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Conventional Cancer Diagnostic Tools in the Modern Times: A Review

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ABSTRACT: Cancer is among the leading causes of mortality worldwide. Due to the high chances of late discovery, which occurs in later stages, is considered fatal. It is one of the most significant health threats of the twenty-first century since it has no boundaries and may harm any human organ in any location. Various factors leading to cancer are intake of alcohol, tobacco, overweight, less physical workout, etc. Since it is a highly fatal disease, the earlier it is detected, the more are the chances of survival of the patient. For the same, many conventional techniques exist to detect cancer at earlier stages. Some of these techniques are computed tomography (CT), molecular resonance imaging (MRI), X-ray techniques, positron emission tomography (PET), ultrasonography, etc. These conventional techniques are cost-effective, time-efficient, and yield good results, though they have some fundamental limitations associated with dynamics of tumor growth and metastasis timing which impose as challenge for earlier detection. This review aims to provide the insight about different conventional approaches for prognosis of cancer in detail with their pros and cons.

Keywords: Cancer, Computed tomography (CT), MRI, PET.

INTRODUCTION

Cancer is one of the leading causes of mortality worldwide, and it is considered very lethal. The term "Cancer" was first introduced in 370 BC by Hippocrates, who proclaimed them to abnormal growing cells because of the genetic alteration (Lukong, 2017). Due to the high prevalence of late detection, generally in advanced stages (Sharma *et al*., 2019; Dhanjal *et al*., 2021). This is why patients with cancer are left devoid of curative therapy (Sutradhar & Amin 2014). According to WHO, approximately 10 million fatalities were expected in 2020 due to cancer, accounting for roughly one in every six deaths (Geeitha and Thangamani 2020). Breast, lung, colon, rectum, and prostate cancers are the most frequent malignancies. Obesity, tobacco and alcohol use, fewer vegetables and fruits in diet, and a sedentary lifestyle constitute almost 33 percent of cancer causes and fatalities (Key *et al*., 2004; Daphal *et al*., 2012; Somani *et al*., 2021). Decades of biomedical research in affluent countries have yielded a slew of excellent cancer prevention and treatment options. Hepatitis B vaccination for liver cancer, cervical cancer screening methods, mammography for breast cancer, surgical prophylaxis, and a fecal occult blood test for colorectal cancer patients at high risk of colorectal cancer are just a few examples (Danaei *et al*., 2005). Cancer is one of the most severe health challenges of the twenty-first century, as it has no bounds and may damage any organ of humans in any location (Bharali & Mousa 2010; Satija *et al*., 2021a; 2021b). Although cancer can be challenging to diagnose, in some cases, the sooner it is identified, the higher the odds of successfully treating it (Sutradhar & Amin 2014). For this purpose, primarily, many conventional techniques come into play to detect cancer malignancies at early stages (Chopra *et al*., 2021; Singh *et al*., 2021). The most common term for such methods is "oncology screening, " further categorized under two different approaches, namely, anatomical-based and functional-based (Rembielak *et al*., 2008; Sharma *et al*., 2012). The former includes ultrasound, molecular resonance imaging (MRI), X-ray-based techniques, and computed tomography (CT) (Karpuz *et al*., 2018). The latter or the functional-based imaging techniques, on the other, include sentinel node mapping, positron emission tomography (PET), radionuclide imaging, single-photon emission tomography (SPECT), functional molecular resonance imaging, molecular resonance spectroscopy, and hybrid imaging, such as PET-CT, SPECT-CT, etc. (Rembielak

