Medical
Physics and Technology

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Chapter 1

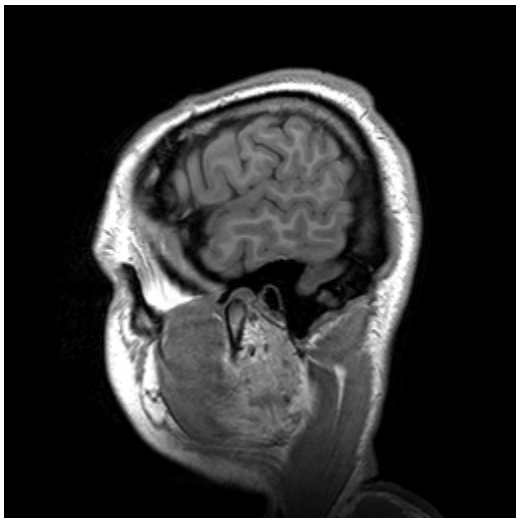
Medical Physics

Medical physics is the application of physics to medicine. It generally concerns physics as applied to medical imaging and radiotherapy, although a **medical physicist** may also work in many other areas of healthcare. A medical physics department may be based in either a hospital or a university and its work is likely to include research, technical development, and clinical healthcare.

Of the large body of medical physicists in academia and clinics, roughly 85% practice or specialize in various forms of therapy, 10% in diagnostic imaging, and 5% in nuclear medicine. Areas of specialty in medical physics however are widely varied in scope and breadth.

==Areas of specialty

Medical imaging



Para-sagittal MRI of the head in a patient with benign familial macrocephaly

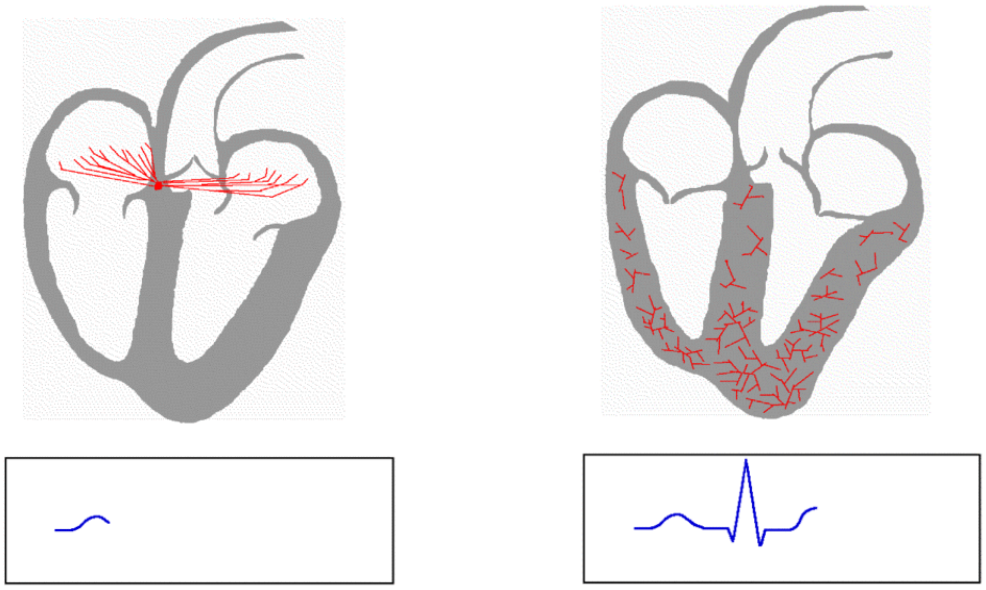
- Diagnostic radiology, including x-rays, fluoroscopy, mammography, dual energy X-ray absorptiometry, angiography and computed tomography
- Ultrasound, including intravascular ultrasound
- Non-ionizing radiation (Lasers, Ultraviolet etc.)

- Nuclear medicine, including single photon emission computed tomography (SPECT) and positron emission tomography (PET)
- Magnetic resonance imaging (MRI), including functional magnetic resonance imaging (fMRI) and other methods for functional neuroimaging of the brain.
    - For example, nuclear magnetic resonance (often referred to as magnetic resonance imaging to avoid the common concerns about radiation), uses the phenomenon of nuclear resonance to image the human body.
- Magnetoencephalography
- Electrical impedance tomography
- Diffuse optical imaging
- Optical coherence tomography

Treatment of disease

- Defibrillation
- Treatment of disease
- High intensity focussed ultrasound, including lithotripsy
- Interventional radiology
- Non-ionising radiation Lasers, Ultraviolet etc. including photodynamic therapy and Lasik
- Nuclear medicine, including unsealed source radiotherapy
- Photomedicine, the use of light to treat and diagnose disease
- Radiotherapy
    - TomoTherapy
    - Cyberknife
    - Gamma knife
    - Proton therapy
    - Brachytherapy
    - Boron Neutron Capture Therapy
- Sealed source radiotherapy
- Terahertz radiation

Physiological measurement techniques



ECG trace

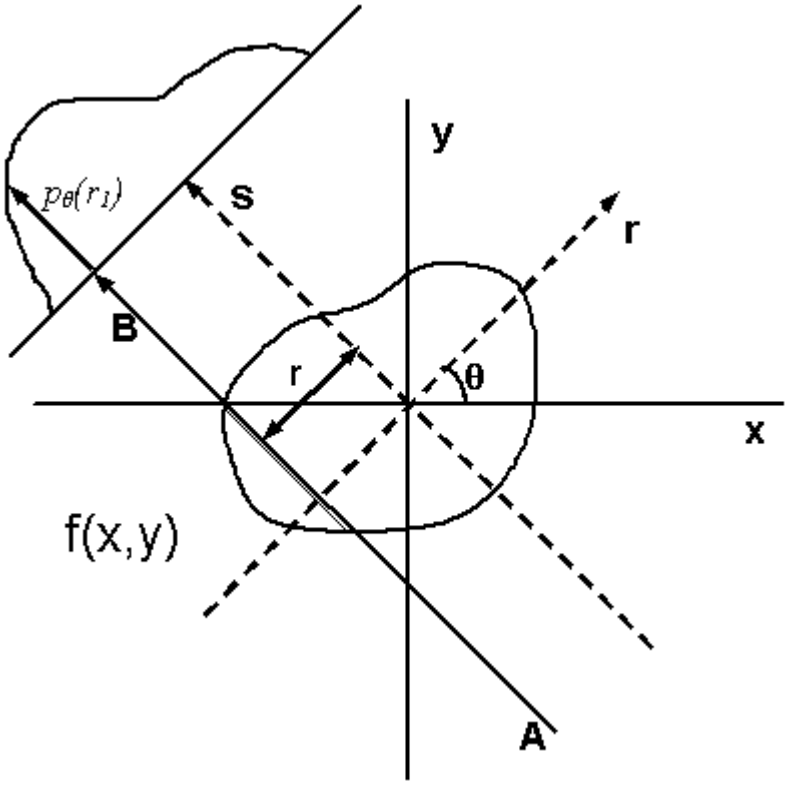
Used to monitor and measure various physiological parameters. Many physiological measurement techniques are non-invasive and can be used in conjunction with, or as an alternative to, other invasive methods.

- Electrocardiography
- electric current
- Electromyography
- Electroencephalography
- Electronystagmography
- Endoscopy
- Medical ultrasonography
- Non-ionising radiation (Lasers, Ultraviolet etc.)
- Near infrared spectroscopy
- Pulse oximetry
- Blood gas monitor
- Blood pressure measurement

Radiation protection

- Background radiation
- Radiation protection
- Dosimetry
- Health Physics
- Radiological Protection of Patients

Medical computing and mathematics



CT image reconstruction

- Medical informatics
- Telemedicine
- Picture archiving and communication systems (PACS)
- DICOM
- Tomographic reconstruction, an ill-posed inverse problem

Education and training

In North America

In North America, medical physics training is offered at a master's, doctorate, post-doctorate and/or residency levels. Several universities offer these degrees in Canada and the United States.

As of October 2010, twenty-seven universities in North America have medical physics graduate programs that are accredited by *The Commission on Accreditation of Medical Physics Education Programs* (CAMPEP). The same organization has accredited forty-three medical physics clinical residency programs.

Professional certification is obtained from the American Board of Radiology, the American Board of Medical Physics, the American Board of Science in Nuclear

Medicine, and the Canadian College of Physicists in Medicine. As of 2012, enrollment in a CAMPEP-accredited residency or graduate program is required to start the ABR certification process. Starting in 2014, completion of a CAMPEP-accredited residency will be required to advance to part 2 of the ABR certification process.

In the United Kingdom

The person concerned must first gain a first or upper second-class honours degree in a physical or engineering science subject before they can start the Part I medical physics training within the National Health Service.

