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MEDICAL IMAGING IN THE DETECTION OF CANCER

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Abstract

Biomedical imaging is playing an important role in all phases of cancer management including screening, staging, monitoring of treatment, and in long term surveillance of cancer patients. Imaging forms an essential part of cancer clinical protocols and is able to furnish morphological, structural, metabolic and functional information. Early detection of cancer through screening based on imaging is probably the major contributor to a reduction in mortality for certain cancers. Imaging techniques currently available or in development for the diagnosis, staging and surgical treatment of cancers include US (ultrasound), CT (Computed Tomography), MRI (Magnetic Resonance Imaging), PET (Positron Emission Tomography) and optical imaging. In recent years, the major advances in imaging and the combination of molecular biology and the imaging sciences have merged into a new research field named 'molecular imaging'. It includes all imaging modalities which include PET-CT, PET- MRI and optical imaging.

Introduction

Biomedical imaging is the main pillars of comprehensive cancer care. It has many advantages including real time monitoring, accessibility without tissue destruction, minimal or no invasiveness. The early detec¬tion of cancer, its prognosis and detailed information about the extent of the disease wouldn't be available to patients without medical imaging. Biomedical imaging is playing an important role in all phases of cancer management including screening, staging, monitoring of treatment, and in long term surveillance of cancer patients.

Over the past decades, substantial efforts have been made to detect malignancies at an earlier state. Imaging plays a major role in the detection of cancer as it provides a detailed insight into the exact location and extent of the disease. Much of the progress made in cancer diagnostics and staging can be attributed to technical advances in ultrasonography (US), computed tomography (CT) and magnetic resonance imaging (MRI) which are essential for providing anatomic details for solid cancers [1]. Imaging plays a major role in the detection of cancer as it provides a detailed insight into the exact location and extent of the disease. It can also provide detailed information about structural or cancer-related changes. Molecular imaging techniques may very well have the potential to improve every aspect of cancer care by opening up entirely new possibilities for the early detection and the effective treatment of cancer, both of which are essential to successfully fight the disease [2]. Currently molecular imaging strategies for whole body imaging modalities for cancer diagnosis and staging in cancer surgery are being developed [3, 4]. While differentiation between benign and malignant tumors on conventional CT and MR scans based on morphologic characteristics can be difficult, molecular imaging allows for a much better assessment of aggressiveness because functional properties of malignant cells are visualized [5]. A very promising set of imaging techniques are available to radiologists through the methods of molecular imaging, which differs from traditional imaging in that bio-marker probes are used to target specific areas or suspicious findings. Molecular imaging in general is an extremely promising field, which benefits all the stages of cancer management where images are involved, i.e., diagnosis, staging, treatment evaluation, and follow-up. The most important feature of these tests is that they combine, in a single scan, morphological (anatomical), physiological (functional) and metabolic information. One of the most promising molecular imaging techniques is positron emission tomography (PET), which is most often combined with CT (PET-CT) and used to track probes in order to detect metastatic disease. Compared to PET-CT, PET-MR provides a better background image with improved soft tissue contrast without radiation exposure.

Ideally, molecular imaging probes will allow for earlier diagnostic imaging of solid cancers as well as facilitating better surgical treatment in the future, leading to an overall improved outcome. This review aims to outline relevant molecular imaging applications currently available or in development for the diagnosis, staging (US, CT, MRI, and PET) and surgical treatment of cancers.

Ultrasound

An ultrasound scan, also referred to as a sonogram, diagnostic sonography, and ultrasonography, is a device that uses high-frequency sound waves to create images of the inside of the body. Ultrasound is safe and painless, and produces pictures of the inside of the body using sound waves.

Ultrasound (US) imaging technology is based on the detection of reflected sound pulses. The pulses are generated by a transducer and propagate into tissue where they are reflected in patterns depending on the tissues' density and compressibility [6]. The transducer collects the sounds that bounce back and a computer then uses those sound waves to create an image. Conventional ultrasound displays the images in thin, flat sections of the body. Advancements in ultrasound technology include three-dimensional (3-D) ultrasound that formats the sound wave data into 3-D images. Doppler ultrasound is a special ultrasound technique that allows the physician to see and evaluate blood flow through arteries and veins in the abdomen, arms, legs, neck and/or brain (in infants and children) or within various body organs such as the liver or kidneys.