et al., 2008, 2011, 2016; Sharma *et al*., 2012). Among these, MRI is considered one of the best imaging techniques. The images of hydrogen atoms are captured in this method, which reflects the response of hydrogen nuclei to radiofrequency radiation and results in high-resolution 3D images (Antoch & Bockisch 2009; Bu *et al*., 2012; Chen *et al*., 2015; Jakhmola *et al*., 2012; Ratzinger *et al*., 2010). In ultrasonography, high-frequency sounds are used to look at the tissues and organs inside the body and require no radiation exposure (Haber, 2000; Puylaert *et al*., 2010; Sharma *et al*., 2012). A PET scanner's fundamental mechanism is to detect photons released by a positron destructing a neighbouring electron (Luna *et al*., 2014; Malla *et al*., 2020). It is quite easy to obtain high resolution virtual 3D images with X-ray computed tomography. It's a hybrid of multi-plane X-ray pictures with high-resolution image reconstruction methods (Histed *et al*., 2012; Luna *et al*., 2014).Although these traditional approaches are cost-effective and yield good results, they have several inherent flaws such as limited tissue penetration depth, low specificity, low spatial resolution, and low sensitivity that may even result in false negatives (Lopci & Fanti, 2013; Rembielak *et al*., 2008, 2016; Sciallero *et al*., 2016). The primary aim of the early detection is to detect the smallest possible tumour cells number, preferably prior to initiation of angiogenic switch (Barba *et al*., 2021). This review intends to summarize various conventional diagnostic techniques for the early detection of cancers. The study also highlights the multiple advantages of one method over the other and their limitations. A short glimpse of the upcoming field of nanotechnology has also been mentioned, which has the potential to overcome the limitations of these conventional methods.

Magnetic Resonance Imaging (MRI): MRI is a non-invasive imaging technique. It is the anatomical imaging approach. It is one of the most powerful diagnostic imaging technologies available, and it has also been widely employed in preclinical research investigations (Haris *et al*., 2015; Thompson *et al*., 2013). It works because atomic nuclei absorb radiofrequency energy in a strong magnetic field. It then sends them out as radio waves, which can be picked up and rebuilt into 3-D pictures (Rifki, 1990; Thompson *et al*., 2013). MRI primarily provides morphological information about the tumour and probable metastases. When screening lymph nodes for metastatic dissemination, their use is usually limited by a lack of helpful information (Haberkorn & Schoenberg, 2001). MRI uses the proton relaxation processes of water in biological systems to deliver pathological and physiological details about living tissue. Because most forms of tissue in the human body are plentiful in hydrogen protons, they will align themselves along the magnetic field lines in a strong magnetic field (Sciallero *et al*., 2016; Sharma *et al*., 2012). A supplemental magnetic field is then used to align the protons' axes. After shutting down the pulse, the protons relax and revert to their natural state. A little radiofrequency signal is released as a result of this, and they resonate (Sharma *et al*., 2012). The images are so exact and multiplanar that they frequently reveal enough detail to see the tissues firsthand. As a result, the use of MRI may limit the number of diagnostic procedures required of a patient (Sharma *et al*., 2012). Scans are perfect for displaying soft tissue structures like ligaments, cartilage, and organs like the heart, brain, and eyes. MRI does not utilize ionizing radiation, and the magnetic fields it employs are not known to be dangerous. Hence it does not give exposure to harmful radiation to patients (Pang & Membrey 2017). The capacity of MRI to identify the higher grade and volume tumours selectively is essential because it might prevent over-detection of inconsequential cancer if used to guide biopsy or select men for biopsy, as well as be utilized in active surveillance for selection as well as monitoring (Thompson *et al*., 2013). In the case of brain tumours, MRI provides higher soft-tissue contrast than conventional cross-sectional imaging modalities, allowing for more accurate detection of mildly infiltrated or damaged parenchymal architecture (Antoch & Bockisch 2009; Smirniotopoulos *et al*., 2007). MRI is the preferred examination method over CT for lung tumour diagnosis. Furthermore, MRI is an excellent tool for determining the extent of Pancoast (superior sulcus) tumours (Radiologists., 2014). Because it can show muscle wall invasion or penetration, MRI is better than CT scanning for staging bladder cancer. Its multiplanar imaging capability further detects tumour involvement in nearby organs. It is the preferred imaging technique for patients who are candidates for harsh treatment (*i.e*., cystectomy or radical radiation). On the other hand, CT of the abdomen and pelvis is appropriate for staging in patients who are not candidates for drastic therapy or who have a clinical suspicion of locally advanced or metastatic illness. Because MRI scanners are relatively costly, the number of scanners available is restricted. There can be a setback in an MRI scan for non-urgent diseases. As coughing or swallowing might make the resultant pictures less clear, MRI scanners are inappropriate for studying conditions such as mouth tumours (Pang & Membrey, 2017). Geometric distortions in MRI images can occur due to differences in magnetic field strength (Evans, 2008). MRI is distinguished by much lengthier examination periods. The imaging methodology heavily influences the examination time (number and type of sequences). A whole-body MR-scan evaluation typically takes between 20 and 60 minutes. Sensitivity to pulmonary lesions is reduced. However, new MR scanning settings are being implemented to address the issue. It is now