Trainees can complete Part I training in fifteen months provided they hold an MSc from an IPEM accredited center in the United Kingdom or the Republic of Ireland (National University of Ireland, Galway). For these candidates, the Part I training consists of pure clinical experience. Trainees applying for Part I trainee holding only a degree in a engineering or physical science subject must undertake a combined study and clinical training programme. This programme consists of two years of clinical placement, during which the trainee will study for an MSc in Medical Physics which is approved by the Institute of Physics and Engineering in Medicine (IPEM). The MSc will be either at University College London, Swansea, Sheffield, Surrey, Birmingham, Leeds, Manchester, Aberdeen, Glasgow, King's or Queen Mary's. Open University also offers a Master of Science in Medical Physics, but the prospective student should first check that this degree will satisfy the accreditation requirements or that it is accepted before embarking on it. Successful completion of the Part I training programme leads to an IPEM Diploma. The trainee can then apply for a Part II position, which will consists of the IPEM's Programme of Advanced Training (PAT) which takes a further two years and leads to Corporate Membership of the IPEM, and registration as a Clinical Scientist (if successful).

Note that some training centres offer a contract for the full four (three) years of the scheme, while some offer only part I training, with a requirement to reapply for part II.

Chapter 2

Medical Imaging

Medical imaging is the technique and process used to create images of the human body (or parts and function thereof) for clinical purposes (medical procedures seeking to reveal, diagnose or examine disease) or medical science (including the study of normal anatomy and physiology). Although imaging of removed organs and tissues can be performed for medical reasons, such procedures are not usually referred to as medical imaging, but rather are a part of pathology.

As a discipline and in its widest sense, it is part of biological imaging and incorporates radiology (in the wider sense), nuclear medicine, investigative radiological sciences, endoscopy, (medical) thermography, medical photography and microscopy (e.g. for human pathological investigations).

Measurement and recording techniques which are not primarily designed to produce images, such as electroencephalography (EEG), magnetoencephalography (MEG), Electrocardiography (EKG) and others, but which produce data susceptible to be represented as maps (i.e. containing positional information), can be seen as forms of medical imaging.

Up until 2010, 5 billion medical imaging studies had been conducted worldwide. Radiation exposure from medical imaging in 2006 made up about 50% of total ionizing radiation exposure in the United States.

Overview

In the clinical context, "invisible light" medical imaging is generally equated to radiology or "clinical imaging" and the medical practitioner responsible for interpreting (and sometimes acquiring) the images is a radiologist. "Visible light" medical imaging involves digital video or still pictures that can be seen without special equipment. Dermatology and wound care are two modalities that utilize visible light imagery. Diagnostic radiography designates the technical aspects of medical imaging and in particular the acquisition of medical images. The *radiographer* or *radiologic technologist* is usually responsible for acquiring medical images of diagnostic quality, although some radiological interventions are performed by radiologists. While radiology is an evaluation of anatomy, nuclear medicine provides functional assessment.

As a field of scientific investigation, medical imaging constitutes a sub-discipline of biomedical engineering, medical physics or medicine depending on the context: Research and development in the area of instrumentation, image acquisition (e.g. radiography), modelling and quantification are usually the preserve of biomedical engineering, medical physics and computer science; Research into the application and interpretation of medical images is usually the preserve of radiology and the medical sub-discipline relevant to medical condition or area of medical science (neuroscience, cardiology, psychiatry, psychology, etc.) under investigation. Many of the techniques developed for medical imaging also have scientific and industrial applications.

Medical imaging is often perceived to designate the set of techniques that noninvasively produce images of the internal aspect of the body. In this restricted sense, medical imaging can be seen as the solution of mathematical inverse problems. This means that cause (the properties of living tissue) is inferred from effect (the observed signal). In the case of ultrasonography the probe consists of ultrasonic pressure waves and echoes inside the tissue show the internal structure. In the case of projection radiography, the probe is X-ray radiation which is absorbed at different rates in different tissue types such as bone, muscle and fat.

The term noninvasive is a term based on the fact that following medical imaging modalities do not penetrate the skin physically. But on the electromagnetic and radiation level, they are quite invasive. From the high energy photons in X-Ray Computed Tomography, to the 2+ Tesla coils of an MRI device, these modalities alter the physical and chemical environment of the body in order to obtain data.

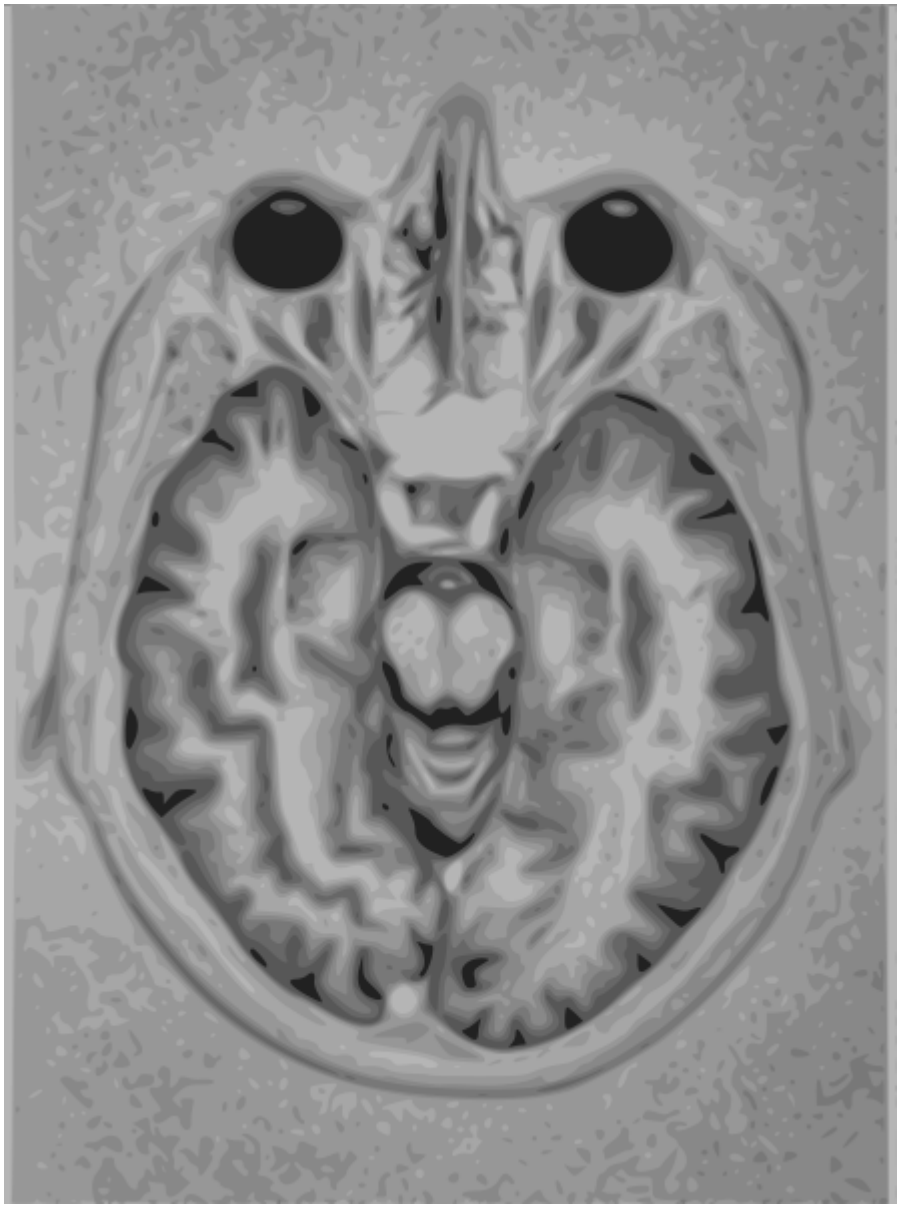
Radiography

Two forms of radiographic images are in use in medical imaging; projection radiography and fluoroscopy, with the latter being useful for catheter guidance. These 2D techniques are still in wide use despite the advance of 3D tomography due to the low cost, high resolution, and depending on application, lower radiation dosages. This imaging modality utilizes a wide beam of x rays for image acquisition and is the first imaging technique available in modern medicine.

- *Fluoroscopy* produces real-time images of internal structures of the body in a similar fashion to radiography, but employs a constant input of x-rays, at a lower dose rate. Contrast media, such as barium, iodine, and air are used to visualize internal organs as they work. Fluoroscopy is also used in image-guided procedures when constant feedback during a procedure is required. An image receptor is required to convert the radiation into an image after it has passed through the area of interest. Early on this was a fluorescing screen, which gave way to an Image Amplifier (IA) which was a large vacuum tube that had the receiving end coated with cesium iodide, and a mirror at the opposite end. Eventually the mirror was replaced with a TV camera.

- *Projectional radiographs*, more commonly known as x-rays, are often used to determine the type and extent of a fracture as well as for detecting pathological changes in the lungs. With the use of radio-opaque contrast media, such as barium, they can also be used to visualize the structure of the stomach and intestines - this can help diagnose ulcers or certain types of colon cancer.

Magnetic resonance imaging (MRI)



A brain MRI representation

A magnetic resonance imaging instrument (MRI scanner), or "nuclear magnetic resonance (NMR) imaging" scanner as it was originally known, uses powerful magnets to polarise and excite hydrogen nuclei (single proton) in water molecules in human tissue, producing a detectable signal which is spatially encoded, resulting in images of the body.