High intensity focused ultrasound (HIFU) is used to rapidly heat and destroy diseased tissue. It is a type of therapeutic ultrasound that induces hyperthermia within a time frame of a second. It should not be confused with traditional hyperthermia that heats over a time frame of an hour and to much lower therapeutic temperatures (generally <450C). When an acoustic wave propagates through tissue, part of it is absorbed and converted to heat. With focused beams, a very small focus can be achieved deep in tissues. At a high enough temperature, the tissue is thermally coagulated due to protein denaturization.

Current applications

Ultrasound is often one of the "first line" tests in the detection of cancer. It can detect abnormal tissues, growths, and cysts. While it can't diagnose cancer, it can detect the abnormal tissues that may possibly be cancerous. Ultrasound is one of the most common diagnostic imaging methods used in the diagnosis of tumours in the thyroid, breast, prostate, liver, pancreatic, ovarian, uterine and kidney. Ultrasound is frequently used to guide biopsies. Ultrasound examinations of the breast can further evaluate a cyst or lump on the breast to see changes in the tissue. Ultrasound is very useful in both the detection of breast cancer and diagnosis because the doctor can do a "fine needle guided biopsy" to aspirate some of the tissue. In cases of pancreatitis and severe upper abdominal pain, an ultrasound can detect the presence of cysts or pseudocysts on the pancreas. An ultrasound can check for cysts on the liver and help differentiate cysts from fatty liver disease or cirrhosis. Cysts and tumors within the bladder can usually be seen very clearly. Ultrasounds can be used to monitor ovarian cysts for changes that may turn into ovarian cancer. High intensity focused ultrasound ablation of prostate cancer have been extensively evaluated [7].

A noninvasive technology platform for gene delivery which combines ultrasound with tumor-targeted microbubbles into breast cancer cells was developed an international research team led by Dr. Tali Ilovitsh. Once the ultrasound is initiated, the microbubbles explode like smart and targeted warheads, creating holes in cancer cells' membranes, allowing gene delivery [8].

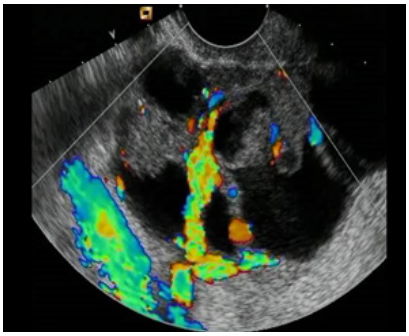

Fig.1. Ovarian cancer diagnosis using ultrasound which detect malignant adnexal masses better than MRI. Adapted from AMP Medical daily by Stephanie Castillo on Tuesday, January 19, 2016-10:50 [9].

Advantages and limitations

US has many advantageous qualities including high spatial and temporal resolution, real time imaging, lack of radiation, portability and low cost [10], so there has been significant effort to develop molecularly targeted probes for this modality. Ultrasound examinations do not use ionizing radiation (as used in X-rays), thus there is no radiation exposure to the patient. Because ultrasound images are captured in real-time, they can show the structure and movement of the body's internal organs, as well as blood flowing through blood vessels. Ultrasound waves are disrupted by air or gas; therefore ultrasound is not an ideal imaging technique for air-filled bowel or organs obscured by the bowel. HIFU approaches the criteria for optimized treatment of localized cancer as, due to the very sharp temperature profile, it can cause complete cell death in tumours without harming nearby healthy tissue.

Computed tomography

Computed tomography is the most important imaging technique in detecting and diagnosing cancer. It uses X-rays to obtain images through slices of the body area. CT generates three dimensional reconstructions of patient anatomy based on differences in X-ray attenuation [11]. It is based on the principle that when X-rays pass through the body they are absorbed or attenuated at differing levels, according to the density and atomic number of the different tissues, creating a matrix or profile of X-ray beams of different strength. This X-ray profile is registered on a detector, thus creating an image. The resulting 3D CT images allow medical physicists and radiation oncologists to visualize tumour masses in three dimensions, which help them plan the treatment.