feasible to detect pulmonary abnormalities as small as 3 mm (Antoch & Bockisch 2009).

Computed Tomography (CT): Computed Tomography scanning (CT-scan) has been utilized as an essential diagnostic tool for imaging, with billions of examinations done every day all around the globe (Fleischmann & Boas, 2011). It comes under anatomical-based methods and is of substantial value in detecting the amount and volume of tumours that can otherwise be difficult to visualize through other techniques available (Elkon *et al*., 1981; Rembielak *et al*., 2011). CT-scanning has also been observed as a morphological alternative for hybrid imaging systems. It mainly provides information regarding the morphology of the tumour and the possible metastatic behaviour (Antoch & Bockisch 2009). It has helped in the imaging and has also contributed to therapy after diagnosis as a follow-up to the tumours (Elkon *et al*., 1981). Nowadays, CT-scan and X-rays have come into great use following advancements in cancer diagnosis methods. The affordable nature, high resolution, and fast acquirement of computed tomography images have added to its applications with X-rays leading to three-dimensional imaging with high resolution (Barkan *et al*., 2018; Histed *et al*., 2012). Image-guided radiation treatment is a CT-based radiotherapy technique that allows the target to be precisely positioned without causing injury to the neighbouring tissues (Sharma *et al*., 2012). CT is a significant step in identifying liver cancer and scanning the entire liver to detect the presence of any lesion with the use of X-ray contrast agents, which can be administered intravenously and orally (Cao *et al*., 2015; Moghadam, 2017). Although CT is effective for capturing crude anatomical details, its poor contrast and usage of ionizing radiation can misidentify benign and malignant tumours and provide no information on lesions' metabolic activities. Furthermore, it has been noted that it is not always successful in finding metastatic lymph nodes (Histed *et al*., 2012; Luna *et al*., 2014). Many new hybrid methodologies have been developed to overcome the shortcomings of the CTscan, including the involvement of contrast agents and nanoparticles (Barkan *et al*., 2018). To detect lung cancer, increasing radiation exposure leads to better imaging quality and puts the human body at risk due to the high X-ray amount. Hence, the amount is reduced, affecting lung imaging quality (Mahersia *et al*., 2015). CT has been integrated with PET (Positron Emission Tomography) in recent times due to their compatible nature and high resolution with proper localization of tumours. It involves the characteristics of both PET and CT, taking the benefit of spatial resolution from CT and metabolic sensitivity from PET (Barkan *et al*., 2018; Griffeth, 2005).

