissue. Nonetheless, the stem cell extraction procedure is considered as an invasive approach and may damage the patient's body. Urine is a good source of stem cells; therefore, finding the new non-invasive method for IPS isolating cells from urine has been under development recently. Also, it has been proven that urine is a suitable body fluid for cancer detection (81, 82). In a recent study, Woo et al. (83) have investigated the detection of an androgen-receptor splice variant 7 (AR-V7) marker associated with castration-resistant prostate cancer RNA of a urine sample of patients. They also have discovered that AR-V7 transcript levels and the AR-V7/AR-FL ratio in urinary EVs were higher in patients with advanced prostate cancer. This study is the first report that acclaimed urine-derived RNA is a reliable source for AR-V7 expression analysis. These results can expand the horizons of knowledge in cancer diagnosis for researchers with liquid biopsy as a non-invasive approach. If the receptors are detectable, they can measure the proteins' level for cancer diagnosis or cancer stage in cancer therapy (84).

Conclusion

In general, early-stage diagnosis of Cancer is a crucial step to overcome. Therefore, try and develop various techniques for rapid and accurate diagnosis is essential. The study of antibodies, along with immunosensor techniques, can accelerate this step. Today's knowledge of genomic assays has been incorporated and combined with proteomic assay methods. Combining the methods has helped imaging techniques such as MRI and CT used for small tumor detection.

Accuracy, and trustworthiness, are the other essential factors that should be considered in cancer diagnosis techniques. Non-invasiveness is another crucial factor that has a high effect on cancer technique development, particularly its noninvasiveness. The usage of body fluids such as oral saliva, urine, and blood, is more attractive for detecting biomarkers with high sensitivity and specificity, and they are also far less invasive for patients. Choose urine as a body fluid with an immunoassay technique that could detect more accurate biomarkers for specific Cancer could significantly advance cancer diagnosis at its early stage.

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Authors' Contributions
A.N. conceived, drafted and edited the manuscript. M.S.A. and M.R. reviewed the manuscript. All authors contributed to the critical reading and discussion of the manuscript. All authors have read and agreed to the published version of the manuscript.

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