Current applications

CT can be used to image lung tumors and bone metastasis, given its fast imaging time and high spatial resolution. Image-guided surgery based on preoperative CT and MRI has become popular especially in brain surgery, and is widely used for the resection of brain tumours. Planning of radiation therapy is also based on CT images, so that the tumour receives sufficient doses of radiation while controlling the dosage to preserve critical organs.

COVID-19 causes severe respiratory distress (ARDS) therefore chest computed tomography (CT) is strongly recommended in suspected COVID-19 cases, for both initial evaluation and follow-up. and have great significance in monitoring disease progression and evaluating therapeutic efficacy. Recent studies have shown the importance of chest CT examination in COVID-19 patients with false-negative RT-PCR results and reported the CT sensitivity as 98% [12].

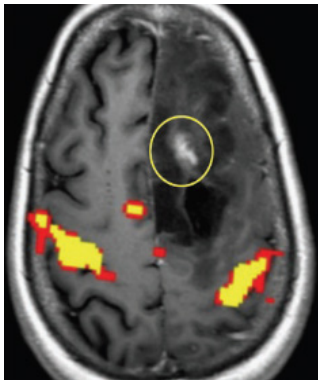

Fig.2. A 2-dimensional image of a brain tumour which allows the neurosurgeon to assess the relationship between the tumour and the motor cortex and plan a safer operation. Adapted from Making Cancer Visible: the Role of Imaging in Oncology. IDOR, 2012 [13].

Advantages and limitations

Due to its speed, high spatial resolution12 – 50 μm [14], and relative cost-effectiveness, CT is the most commonly used imaging technique in cancer diagnosis today to detect morphological abnormalities. However, current CT technology has some limitations which make it a less than ideal application for molecular probes for the detection of solid cancers. CT has relatively low soft tissue contrast for tumors and surrounding tissue, but with iodinated contrast agents. These agents work by blocking X-rays, thereby providing contrast and enhancing a part of the body. Iodine-based contrast agents produce side effects, such as vomiting, itching, and anaphylactic shock. CT contrast agents do not have amplification ability, therefore a large amount of heavy molecules is required to achieve satisfactory sensitivity, raising toxicity concerns and so far limiting the development of iodine based CT molecular imaging probes for cancer. More recently, the emergence of nanomaterials has revealed new possibilities for imaging cancer with targeted molecular imaging probes for CT. For example, bismuth sulfide nanoparticles provide more enhanced sensitivity than iodine based probes because of their higher atomic number while at the same time overcoming some additional limitations of iodine based contrast agents, such as their rapid excretion [15]. CT imaging involves the use of X-rays, which are a form of ionizing radiation. Exposure to ionizing radiation is known to increase the risk of cancer. The radiation dose of CT, however, is not negligible and this limits repeated imaging in human studies due to health risks [16].

Magnetic resonance imaging (MRI)

Magnetic resonance imaging (MRI) is a non-ionizing technique with full three dimensional capabilities, excellent soft-tissue contrast, and high spatial resolution (about 1mm). The use of MRI to visualize morphological alterations rests on its ability to detect changes in proton density and magnetic spin relaxation times, which are characteristic of the environment presented by the diseased tissue.

MRI technology is based in principle on creating a magnetic field surrounding the patient which aligns magnetic dipoles such as hydrogen atoms in water. During the examination, a radio signal is turned on and off, and subsequently the energy that is absorbed by different atoms in the body is echoed or reflected back out of the body. After a temporary radiofrequency pulse changes the alignment of the dipoles they return to their baseline orientation at a rate which is determined by their physiochemical environment and which is detected and translated into a MR signal [17, 18]. These echoes are continuously measured by the MR scanner and a digital computer reconstructs these echoes into images. Superparamagnetic iron oxide nanoparticles (SPIONs) have proven to be highly effective contrast agents for the magnetic resonance imaging diagnosis of solid tumors. Magnetic iron oxide (IO) nanoparticles with a long blood retention time, biodegradability and low toxicity have emerged as one of the primary nanomaterials for biomedical applications in vitro and in vivo. Superparamagnetic iron oxide nanoparticles (SPIO) used today can be conjugated with specific targeting ligands and serve as molecular imaging probes [19]. SPIOs have a polymer coating which may be modified to specifically target receptor molecules or proteins [20]. They have been successfully used to detect lymph node metastases in prostate cancer [21, 22]. Imaging tumor cells with SPIOs faces some challenges because the nanoparticles tend to remain in the vasculature and are metabolized by the reticuloendothelial system. Nevertheless, studies with SPIOs have shown success targeting malignant cells expressing elevated levels of transferrin receptors [23] and especially folate receptors [24, 25], which are overexpressed on certain types of cancer, such as ovarian and breast cancers [26, 27].