Positron Emission Tomography (PET). As a clinical modality, Positron emission tomography (PET) has emerged as a viable option for distant assessment and reassessment of a wide range of malignancies. Systemic administration of tracer amounts of radiolabeled therapeutics that are selective and specific for the target of interest is required (Goel *et al*., 2017). Positron emission tomography (PET) has emerged as a valuable technique in gynecologic oncology. A PET-based metabolic biopsy may aid in assessing when pathology is unavailable or the lesion cannot be established by pathology. Compared to CT or MRI, PET in ovarian cancer has been seen as a viable method in diagnosing recurrent ovarian cancer (Chou *et al*., 2017). A PET scan for diagnosis implies the staging and therapeutic strategic approach. It enables even more reliable confined for adenocarcinomas imaging, attributed to its improved capacity to determine, based on inter nodular cancer for the administration of chemotherapy management and identification of disseminated tumours not detected by traditional imaging (Vokes *et al*., 2018). As a result, PET might be applied to make prognostic predictions for non-small cell lung cancer (NSCLC) patients (Pu *et al*., 2021). Early identification and precise tumour staging with the use of FDG in positron emission tomography might help detect precursor (pancreatic intraepithelial neoplasms) lesions of pancreatic cancer (PC) and increase survival rates (Sánchez-Bueno *et al*., 2016). PET is a nuclear oncology screening that includes F18-fluoro-2-deoxy-D-glucose (FDG) as a marker and is effective for disease staging. It utilizes a scintillation detector to examine the adsorption of FDG into different tissues qualitatively and quantitatively (Raman *et al*., 2015). FDG, a carbohydrate analogue specifically absorbed by quickly metabolizing cells, is the most extensively used PET tracer, and it has been clinically authorized for distant staging (Heusch *et al*., 2014). Although glucose metabolism seems exclusive to cancer cells, FDG imaging can be counterproductive in some circumstances (Goel *et al*., 2017). The Positron emission tomography deciphers with the help of fluoro-2 deoxy-glucose have been demonstrated to be an effective as well as a helpful approach to lung cancer in the clinical diagnosis and administration, based on the effectiveness in diagnosing and assessing response for anti-cancer or cancer prevention (Ghadiri-Sani *et al*., 2016). PET has several shortcomings, including being inadequate for determining local tumour progression and vascular participation while not being regarded as a viable first-line scan for detecting a primary pancreatic cancer. On the other hand, the absence of FDG intake and sensitivity in tiny lesions < 1 cm in size does not always imply benignity. But they're still an intriguing possibility for distant assessment, with some research indicating that they can assist in detecting distant metastases (Raman e*t al*., 2015).

Ultrasound Imaging (USI). Also known as ultrasonography or sonogram, it is a quick, pain-free, and safe method involving no special preparation and

allows easy monitoring of the target organ (Zhou, 2013). It uses high-frequency sound waves and detects images that cannot be visualized through X-rays involving zero exposure to any kind of radiation. It is also an inexpensive technique compared to MRI, CT, PET, or X-rays with high soft-tissue resolution (Rembielak *et al*., 2011; Sharma *et al*., 2012). Though ultrasound cannot distinguish between a benign and a malignant tumour, it can identify small lesions present in the soft tissues without the use of any staining in the living tissue (Wang & Yang, 2021). It can detect morphological changes in the tissue and perform tomographic imaging of the specific organs with crisp localization, leading to finding carcinogenic lesions easier (H. Zhou *et al*., 2021). Ultrasound of the abdomen and the lower abdomen demands the urinary bladder to be almost complete as sound waves (known as Doppler ultrasound) travel better in the fluid environment leading to better detection of the gynaecologicaltumours, cysts, or metastatic lesions present in the organs (Fischerova, 2011; Wang & Yang, 2021). It is usually beneficial for superficial organs like the breast and thyroid and is also used when mammography fails to visualize the dense breast tissues (Barkan *et al*., 2018; Sharma *et al*., 2012). Types of ultrasonography include endoscopic ultrasonography, endovaginal ultrasonography, abdominal ultrasonography, endorectal ultrasonography as well as transrectal ultrasonography, which are used for the determination of pancreatic cancer, the thickness of the endometrium, liver lesions, rectal tumors, and prostate cancer respectively (Anastasio & La Riviere 2012; Barkan *et al*., 2018; Minnard *et al*., 1998; Shafford *et al*., 1999). However, whole-body imaging remains an issue as it is only applicable to soft tissues, and visualization of hard tissues cannot be done and is limited to the vasculature. Furthermore, visualizing structures with a certain depth and the test's dependency on the operator pose issues (Barkan *et al*., 2018).