MRI uses three electromagnetic fields: a very strong (on the order of units of teslas) static magnetic field to polarize the hydrogen nuclei, called the static field; a weaker time-varying (on the order of 1 kHz) field(s) for spatial encoding, called the gradient field(s); and a weak radio-frequency (RF) field for manipulation of the hydrogen nuclei to produce measurable signals, collected through an RF antenna.

Like CT, MRI traditionally creates a two dimensional image of a thin "slice" of the body and is therefore considered a tomographic imaging technique. Modern MRI instruments are capable of producing images in the form of 3D blocks, which may be considered a generalisation of the single-slice, tomographic, concept. Unlike CT, MRI does not involve the use of ionizing radiation and is therefore not associated with the same health hazards. For example, because MRI has only been in use since the early 1980s, there are no known long-term effects of exposure to strong static fields and therefore there is no limit to the number of scans to which an individual can be subjected, in contrast with X-ray and CT. However, there are well-identified health risks associated with tissue heating from exposure to the RF field and the presence of implanted devices in the body, such as pace makers. These risks are strictly controlled as part of the design of the instrument and the scanning protocols used.

Because CT and MRI are sensitive to different tissue properties, the appearance of the images obtained with the two techniques differ markedly. In CT, X-rays must be blocked by some form of dense tissue to create an image, so the image quality when looking at soft tissues will be poor. In MRI, while any nucleus with a net nuclear spin can be used, the proton of the hydrogen atom remains the most widely used, especially in the clinical setting, because it is so ubiquitous and returns a large signal. This nucleus, present in water molecules, allows the excellent soft-tissue contrast achievable with MRI.

Nuclear medicine

Nuclear medicine encompasses both diagnostic imaging and treatment of disease, and may also be referred to as molecular medicine or molecular imaging & therapeutics. Nuclear medicine uses certain properties of isotopes and the energetic particles emitted from radioactive material to diagnose or treat various pathology. Different from the typical concept of anatomic radiology, nuclear medicine enables assessment of physiology. This function-based approach to medical evaluation has useful applications in most subspecialties, notably oncology, neurology, and cardiology. *Gamma cameras* are used in e.g. scintigraphy, SPECT and PET to detect regions of biologic activity that may be associated with disease. Relatively short lived isotope, such as ^{123}I is administered to the patient. Isotopes are often preferentially absorbed by biologically active tissue in the body, and can be used to identify tumors or fracture points in bone. Images are acquired after collimated photons are detected by a crystal that gives off a light signal, which is in turn amplified and converted into count data.

- *Scintigraphy* ("scint") is a form of diagnostic test wherein radioisotopes are taken internally, for example intravenously or orally. Then, gamma cameras capture and

form two-dimensional images from the radiation emitted by the radiopharmaceuticals.

- *SPECT* is a 3D tomographic technique that uses gamma camera data from many projections and can be reconstructed in different planes. A dual detector head gamma camera combined with a CT scanner, which provides localization of functional SPECT data, is termed a SPECT/CT camera, and has shown utility in advancing the field of molecular imaging. In most other medical imaging modalities, energy is passed through the body and the reaction or result is read by detectors. In SPECT imaging, the patient is injected with a radioisotope, most commonly Thallium 201TI, Technetium 99mTC, Iodine 123I, and Gallium 67Ga

. The radioactive gamma rays are emitted through the body as the natural decaying process of these isotopes takes place. The emissions of the gamma rays are captured by detectors that surround the body. This essentially means that the human is now the source of the radioactivity, rather than the medical imaging devices such as X-Ray, CT, or Ultrasound.

- *Positron emission tomography* (PET) uses coincidence detection to image functional processes. Short-lived positron emitting isotope, such as ^{18}F, is incorporated with an organic substance such as glucose, creating F18-fluorodeoxyglucose, which can be used as a marker of metabolic utilization. Images of activity distribution throughout the body can show rapidly growing tissue, like tumor, metastasis, or infection. PET images can be viewed in comparison to computed tomography scans to determine an anatomic correlate. Modern scanners combine PET with a CT, or even MRI, to optimize the image reconstruction involved with positron imaging. This is performed on the same equipment without physically moving the patient off of the gantry. The resultant hybrid of functional and anatomic imaging information is a useful tool in non-invasive diagnosis and patient management.

Photo acoustic imaging

Photoacoustic imaging is a recently developed hybrid biomedical imaging modality based on the photoacoustic effect. It combines the advantages of optical absorption contrast with ultrasonic spatial resolution for deep imaging in (optical) diffusive or quasi-diffusive regime. Recent studies have shown that photoacoustic imaging can be used in vivo for tumor angiogenesis monitoring, blood oxygenation mapping, functional brain imaging, and skin melanoma detection, etc.

Breast Thermography

Digital infrared imaging thermography is based on the principle that metabolic activity and vascular circulation in both pre-cancerous tissue and the area surrounding a developing breast cancer is almost always higher than in normal breast tissue. Cancerous tumors require an ever-increasing supply of nutrients and therefore increase circulation to their cells by holding open existing blood vessels, opening dormant vessels, and creating

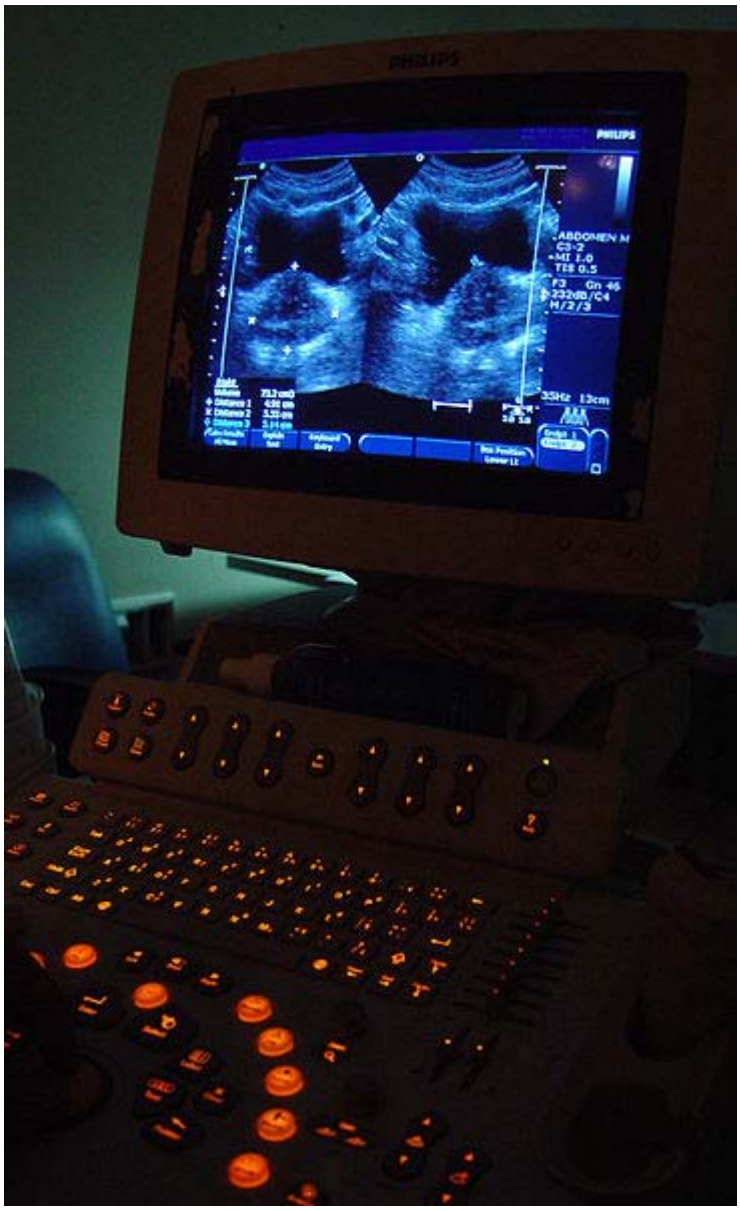
new ones (neoangiogenesis). This process frequently results in an increase in regional surface temperatures of the breast. Digital infrared imaging uses extremely sensitive medical infrared cameras and sophisticated computers to detect, analyze, and produce high-resolution diagnostic images of these temperature variations. Because of DII's sensitivity, these temperature variations may be among the earliest signs of breast cancer and/or a pre-cancerous state of the breast.