Current applications

Magnetic resonance imaging (MRI) has improved sensitivity for soft tissue and subtle metastases in brain, liver, and pelvic structures and is used as a problem solving tool in cancer diagnosis and imaging. MRI uses magnetic fields with radiofrequency pulses to produce computer images based on stimulating water molecules in the body. MRI is considered the best imaging modality for soft tissue pathology. MRI is ideal for evaluating prostate cancer, gynecological cancers, hepatocellular cancer and liver metastases, renal cell carcinoma, pancreatic adenocarcinoma, soft tissue sarcomas, certain primary bone cancers, multiple myeloma, malignant melanoma, and other malignancies [28]. Background Whole-body magnetic resonance imaging (WB-MRI) has become established for the management of patients with multiple epithelial and non-epithelial cancers, and recently its use has been extended to early cancer detection The earlier detection and appropriate targeted interventions can modify the risk of disease development and so promote precision health. Thereafter, highly specific imaging tests such as WB-MRI are used for the detection and diagnosis of malignant tumours [29].

Advantages and limitations

MRI offers high spatial resolution and excellent anatomical detail without any exposure to radiation for the patient making it an essential modality for the detection of solid cancers. MRI is useful in detecting brain and bone metastasis. MRI is an excellent anatomical imaging technique, but it is incapable of measuring molecular events such as protease activity and gene expression. In some situations however, MRI is not recommended, for instance in patients with a pacemaker or other metallic implant, because of the magnetic field used during the examination.

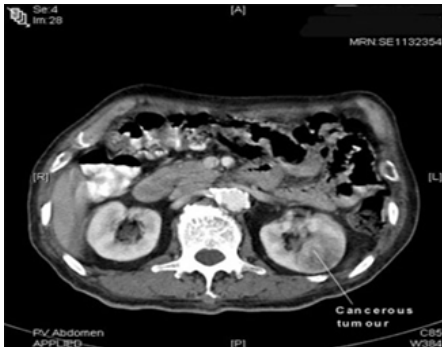

Fig.3. CT scan of kidney cancer. Adapted from Cancer, Continence & Robotics Surgery by Dr. Chin Chong Min [30].

Positron emission tomography (PET)

PET is a highly sensitive, minimally-invasive technology that is ideally suited for pre-clinical and clinical imaging of cancer biology. By using radioactive tracers, three dimensional images can be reconstructed to show the concentration and locations of metabolic molecules of interest. PET is an espe¬cially sensitive imaging tool, which relies on the unusually high rate of metabolic activity that occurs in cancer tissue to pro¬duce three-dimensional images of particu¬lar functional processes. The combination of PET with CT or MR provides far superior images, which help the radiologist to accu¬rately localise the active cancer tissue to a particular site or organ.

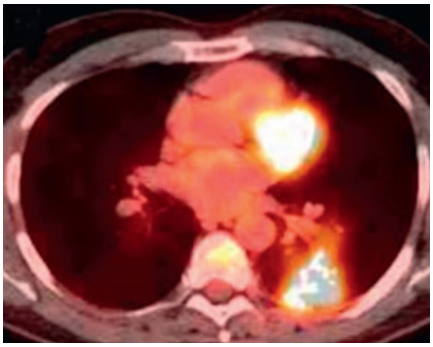

Fig.4. Positron emission tomography (PET) scans are used in the clinic to assist with diagnosis and staging in lung cancer Adapted from The Aspergillus website blog-Pulmonary aspergillus: an alternative to lung cancer after a positive PET scan [31].