Fluorescence Imaging (FI). Fluorescence imaging is a non-invasive imaging method that can visualize biological processes in a living organism. Fluorescence is a type of luminescence that occurs when matter absorbs electromagnetic energy and emits light of a specific wavelength. Fluorophores are molecules that re-emit light after being exposed to it (Hu *et al*., 2019; Sirbu *et al*., 2019). In oncology, fluorescence imaging (FI) is quite promising for the diagnosis of cancerous cells. To enhance the identification of early neoplasia based on molecular markers, fluorescence imaging (FI) for cancer cell targeting employs several optical imaging methods. The objective of cancer imaging should be to discover or image as few tumour cells as possible, ideally before the angiogenic switch occurs (Frangioni, 2008). Compared to currently existing approaches, FI may help detect malignant lesions with greater specificity and sensitivity. Furthermore, FI may offer a less intrusive and cost-effective method of detecting malignant and pre-cancerous tumours. Other imaging methods have been recently reported for the non-invasive longitudinal detection of small micrometastases and single cancer cells in a mouse brain (Naumov *et al*., 2006). The capacity to detect lesions sooner than traditional approaches will result in improved treatment results and lower treatment costs since it will eliminate the requirement for multimodality care, which is essential for individuals diagnosed at advanced presentation (Tipirneni *et al*., 2017). FIS (fluorescence imaging system), setup and apparatus-wise, is portable equipment that allows for real-time quantitative fluorescent imaging. An infrared camera and an amplifier are included in the system. Fluorescence picture acquisition is secured by a captor, which filters the light so that only near-infrared wavelengths can be observed. At the same time,a laser provides fluorescence excitation (LED generating an infrared radiance) across the operating area. It is not necessary to sanitize the camera or the cable. (Rossi *et al*., 2018) Because of the distance of the connection, the amplifier and the screen are far enough apart that a nonsterile individual may carry the IR camera (infrared) above the sterilized operating field. Five fluorescent imaging technologies are currently available in this modern era for cancer diagnosis. High-resolution microendoscopy, in short, is also stated as the HRME technique. Here all the fluorescent methods work on the intensity of their penetration depth. So, HRME shows a 50 µm depth, which gives a high-resolution result. Further, it has some limitations, like it only applies to the mucosa on the surface and shows applications like Handheld fluorescence imaging (Joshi *et al*., 2016). Optical coherence tomography (OCT) gives penetration depth up to 3mm and shows limitations like stability and sterility issues, problems with reproducibility, and suboptimal resolution. The results rely enormously on the operator and its applications, like fluorescence imaging during surgery and fluorescence imaging using a handheld device (Joshi *et al*., 2016). The autofluorescence technique shows up to 5mm depth of penetration, which decreases the specificity. This can also be visualized in this technique as limitations like high background and low specificity. Its usefulness can be seen in applications like fluorescence imaging using a handheld device and fluorescence imaging during surgery (Tipirneni *et al*., 2017). Near-infrared imaging, which is also known as NIR imaging this technique show depth of penetration up to 10 mm it has improved factors in its specificity but shows limitations like Depth penetration has improved, Reduced autofluorescence in the background and become specific to the tumour, and has increment in application along with the previous application it also has endoscopic fluorescence imaging and Fluorescent lymphoscintigraphy (Joshi *et al*., 2016). Photoacoustic

imaging is the last technique in the series of five fluorescence techniques which shows penetration depth around 3 to 20 mm it has limitations of improved depth penetration. Still, it has a similar field of application to intraoperative fluorescence imaging and fluorescent lymphoscintigraphy (Tipirneni *et al*., 2017). As seen above, these conventional methods are good tools for cancer diagnosis, but only to some extent. This boundary is formed by the intrinsic limitations of these diagnostic techniques, such as low specificity, low sensitivity, etc., which might also result in false results. This can lead to late identification and eventually the patient's death due to delayed detection and treatment. So, to overcome these limitations, nanotechnology is emerging and advancing at an incredible pace. These nanotechnological tools, alone or along with the conventional methods, can entirely change the course of cancer diagnosis, breaking the barriers of traditional techniques. As a result, nanotechnology can make cancer diagnosis cheaper, more reliable and accurate, quick and safe, and more affordable in terms of the maintenance cost of the machinery.