Tomography

Tomography is the method of imaging a single plane, or slice, of an object resulting in a tomogram. There are several forms of tomography:

- Linear tomography: This is the most basic form of tomography. The X-ray tube moved from point "A" to point "B" above the patient, while the cassette holder (or "bucky") moves simultaneously under the patient from point "B" to point "A." The fulcrum, or pivot point, is set to the area of interest. In this manner, the points above and below the focal plane are blurred out, just as the background is blurred when panning a camera during exposure. No longer carried out and replaced by computed tomography.
- Poly tomography: This was a complex form of tomography. With this technique, a number of geometrical movements were programmed, such as hypocycloidic, circular, figure 8, and elliptical. Philips Medical Systems produced one such device called the 'Polytome.' This unit was still in use into the 1990s, as its resulting images for small or difficult physiology, such as the inner ear, was still difficult to image with CTs at that time. As the resolution of CTs got better, this procedure was taken over by the CT.
- Zonography: This is a variant of linear tomography, where a limited arc of movement is used. It is still used in some centres for visualising the kidney during an intravenous urogram (IVU).
- Orthopantomography (OPT or OPG): The only common tomographic examination in use. This makes use of a complex movement to allow the radiographic examination of the mandible, as if it were a flat bone. It is often referred to as a "Panorex", but this is incorrect, as it is a trademark of a specific company.
- Computed Tomography (CT), or Computed Axial Tomography (CAT: A CT scan, also known as a CAT scan), is a helical tomography (latest generation), which traditionally produces a 2D image of the structures in a thin section of the body. It uses X-rays. It has a greater ionizing radiation dose burden than projection radiography; repeated scans must be limited to avoid health effects. CT is based on the same principles as X-Ray projections but in this case, the patient is enclosed in a surrounding ring of detectors assigned with 500-1000 scintillation detectors. This being the fourth-generation X-Ray CT scanner geometry. Previously in older generation scanners, the X-Ray beam was paired by a translating source and detector.

Ultrasound



Ultrasound representation of Urinary bladder (black butterfly-like shape) and hyperplastic prostate

Medical ultrasonography uses high frequency broadband sound waves in the megahertz range that are reflected by tissue to varying degrees to produce (up to 3D) images. This is commonly associated with imaging the fetus in pregnant women. Uses of ultrasound are much broader, however. Other important uses include imaging the abdominal organs, heart, breast, muscles, tendons, arteries and veins. While it may provide less anatomical detail than techniques such as CT or MRI, it has several advantages which make it ideal in numerous situations, in particular that it studies the function of moving structures in real-time, emits no ionizing radiation, and contains speckle that can be used in elastography. Ultrasound is also used as a popular research tool for capturing raw data,

that can be made available through an Ultrasound research interface, for the purpose of tissue characterization and implementation of new image processing techniques. The concepts of ultrasound differ from other medical imaging modalities in the fact that it is operated by the transmission and receipt of sound waves. The high frequency sound waves are sent into the tissue and depending on the composition of the different tissues; the signal will be attenuated and returned at separate intervals. A path of reflected sound waves in a multilayered structure can be defined by an input acoustic impedance(Ultrasound sound wave) and the Reflection and transmission coefficients of the relative structures. It is very safe to use and does not appear to cause any adverse effects, although information on this is not well documented. It is also relatively inexpensive and quick to perform. Ultrasound scanners can be taken to critically ill patients in intensive care units, avoiding the danger caused while moving the patient to the radiology department. The real time moving image obtained can be used to guide drainage and biopsy procedures. Doppler capabilities on modern scanners allow the blood flow in arteries and veins to be assessed.

Medical imaging topics

Maximizing imaging procedure use

The amount of data obtained in a single MR or CT scan is very extensive. Some of the data that radiologists discard could save patients time and money, while reducing their exposure to radiation and risk of complications from invasive procedures.

Creation of three-dimensional images

Recently, techniques have been developed to enable CT, MRI and ultrasound scanning software to produce 3D images for the physician. Traditionally CT and MRI scans produced 2D static output on film. To produce 3D images, many scans are made, then combined by computers to produce a 3D model, which can then be manipulated by the physician. 3D ultrasounds are produced using a somewhat similar technique. In diagnosing disease of the viscera of abdomen,ultrasound is particularly sensitive on imaging of biliary tract,urinary tract and female reproductive organs (ovary,fallopian tubes). As for example,diagnosis of gall stone by dilatation of common bile duct and stone in common bile duct. With the ability to visualize important structures in great detail, 3D visualization methods are a valuable resource for the diagnosis and surgical treatment of many pathologies. It was a key resource for the famous, but ultimately unsuccessful attempt by Singaporean surgeons to separate Iranian twins Ladan and Laleh Bijani in 2003. The 3D equipment was used previously for similar operations with great success.

Other proposed or developed techniques include:

- Diffuse optical tomography
- Elastography
- Electrical impedance tomography

- Optoacoustic imaging
- Ophthalmology
    - A-scan
    - B-scan
    - Corneal topography
    - Optical coherence tomography
    - Scanning laser ophthalmoscopy

Some of these techniques are still at a research stage and not yet used in clinical routines.

Compression of medical images

Medical imaging techniques produce very large amounts of data, especially from CT, MRI and PET modalities. As a result, storage and communications of electronic image data are prohibitive without the use of compression. JPEG 2000 is the state-of-the-art image compression DICOM standard for storage and transmission of medical images. The cost and feasibility of accessing large image data sets over low or various bandwidths are further addressed by use of another DICOM standard, called JPIP, to enable efficient streaming of the JPEG 2000 compressed image data.

Non-diagnostic imaging

Neuroimaging has also been used in experimental circumstances to allow people (especially disabled persons) to control outside devices, acting as a brain computer interface.

Archiving and recording

Used primarily in ultrasound imaging, capturing the image a medical imaging device is required for archiving and telemedicine applications. In most scenarios, a frame grabber is used in order to capture the video signal from the medical device and relay it to a computer for further processing and operations.

Open source software for medical image analysis

Several open source software packages are available for performing analysis of medical images:

- ImageJ
- 3D Slicer
- ITK
- OsiriX
- GemIdent
- MicroDicom
- FreeSurfer

Use in pharmaceutical clinical trials

Medical imaging has become a major tool in clinical trials since it enables rapid diagnosis with visualization and quantitative assessment.

A typical clinical trial goes through multiple phases and can take up to eight years. Clinical endpoints or outcomes are used to determine whether the therapy is safe and effective. Once a patient reaches the endpoint, he/she is generally excluded from further experimental interaction. Trials that rely solely on clinical endpoints are very costly as they have long durations and tend to need large number of patients.

In contrast to clinical endpoints, surrogate endpoints have been shown to cut down the time required to confirm whether a drug has clinical benefits. Imaging biomarkers (a characteristic that is objectively measured by an imaging technique, which is used as an indicator of pharmacological response to a therapy) and surrogate endpoints have shown to facilitate the use of small group sizes, obtaining quick results with good statistical power.

Imaging is able to reveal subtle change that is indicative of the progression of therapy that may be missed out by more subjective, traditional approaches. Statistical bias is reduced as the findings are evaluated without any direct patient contact.

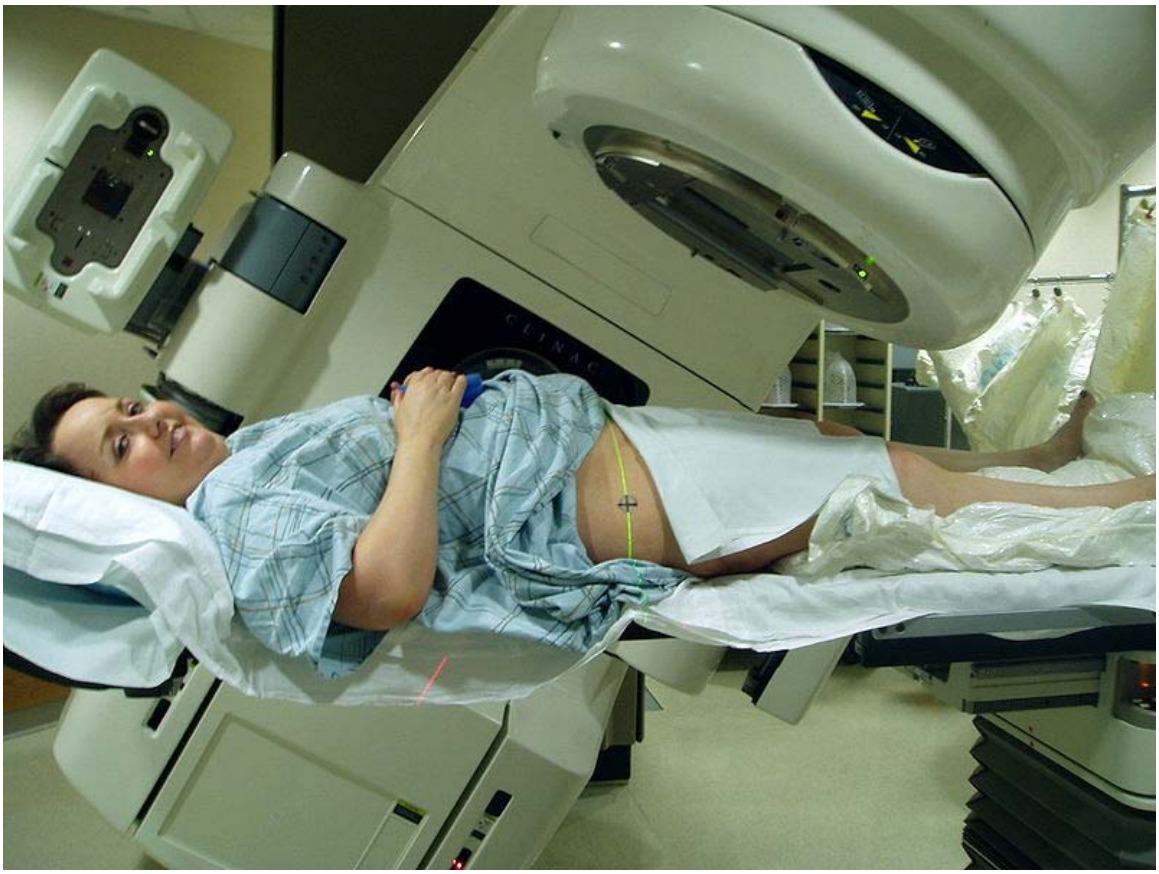
For example, measurement of tumour shrinkage is a commonly used surrogate endpoint in solid tumour response evaluation. This allows for faster and more objective assessment of the effects of anticancer drugs. In evaluating the extent of Alzheimer's disease, it is still prevalent to use behavioural and cognitive tests. MRI scans on the entire brain can accurately pinpoint hippocampal atrophy rate while PET scans is able to measure the brain's metabolic activity by measuring regional glucose metabolism.