Positron emission tomography (PET) scans are a noninvasive imaging modality utilizing positron emitting radioisotopes to label molecules and create different images depending on its tissue concentrations. The most common radiotracer used in oncology is F18 fluorodeoxyglucose (FDG) that is a glucose analog with a half-life of 110 min. When these tiny positive electrons encounter a regular negative electron they form a nuclear reaction emitting two photons of high energy at 1800, annihilation rays, that can be detected by the PET crystal detector. FDG is transported via different glucose transporters into the cell then phosphorylated by hexokinase but further glucose metabolism is prevented by the fluorine atom and FDG is trapped inside the cell. Metabolically active cancer cells use more glucose and express higher levels of glucose transporter (GLUT-1) than normal cells, hence, more FDG is expressed in malignancies [32].

Current applications

Since the study of cancer cells in their normal environment within intact living subjects is essential, PET is ideally suited for monitoring molecular events early in the course of a disease, as well as during pharmacological or radiation therapy. PET scans can be used to look at oncology indications, such as lymphoma, melanoma, lung cancer, colorectal cancer, head and neck cancer, breast cancer, thyroid cancer, esophageal cancer and others. PET is useful in systems biology studies related to bone metabolism and metastasis.

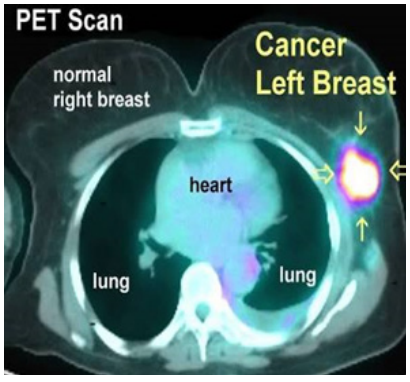

Fig.5. Positron emission tomography (PET) scan of breast cancer. Adapted from About cancer- PET Scans in cancer cases [33].

Advantages and limitations

PET with offers the advantage of providing high tissue resolution, without contrast agents or additional ionizing radiation. This is an important advantage for patients with renal impairment because of superior tissue contrast without imaging agents. It is also an advantage for imaging of the urinary tract, because the high concentration of excreted iodine

contrast agent, which hampers the appropriate attenuation correction with contrast-enhanced CT combined with PET, is avoided.

Unlike computed tomography (CT) or magnetic resonance imaging (MRI), which show anatomic detail, PET images biochemical or physiologic phenomena. Because of this, PET offers substantial advantages over anatomic imaging modalities in oncologic imaging. PET can often distinguish between benign and malignant lesions when CT and MRI cannot. Combining CT and PET may provide a more complete picture of a tumor's location and growth or spread than either test alone. The combined procedure may improve the ability to diagnose cancer, to determine how far a tumor has spread, to plan treatment, and to monitor response to treatment. Combined PET/CT may also reduce the number of additional imaging tests and other procedures a patient needs.

PET imaging alone has several limitations. There is low spatial resolution and difficulty interpreting abnormalities in the setting of physiological FDG uptake in normal anatomical structures, as well as normal variants. In addition, not only does malignancy show abnormal uptake, but other pathological processes including inflammation and infection can also have prominent FDG uptake [34]. Also the degree of malignancy correlates with the intensity of FDG uptake. Highly aggressive tumors have intense uptake while less aggressive tumors such as prostate cancer or low grade lymphoma have only mild uptake. In addition, many benign tumors, most notably thyroid adenomas and benign primary parotid tumors, may have intense focal uptake [35].

To compensate for all these limitations, CT was added to the PET scan to provide both higher sensitivity as well as higher specificity. PET-CT is currently used for initial staging of cancer, evaluating the response to chemotherapy and radiation therapy, provide prognosis, and surveillance of recurrent disease. Combining PET with CT reduces the limitations of PET imaging alone, such as poor spatial resolution and difficulty in differentiating tumour from infection or inflammation. Since functional imaging can provide much faster response than anatomic changes to targeted therapies, PET has been incorporated in development of new cancer drug discovery and has been used in early clinical trial development [36]. However, use of PET-CT has a relatively high radiation exposure level that is often 2–3 times the administered FDG radiation levels depending on the CT protocol used and may lack anatomic details in soft tissue of head and neck and pelvic structures [37]. Similarly, combined PET and MRI is currently being developed [38, 39]. MRI has shown to have higher sensitivity in soft tissue, head and neck pathology, and pelvic disease, as well as, detecting small metastases in the liver and bone compared to CT. Positron emission tomography (PET) can early detect pathophysiological changes in affected tissues in oncological patients, including patients with lung cancer (LC) or pleural tumours (PT) [40]. Combining MRI with PET allows for detection of metastases that may have been missed with current imaging modalities.