Table 1: Given below mentions the various advantages and disadvantages of the above discussed conventional cancer diagnostic techniques.

Conventional Techniques	Advantages	Disadvantages	References
Magnetic Resonance Imaging (MRI)	• No radiation exposure to the patient • Gives multiplanar imaging • High contrast images • Provides a high-resolution image	• It can't be done for patients with metallic implants and prostheses • High-cost machinery, so fewer machines may be available • Not reliable for studying mouth cancer • Expensive	(Pang & Membrey, 2017; Sharma *et al*., 2012)
Computed Tomography (CT)	• Cost-effective • High-resolution images • It is anatomical imaging • Whole-body imaging is possible with this • Due to radiation, the penetration depth capability is unlimited	• The patient is exposed to ionizing radiation. • It has a poor contrast • No information on the metabolic activities of the tumors	(Barkan *et al*., 2018; Histed *et al*., 2012; Luna *et al*., 2014).
Positron Emission Tomography (PET)	• Whole-body imaging is possible with this • It can be used as a hybrid to get anatomical details by merging with CT or MRI • Due to radiation, the penetration depth capability is unlimited	• Expensive • The patient is exposed to radiation • Unable to determine local tumor progression. • It has a low spatial resolution	(Goel *et al*., 2017; Chou *et al*., 2017 ;Raman *et al*., 2015;Ghadiri-Sani *et al*., 2016).
Ultrasound Imaging (USI)	• No radiation exposure to the patient • Quick and safe • Cost-effective • High-resolution images of soft tissues • Small lesions can be detected without staining • Highly effective for superficial organs	• Only limited to soft tissues. • Whole-body imaging remains impossible • Limited penetration depth • Accuracy depends on the operator • Cannot differentiate between benign and malignant tumours	(Barkan *et al*., 2018; Rembielak *et al*., 2011; Sharma *et al*., 2012; Zhou, 2013)
Fluorescence Imaging (FI)	• No radiation exposure to the patient. • Higher sensitivity to malignant lesions. • Cost-efficient.	• The quality of the result depends on the operator. • Low specificity. • High background.	(Naumov *et al*., 2006; Tipirneni *et al*., 2017)

CONCLUSION AND FUTURE SCOPE

This study summarizes current advances in using conventional diagnostic tools for cancer diagnosis. This may be performed by employing a variety of imaging techniques based on various concepts, ranging from anatomical to functional, each with its own set of flaws and strengths. It will be easier to deal with cancer if it is detected early on. As a result, oncology imaging is an integral part of cancer treatment. Several studies have been conducted in the last few years to create diagnostic tools for the detection of cancer, like magnetic resonance imaging which uses nuclear magnetic resonance (NMR) to visualize cancer cells; computed tomography uses x-rays that allow for three-dimensional imaging with excellent resolution., positron emission tomography which is a type of nuclear oncology screening that contains the marker F-18 fluoro 2 deoxyglucose (FDG) and is useful for

disease staging, ultrasound imaging that employs high-frequency sound waves to identify pictures that can't be seen with X-rays while posing no risk of radiation exposure, fluorescence imaging, a non-invasive imaging technique for observing biological processes in living organisms. This article briefly provides a quick overview of the most common imaging methods currently in use, their advantages and their limitations. With the advancement of technology, many new and better imaging techniques are expected to be discovered. Furthermore, progressive development in the field of nanotechnology is showing broad range of application and can also be utilized in the detection approaches to overcome the limitation of conventional detection techniques.

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