An imaging-based trial will usually be made up of three components:

1. A realistic imaging protocol. The protocol is an outline that standardizes (as far as practically possible) the way in which the images are acquired using the various modalities (PET, SPECT, CT, MRI). It covers the specifics in which images are to be stored, processed and evaluated.
2. An imaging centre that is responsible for collecting the images, perform quality control and provide tools for data storage, distribution and analysis. It is important for images acquired at different time points are displayed in a standardised format to maintain the reliability of the evaluation. Certain specialised imaging contract research organizations provide to end medical imaging services, from protocol design and site management through to data quality assurance and image analysis.
3. Clinical sites that recruit patients to generate the images to send back to the imaging centre.

Chapter 3

Radiation Therapy



Radiation therapy of the pelvis. Lasers and a mould under the legs are used to determine exact position.

Axesse Radiotherapy

Radiation therapy (in the USA), **radiation oncology**, or **radiotherapy** (in the UK, Canada and Australia), sometimes abbreviated to XRT, is the medical use of ionizing radiation as part of cancer treatment to control malignant cells (not to be confused with radiology, the use of radiation in medical imaging and diagnosis). Radiotherapy may be used for curative or adjuvant treatment. It is used as palliative treatment (where cure is not possible and the aim is for local disease control or symptomatic relief) or as therapeutic treatment (where the therapy has survival benefit and it can be curative). Total body irradiation (TBI) is a radiotherapy technique used to prepare the body to receive a bone marrow transplant. Radiotherapy has several applications in non-malignant conditions, such as the treatment of trigeminal neuralgia, severe thyroid eye disease, pterygium, pigmented villonodular synovitis, prevention of keloid scar growth, and prevention of heterotopic ossification. The use of radiotherapy in non-malignant conditions is limited partly by worries about the risk of radiation-induced cancers.

Radiotherapy is used for the treatment of malignant cancer, and may be used as a primary or adjuvant modality. It is also common to combine radiotherapy with surgery, chemotherapy, hormone therapy, Immunotherapy or some mixture of the four. Most common cancer types can be treated with radiotherapy in some way. The precise treatment intent (curative, adjuvant, neoadjuvant, therapeutic, or palliative) will depend on the tumor type, location, and stage, as well as the general health of the patient.

Radiation therapy is commonly applied to the cancerous tumor. The radiation fields may also include the draining lymph nodes if they are clinically or radiologically involved with tumor, or if there is thought to be a risk of subclinical malignant spread. It is necessary to include a margin of normal tissue around the tumor to allow for uncertainties in daily set-up and internal tumor motion. These uncertainties can be caused by internal movement (for example, respiration and bladder filling) and movement of external skin marks relative to the tumor position.

To spare normal tissues (such as skin or organs which radiation must pass through in order to treat the tumor), shaped radiation beams are aimed from several angles of exposure to intersect at the tumor, providing a much larger absorbed dose there than in the surrounding, healthy tissue.

Brachytherapy, in which a radiation source is placed inside or next to the area requiring treatment, is another form of radiation therapy that minimizes exposure to healthy tissue during procedures to treat cancers of the breast, prostate and other organs.

Mechanism of action

Radiation therapy works by damaging the DNA of cancerous cells. This DNA damage is caused by one of two types of energy, photon or charged particle. This damage is either direct or indirect ionizing the atoms which make up the DNA chain. Indirect ionization happens as a result of the ionization of water, forming free radicals, notably hydroxyl radicals, which then damage the DNA. In the older, most common form of radiation therapy, Intensity-modulated radiotherapy (IMRT) (photons), most of the radiation effect is through free radicals. Because cells have mechanisms for repairing single-strand DNA damage, double-stranded DNA breaks prove to be the most significant technique to cause cell death. Cancer cells generally are undifferentiated and stem cell-like, they reproduce more, and have a diminished ability to repair sub-lethal damage compared to most healthy differentiated cells. This single-strand DNA damage is then passed on through cell division, accumulating damage to the cancer cell's DNA, causing them to die or reproduce more slowly.

One of the major limitations of photon radiotherapy is that the cells of solid tumors become deficient in oxygen. Solid tumors can outgrow their blood supply, causing a low-oxygen state known as hypoxia. Oxygen is a potent radiosensitizer, increasing the effectiveness of a given dose of radiation by forming DNA-damaging free radicals. Tumor cells in a hypoxic environment may be as much as 2 to 3 times more resistant to radiation damage than those in a normal oxygen environment. Much research has been

devoted to overcoming hypoxia including the use of high pressure oxygen tanks, blood substitutes that carry increased oxygen, hypoxic cell radiosensitizer drug's such as misonidazole and metronidazole, and hypoxic cytotoxins (tissue poisons), such as tirapazamine.

Direct damage to cancer cell DNA occurs through high-LET (linear energy transfer) charged particles such as proton, boron, carbon or neon ions which have an antitumor effect which is independent of tumor oxygen supply because these particles act mostly via direct energy transfer usually causing double-stranded DNA breaks. Due to their relatively large mass, protons and other charged particles have little lateral side scatter in the tissue; the beam does not broaden much, stays focused on the tumor shape and delivers small dose side-effects to surrounding tissue. They also more precisely target the tumor using the Bragg peak effect. The cyclotron's, dielectric wall accelerator (DWA), or Still River Systems's super conducting high field magnet (two new compact protron replacements) provide the energy source for charged particle therapy. These particles can be charged to different amounts to provide the desired tissue penetration. This procedure avoids healthy tissue because it releases its energy at the last few milimeters calibrated to be at the target tumor and stops. Because IMRT has little mass it cannot be controlled to as fine a degree as charged particles and is still damaging healthy cells when it exits the body. This is critically important in almost all cases where the close proximity of other organs makes any stray ionization very damaging example: (head and neck cancers). This damage causes secondary inducted cancers. This x-ray exposure is especially bad for children, due to their growing bodies. They have a 30% chance of a second malignancy after 5 years post initial RT.

Dose

The amount of radiation used in photon radiation therapy is measured in gray (Gy), and varies depending on the type and stage of cancer being treated. For curative cases, the typical dose for a solid epithelial tumor ranges from 60 to 80 Gy, while lymphomas are treated with 20 to 40 Gy.

Preventative (adjuvant) doses are typically around 45 - 60 Gy in 1.8 - 2 Gy fractions (for Breast, Head, and Neck cancers.) Many other factors are considered by radiation oncologists when selecting a dose, including whether the patient is receiving chemotherapy, patient comorbidities, whether radiation therapy is being administered before or after surgery, and the degree of success of surgery.

Delivery parameters of a prescribed dose are determined during treatment planning (part of dosimetry). Treatment planning is generally performed on dedicated computers using specialized treatment planning software. Depending on the radiation delivery method, several angles or sources may be used to sum to the total necessary dose. The planner will try to design a plan that delivers a uniform prescription dose to the tumor and minimizes dose to surrounding healthy tissues.

Fractionation

The total dose is fractionated (spread out over time) for several important reasons. Fractionation allows normal cells time to recover, while tumor cells are generally less efficient in repair between fractions. Fractionation also allows tumor cells that were in a relatively radio-resistant phase of the cell cycle during one treatment to cycle into a sensitive phase of the cycle before the next fraction is given. Similarly, tumor cells that were chronically or acutely hypoxic (and therefore more radioresistant) may reoxygenate between fractions, improving the tumor cell kill. Fractionation regimes are individualised between different radiotherapy centres and even between individual doctors. In North America, Australia, and Europe, the typical fractionation schedule for adults is 1.8 to 2 Gy per day, five days a week. In some cancer types, prolongation of the fraction schedule over too long can allow for the tumor to begin repopulating, and for these tumor types, including head-and-neck and cervical squamous cell cancers, radiation treatment is preferably completed within a certain amount of time. For children, a typical fraction size may be 1.5 to 1.8 Gy per day, as smaller fraction sizes are associated with reduced incidence and severity of late-onset side effects in normal tissues.

In some cases, two fractions per day are used near the end of a course of treatment. This schedule, known as a concomitant boost regimen or hyperfractionation, is used on tumors that regenerate more quickly when they are smaller. In particular, tumors in the head-and-neck demonstrate this behavior.

One of the best-known alternative fractionation schedules is Continuous Hyperfractionated Accelerated Radiotherapy (CHART). CHART, used to treat lung cancer, consists of three smaller fractions per day. Although reasonably successful, CHART can be a strain on radiation therapy departments.