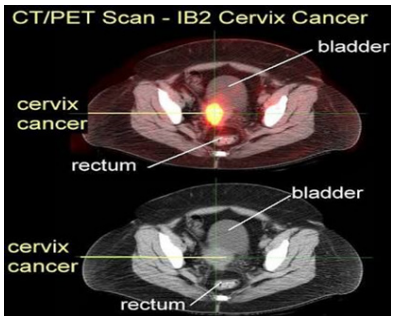

Fig.6. PET-CT scan of cervix cancer. Adapted from: About cancer- PET scans are even better than CT scans [41].

Compared to PET-CT, PET- MRI provides a better background image with improved soft tissue contrast without radiation exposure. Moreover, integration of molecular and functional information generated from PET and MRI could provide useful information in characterizing the cancer. MRI provides high spatial resolution without ionising radiation. MRI is superior to CT for the detection of liver, bone marrow, and CNS lesions [42, 43] and combined PET and MRI may prove better than PET with CT in the diagnosis and management of cancers within these anatomical regions [44-48]. Hybrid imaging utilizing PET-CT and PET-MRI are novel imaging modalities that are changing the current landscape in cancer diagnosis, staging, and treatment response.

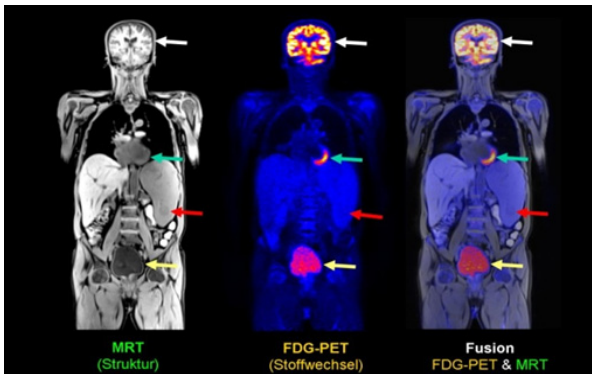

Fig. 7. This MRI scan shows how cancer would grow in the future. Adapted from rediff news October 2014 08:44 IST [49].

PET-MRI has a significant reduction in radiation exposure compared to PET-CT which may benefit younger patients or patients that require frequent repeat PET imaging. MRI offers superior soft tissue resolution compared to CT in rectal and pancreatic cancer. As novel hybrid imaging technology improves, PET-MRI has great potential in the assessment of esophageal cancer, colorectal cancer, stomach cancer, and pancreatic cancer in terms of primary lesion evaluation, nodal involvement, and liver metastases with a high degree of diagnostic accuracy and specificity.

Optical imaging techniques

Optical imaging consists mostly of NIRF (near-infrared fluorescence), reflectance imaging, and bioluminescence imaging. Optical imaging is a novel imaging technique that uses near-infrared (NIR) light to assess optical properties of tissues, and is expected to play an important role in breast cancer detection. The light used in optical imaging is commonly monochromic and in the near-infrared (NIR) range permitting imaging up to several centimeters deep in soft tissue. Different tissue components have unique scattering and absorption characteristics for each wavelength. NIR in the wavelength range of 600–1000 nm is used to allow for sufficient tissue penetration. After passing through the breast, the remaining light is registered by detectors and advanced computer algorithms are used to reconstruct the images [50, 51].