Another increasingly well-known alternative fractionation schedule, used to treat breast cancer, is called Accelerated Partial Breast Irradiation (APBI). APBI can be performed with either brachytherapy or with external beam radiation. APBI normally involves two high-dose fractions per day for five days, compared to whole breast irradiation, in which a single, smaller fraction is given five times a week over a six-to-seven-week period.

Implants can be fractionated over minutes or hours, or they can be permanent seeds which slowly deliver radiation until they become inactive.

Effect on different types of cancer

Different cancers respond differently to radiation therapy.

The response of a cancer to radiation is described by its radiosensitivity. Highly radiosensitive cancer cells are rapidly killed by modest doses of radiation. These include leukemias, most lymphomas and germ cell tumors. The majority of epithelial cancers are only moderately radiosensitive, and require a significantly higher dose of radiation (60-70Gy) to achieve a radical cure. Some types of cancer are notably radioresistant, that is,

much higher doses are required to produce a radical cure than may be safe in clinical practice. Renal cell cancer and melanoma are generally considered to be radioresistant.

It is important to distinguish the radiosensitivity of a particular tumor, which to some extent is a laboratory measure, from the radiation "curability" of a cancer in actual clinical practice. For example, leukemias are not generally curable with radiotherapy, because they are disseminated through the body. Lymphoma may be radically curable if it is localised to one area of the body. Similarly, many of the common, moderately radioresponsive tumors are routinely treated with curative doses of radiotherapy if they are at an early stage. For example: non-melanoma skin cancer, head and neck cancer, breast cancer, non-small cell lung cancer, cervical cancer, anal cancer, prostate cancer. Metastatic cancers are generally incurable with radiotherapy because it is not possible to treat the whole body.

Before treatment, a CT scan is often performed to identify the tumor and surrounding normal structures. The patient is then sent for a simulation so that molds can be created to be used during treatment. The patient receives small skin marks to guide the placement of treatment fields.

The response of a tumor to radiotherapy is also related to its size. For complex reasons, very large tumors respond less well to radiation than smaller tumors or microscopic disease. Various strategies are used to overcome this effect. The most common technique is surgical resection prior to radiotherapy. This is most commonly seen in the treatment of breast cancer with wide local excision or mastectomy followed by adjuvant radiotherapy such as brachytherapy. Another method is to shrink the tumor with neoadjuvant chemotherapy prior to radical radiotherapy. A third technique is to enhance the radiosensitivity of the cancer by giving certain drugs during a course of radiotherapy. Examples of radiosensiting drugs include: Cisplatin, Nimorazole, and Cetuximab.

History of radiation therapy

Radiation therapy has been in use as a cancer treatment for more than 100 years, with its earliest roots traced from the discovery of x-rays in 1895 by Wilhelm Röntgen.

The field of radiation therapy began to grow in the early 1900s largely due to the groundbreaking work of Nobel Prize-winning scientist Marie Curie, who discovered the radioactive elements polonium and radium. This began a new era in medical treatment and research. Radium was used in various forms until the mid-1900s when cobalt and caesium units came into use. Medical linear accelerators have been used too as sources of radiation since the late 1940s.

With Godfrey Hounsfield’s invention of computed tomography (CT) in 1971, three-dimensional planning became a possibility and created a shift from 2-D to 3-D radiation delivery; CT-based planning allows physicians to more accurately determine the dose distribution using axial tomographic images of the patient's anatomy. Orthovoltage and

cobalt units have largely been replaced by megavoltage linear accelerators, useful for their penetrating energies and lack of physical radiation source.

The advent of new imaging technologies, including magnetic resonance imaging (MRI) in the 1970s and positron emission tomography (PET) in the 1980s, has moved radiation therapy from 3-D conformal to intensity-modulated radiation therapy (IMRT) and image-guided radiation therapy (IGRT) Tomotherapy. These advances allowed radiation oncologists to better see and target tumors, which have resulted in better treatment outcomes, more organ preservation and fewer side effects.

Types of radiation therapy

Historically, the three main divisions of radiotherapy are external beam radiotherapy (EBRT or XRT) or teletherapy, brachytherapy or sealed source radiotherapy, and systemic radioisotope therapy or unsealed source radiotherapy. The differences relate to the position of the radiation source; external is outside the body, brachytherapy uses sealed radioactive sources placed precisely in the area under treatment, and systemic radioisotopes are given by infusion or oral ingestion. Brachytherapy can use temporary or permanent placement of radioactive sources. The temporary sources are usually placed by a technique called afterloading. In afterloading a hollow tube or applicator is placed surgically in the organ to be treated, and the sources are loaded into the applicator after the applicator is implanted. This minimizes radiation exposure to health care personnel. Particle therapy is a special case of external beam radiotherapy where the particles are protons or heavier ions. Intraoperative radiotherapy or IORT is a special type of radiotherapy that is delivered immediately after surgical removal of the cancer. This method has been employed in breast cancer (TARGeted Introperative radioTherapy or TARGIT), brain tumors and rectal cancers.

External beam radiotherapy

The following three sections refer to treatment using x-rays.

Conventional external beam radiotherapy

Conventional external beam radiotherapy (2DXRT) is delivered via two-dimensional beams using linear accelerator machines. 2DXRT mainly consists of a single beam of radiation delivered to the patient from several directions: often front or back, and both sides. *Conventional* refers to the way the treatment is *planned* or *simulated* on a specially calibrated diagnostic x-ray machine known as a simulator because it recreates the linear accelerator actions (or sometimes by eye), and to the usually well-established arrangements of the radiation beams to achieve a desired *plan*. The aim of simulation is to accurately target or localize the volume which is to be treated. This technique is well established and is generally quick and reliable. The worry is that some high-dose treatments may be limited by the radiation toxicity capacity of healthy tissues which lay close to the target tumor volume. An example of this problem is seen in radiation of the prostate gland, where the sensitivity of the adjacent rectum limited the dose which could

be safely prescribed using 2DXRT planning to such an extent that tumor control may not be easily achievable. Prior to the invention of the CT, physicians and physicists had limited knowledge about the true radiation dosage delivered to both cancerous and healthy tissue. For this reason, 3-dimensional conformal radiotherapy is becoming the standard treatment for a number of tumor sites.

Stereotactic Radiation

Stereotactic radiation is a specialized type of external beam radiation therapy. It uses focused radiation beams targeting a well-defined tumor using extremely detailed imaging scans. Radiation oncologists perform stereotactic treatments, often with the help of a neurosurgeon for tumors in the brain or spine.

There are two types of stereotactic radiation. **Stereotactic radiosurgery** (SRS) is when doctors use a single or several stereotactic radiation treatments of the brain or spine. **Stereotactic body radiation therapy** (SBRT) refers to one or several stereotactic radiation treatments with the body, such as the lungs.

Some doctors say an advantage to stereotactic treatments are they deliver the right amount of radiation to the cancer in a shorter amount of time than traditional treatments, which can often take six to 11 weeks. Plus treatments are given with extreme accuracy, which should limit the effect of the radiation on healthy tissues. One problem with stereotactic treatments is that they are only suitable for certain small tumors.

Stereotactic treatments can be confusing because many hospitals call the treatments by the name of the manufacturer rather than calling it SRS or SBRT. Brand names for these treatments include Axesse, Cyberknife, Gamma Knife, Novalis, Primatom, Synergy, X-Knife, TomoTherapy and Trilogy. This list changes as equipment manufacturers continue to develop new, specialized technologies to treat cancers.

Virtual simulation, 3-dimensional conformal radiotherapy, and intensity-modulated radiotherapy

The planning of radiotherapy treatment has been revolutionized by the ability to delineate tumors and adjacent normal structures in three dimensions using specialized CT and/or MRI scanners and planning software.

Virtual simulation, the most basic form of planning, allows more accurate placement of radiation beams than is possible using conventional X-rays, where soft-tissue structures are often difficult to assess and normal tissues difficult to protect.

An enhancement of virtual simulation is **3-Dimensional Conformal Radiotherapy (3DCRT)**, in which the profile of each radiation beam is shaped to fit the profile of the target from a beam's eye view (BEV) using a multileaf collimator (MLC) and a variable number of beams. When the treatment volume conforms to the shape of the tumor, the relative toxicity of radiation to the surrounding normal tissues is reduced, allowing a

higher dose of radiation to be delivered to the tumor than conventional techniques would allow.

Intensity-Modulated Radiation Therapy (IMRT) is an advanced type of high-precision radiation that is the next generation of 3DCRT. IMRT also improves the ability to conform the treatment volume to concave tumor shapes, for example when the tumor is wrapped around a vulnerable structure such as the spinal cord or a major organ or blood vessel. Computer-controlled x-ray accelerators distribute precise radiation doses to malignant tumors or specific areas within the tumor. The pattern of radiation delivery is determined using highly tailored computing applications to perform optimization and treatment simulation (Treatment Planning). The radiation dose is consistent with the 3-D shape of the tumor by controlling, or modulating, the radiation beam's intensity. The radiation dose intensity is elevated near the gross tumor volume while radiation among the neighboring normal tissue is decreased or avoided completely. The customized radiation dose is intended to maximize tumor dose while simultaneously protecting the surrounding normal tissue. This may result in better tumor targeting, lessened side effects, and improved treatment outcomes than even 3DCRT.

3DCRT is still used extensively for many body sites but the use of IMRT is growing in more complicated body sites such as CNS, head and neck, prostate, breast and lung. Unfortunately, IMRT is limited by its need for additional time from experienced medical personnel. This is because physicians must manually delineate the tumors one CT image at a time through the entire disease site which can take much longer than 3DCRT preparation. Then, medical physicists and dosimetrists must be engaged to create a viable treatment plan. Also, the IMRT technology has only been used commercially since the late 1990s even at the most advanced cancer centers, so radiation oncologists who did not learn it as part of their residency program must find additional sources of education before implementing IMRT.

Proof of improved survival benefit from either of these two techniques over conventional radiotherapy (2DXRT) is growing for many tumor sites, but the ability to reduce toxicity is generally accepted. Both techniques enable dose escalation, potentially increasing usefulness. There has been some concern, particularly with 3DCRT, about increased exposure of normal tissue to radiation and the consequent potential for secondary malignancy. Overconfidence in the accuracy of imaging may increase the chance of missing lesions that are invisible on the planning scans (and therefore not included in the treatment plan) or that move between or during a treatment (for example, due to respiration or inadequate patient immobilization). New techniques are being developed to better control this uncertainty—for example, real-time imaging combined with real-time adjustment of the therapeutic beams. This new technology is called image-guided radiation therapy (IGRT) or four-dimensional radiotherapy.

Particle Therapy

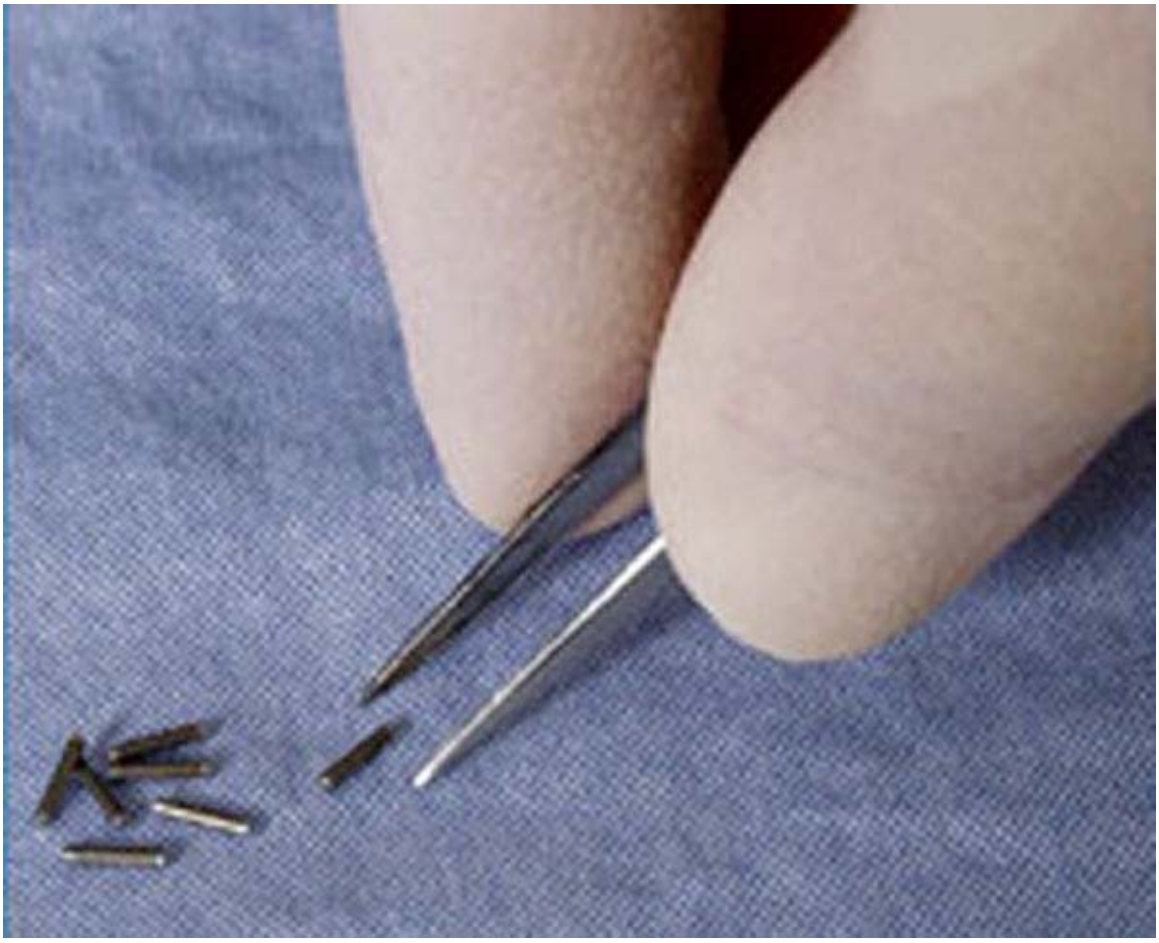
In particle therapy (Proton therapy), energetic ionizing particles (protons or carbon ions) are directed at the target tumor. The dose increases while the particle penetrates the

tissue, up to a maximum (the Bragg peak) that occurs near the end of the particle's range, and it then drops to (almost) zero. The advantage of this energy deposition profile is that less energy is deposited into the healthy tissue surrounding the target tissue.

Brachytherapy

Researcher Cate Yashar, M.D. With SAVI brachytherapy device.

Brachytherapy (internal radiotherapy) is delivered by placing radiation source(s) inside or next to the area requiring treatment. Brachytherapy is commonly used as an effective treatment for cervical, prostate, breast, and skin cancer and can also be used to treat tumours in many other body sites. As with stereotactic radiation, brachytherapy treatments are often known by their brand names. For example, brand names for breast cancer brachytherapy treatments include SAVI, MammoSite, and Contura. Brand names for prostate cancer include Proxcelan, TheraSeed, and I-Seed.



Brachytherapy seeds used to treat prostate cancer

In brachytherapy, radiation sources are precisely placed directly at the site of the cancerous tumour. This means that the irradiation only affects a very localized area – exposure to radiation of healthy tissues further away from the sources is reduced. These characteristics of brachytherapy provide advantages over external beam radiotherapy - the tumour can be treated with very high doses of localized radiation, whilst reducing the probability of unnecessary damage to surrounding healthy tissues. A course of brachytherapy can often be completed in less time than other radiotherapy techniques. This can help reduce the chance of surviving cancer cells dividing and growing in the intervals between each radiotherapy dose.

As one example of the localized nature of breast brachytherapy, the SAVI device delivers the radiation dose through multiple catheters, each of which can be individually controlled. This approach decreases the exposure of healthy tissue and resulting side effects, compared both to external beam radiotherapy and older methods of breast brachytherapy.

Radioisotope Therapy (RIT)

Systemic radioisotope therapy is a form of targeted therapy. Targeting can be due to the chemical properties of the isotope such as radioiodine which is specifically absorbed by the thyroid gland a thousandfold better than other bodily organs. Targeting can also be achieved by attaching the radioisotope to another molecule or antibody to guide it to the target tissue. The radioisotopes are delivered through infusion (into the bloodstream) or ingestion. Examples are the infusion of metaiodobenzylguanidine (MIBG) to treat neuroblastoma, of oral iodine-131 to treat thyroid cancer or thyrotoxicosis, and of hormone-bound lutetium-177 and yttrium-90 to treat neuroendocrine tumors (peptide receptor radionuclide therapy). Another example is the injection of radioactive glass or resin microspheres into the hepatic artery to radioembolize liver tumors or liver metastases.

A major use of systemic radioisotope therapy is in the treatment of bone metastasis from cancer. The radioisotopes travel selectively to areas of damaged bone, and spare normal undamaged bone. Isotopes commonly used in the treatment of bone metastasis are strontium-89 and samarium (^{153}Sm) lexidronam.

In 2002, the United States Food and Drug Administration (FDA) approved ibritumomab tiuxetan (Zevalin), which is an anti-CD20 monoclonal antibody conjugated to yttrium-90. In 2003, the FDA approved the tositumomab/iodine (^{131}I) tositumomab regimen (Bexxar), which is a combination of an iodine-131 labelled and an unlabelled anti-CD20 monoclonal antibody. These medications were the first agents of what is known as radioimmunotherapy, and they were approved for the treatment of refractory non-Hodgkins lymphoma.

Side effects

Radiation therapy is in itself painless. Many low-dose palliative treatments (for example, radiotherapy to bony metastases) cause minimal or no side effects, although short-term pain flare up can be experienced in the days following treatment due to oedema compressing nerves in the treated area. Treatment to higher doses causes varying side effects during treatment (acute side effects), in the months or years following treatment (long-term side effects), or after re-treatment (cumulative side effects). The nature, severity, and longevity of side effects depends on the organs that receive the radiation, the treatment itself (type of radiation, dose, fractionation, concurrent chemotherapy), and the patient.