Non-invasive, in-vivo optical imaging with activatable technology can be achieved with near-infrared emission range agents. Such probes include indocyanine-green, the absorption and emission peaks of indocyanine-green (780 nm and 820 nm, respectively) provide adequate tissue penetration for non-invasive imaging and has lower associated autofluorescence. Indocyanine-green-labelled activatable humanised EGFR antibodies, which are approved by FDA, do not fluoresce. However, upon target binding and internalisation by tumour cells expressing HER1 or HER2, the fluorescence intensity of the probe is regained, thus selectively imaging tissues with specific molecular profiles [52].

When fluorescent probes are excited by NIR light, they emit photons at predefined wavelength ranges, detectable by an optical imaging system. Until now, studies have focused on using the intrinsic optical properties of the breast to visualize lesions without the use of fluorescent contrast agents. These studies described higher absorption for carcinomas than for the surrounding parenchyma due to increased blood content associated with angiogenesis [53–56]. In a malignant tumor, hemoglobin concentration is directly related to angiogenesis, the key factor required for tumor growth and metastases [57]. In addition, the proportions of oxy- and deoxyhemoglobin change in such a tumor due to its metabolism [58]. By measuring concentrations of the breast components, discrimination of benign and malignant tumors may be possible with diffuse optical imaging.

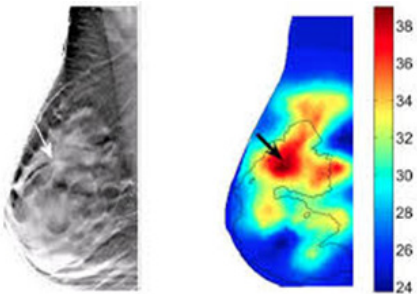

Fig.8. An optical imaging technique help to reduce the number of unnecessary biopsies in breast cancer screening. As shown on the right, the technique reveals the hemoglobin concentrations associated with the formation and growth of tumors. A scan with the X-ray-based technique digital breast tomosynthesis is shown on the left. The arrow in each image points to the 2-cm invasive carcinoma in the breast. Adapted from Athinoula A.Martinos Center for Biomedical imaging - Optical imaging could lead to fewer biopsies in breast cancer screening by Gary Boas February 9, 2015. [59].

Advantages and limitations

A novel optical spectroscopy-based imaging tools can provide real-time imaging of human tissues in vivo to reveal the biochemical and/or molecular information; therefore they could significantly improve the identification of malignancies at curable stages in case of breast cancer [60]. Major advantages of optical imaging are that it does not use any radioactive components (as in PET) which can result in repeated use even in young women, and that its sensitivity is very high (nanomolar to picomolar concentration range) compared to MRI, it is relatively inexpensive, and is easily accessible. However, this technique is still in a very early phase of development. In contrast to X-ray, computed tomography (CT) and positron emission tomography (PET), optical imaging uses no ionizing radiation. Repeated imaging is therefore possible without radiation risks.

Main challenges in optical imaging are depth penetration, signal quantification, and development, validation and approval of relevant imaging agents for human use. Light penetration in tissue is limited, but with the use of near infrared light, and the development of more sensitive detection equipment, penetration in human tissue is now possible up to 15 centimeters deep.

Conclusion

Early detection, accurate staging and complete surgical removal are crucial in order to successfully treat and potentially cure patients with solid cancers. Where cancer is concerned, sooner is always better and this is particularly true in terms of the initial detection of tumours and recurrence following treatment. Hybrid imaging techniques are able to supply complementary information for improved staging and therapy planning. Image guided and targeted minimally invasive therapy has the promise to improve outcome and reduce collateral effects. The most desired improvements in cancer imaging include earlier detection of disease, improved accuracy in molecular characterisation of tumours and the tumour microenvironment, and earlier detection of response to therapy. Molecular imaging and technology like positron emission tomography (PET) could be used more widely to discern the precise metabolism of cancer tumours, giving oncol¬ogists more detailed information regarding the nature of the cancer. The benefits imaging brings to cancer care at present are clear. It allows the physi¬cian, in cooperation with the radiologist, to discern signs of cancer, non-invasively and efficiently. Improvements within the field of medical imaging could have the potential to buy valuable time for patients by pinpointing a possible recurrence earlier than is cur¬rently possible. While this ability by itself makes a huge impact on cancer care, it is constantly developing and new techniques to improve patient care should emerge in the years ahead.

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