Most side effects are predictable and expected. Side effects from radiation are usually limited to the area of the patient's body that is under treatment. One of the aims of modern radiotherapy is to reduce side effects to a minimum, and to help the patient to understand and to deal with those side effects which are unavoidable.

The main side effects reported are fatigue and skin irritation, like a mild to moderate sun burn. The fatigue often sets in during the middle of a course of treatment and can last for

weeks after treatment ends. The skin irritation will also go away, but it may not be as elastic as it was before.

Acute side effects

Damage to the epithelial surfaces. Epithelial surfaces may sustain damage from radiation therapy. Depending on the area being treated, this may include the skin, oral mucosa, pharyngeal, bowel mucosa and ureter. The rates of onset of damage and recovery from it depend upon the turnover rate of epithelial cells. Typically the skin starts to become pink and sore several weeks into treatment. The reaction may become more severe during the treatment and for up to about one week following the end of radiotherapy, and the skin may break down. Although this moist desquamation is uncomfortable, recovery is usually quick. Skin reactions tend to be worse in areas where there are natural folds in the skin, such as underneath the female breast, behind the ear, and in the groin.

If the head and neck area is treated, temporary soreness and ulceration commonly occur in the mouth and throat. If severe, this can affect swallowing, and the patient may need painkillers and nutritional support/food supplements. The esophagus can also become sore if it is treated directly, or if, as commonly occurs, it receives a dose of collateral radiation during treatment of lung cancer.

The lower bowel may be treated directly with radiation (treatment of rectal or anal cancer) or be exposed by radiotherapy to other pelvic structures (prostate, bladder, female genital tract). Typical symptoms are soreness, diarrhoea, and nausea.

Swelling (edema or oedema). As part of the general inflammation that occurs, swelling of soft tissues may cause problems during radiotherapy. This is a concern during treatment of brain tumors and brain metastases, especially where there is pre-existing raised intracranial pressure or where the tumor is causing near-total obstruction of a lumen (e.g., trachea or main bronchus). Surgical intervention may be considered prior to treatment with radiation. If surgery is deemed unnecessary or inappropriate, the patient may receive steroids during radiotherapy to reduce swelling.

Infertility. The gonads (ovaries and testicles) are very sensitive to radiation. They may be unable to produce gametes following **direct** exposure to most normal treatment doses of radiation. Treatment planning for all body sites is designed to minimize, if not completely exclude dose to the gonads if they are not the primary area of treatment.

Late side effects

Late side effects occur months to years after treatment and are generally limited to the area that has been treated. They are often due to damage of blood vessels and connective tissue cells. Many late effects are reduced by fractionating treatment into smaller parts.

Fibrosis
: Tissues which have been irradiated tend to become less elastic over time due to a diffuse scarring process.

Epilation (Hair Loss)
: Epilation may occur on any hair bearing skin with doses above 1 Gy. It only occurs within the radiation field/s. Hair loss may be permanent with a single dose of 10 Gy, but if the dose is fractionated permanent hair loss may not occur until dose exceeds 45 Gy.

Dryness
: The salivary glands and tear glands have a radiation tolerance of about 30 Gy in 2 Gy fractions, a dose which is exceeded by most radical head and neck cancer treatments. Dry mouth (xerostomia) and dry eyes (xerophthalmia) can become irritating long-term problems and severely reduce the patient's quality of life. Similarly, sweat glands in treated skin (such as the armpit) tend to stop working, and the naturally moist vaginal mucosa is often dry following pelvic irradiation.

Lymphedema
: Lymphedema, a condition of localized fluid retention and tissue swelling, can result from damage to the lymphatic system sustained during radiotherapy. It is the most commonly reported complication in breast radiotherapy patients.

Cancer
: Radiation is a potential cause of cancer, and secondary malignancies are seen in a very small minority of patients - usually less than 1/1000. It usually occurs 20 - 30 years following treatment, although some haematological malignancies may develop within 5 - 10 years. In the vast majority of cases, this risk is greatly outweighed by the reduction in risk conferred by treating the primary cancer. The cancer occurs within the treated area of the patient.

Heart disease
: Radiation has potentially excess risk of death from heart disease seen after some past breast cancer RT regimens.

Cognitive decline
: In cases of radiation applied to the head radiation therapy may cause cognitive decline.

Radiation Proctitis
: This can involve long-term effects on the rectum including bleeding, diarrhoea and urgency and is associated with radiotherapy to pelvic organs. Pelvic radiotherapy can also cause radiation cystitis when the bladder is affected

Cumulative side effects

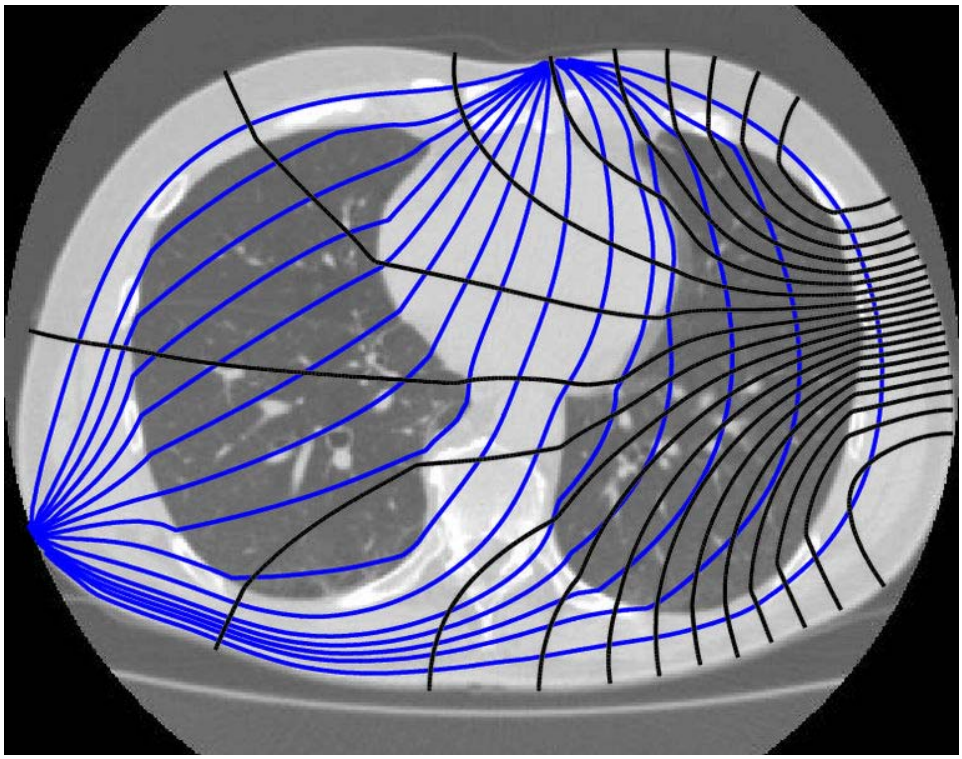
Cumulative effects from this process should not be confused with long-term effects—when short-term effects have disappeared and long-term effects are subclinical, reirradiation can still be problematic.

Radiation therapy accidents

There are rigorous procedures in place to minimise the risk of accidental overexposure of radiotherapy to patients. However, mistakes do occasionally occur; for example, the radiation therapy machine Therac-25 was responsible for at least six accidents between 1985 and 1987, where patients were given up to one hundred times the intended dose; two people were killed directly by the radiation overdoses. From 2005 to 2010, a hospital in Missouri overexposed 76 patients (most with brain cancer) during a five-year period because new radiation equipment had been set up incorrectly. Although medical errors are exceptionally rare, radiation oncologists, medical physicists and other members of the radiation therapy treatment team are working diligently to eliminate them. ASTRO has launched a safety initiative called Target Safely that, among other things, aims to record errors nation wide so that doctors can learn from each and every mistake and prevent them from happening. ASTRO also publishes a list of questions for patients to ask their doctors about radiation safety to ensure every treatment is as safe as possible.

Chapter 4

Electrical Impedance Tomography



A cross section of a human thorax from an X-ray CT showing a current being applied across two electrodes with calculated current stream lines (red) and equi-potentials(white). Note now the current stream lines are bent by the change in conductivity between different organs.

Electrical impedance tomography (**EIT**) is a medical imaging technique in which an image of the conductivity or permittivity of part of the body is inferred from surface electrical measurements. Typically, conducting electrodes are attached to the skin of the subject and small alternating currents are applied to some or all of the electrodes. The resulting electrical potentials are measured, and the process may be repeated for numerous different configurations of applied current.

Proposed applications include monitoring of lung function, detection of cancer in the skin and breast and location of epileptic foci. All applications are currently considered experimental.

The invention of EIT as a medical imaging technique is usually attributed to John G. Webster and a publication in 1978, although the first practical realisation of a medical EIT system was detailed in 1984 due to the work of David C. Barber and Brian H. Brown.

Mathematically, the problem of recovering conductivity from surface measurements of current and potential is a non-linear inverse problem and is severely ill-posed. The mathematical formulation of the problem is due to Alberto Calderón, and in the mathematical literature of inverse problems it is often referred to as "Calderón's Inverse Problem" or the "Calderón Problem". There is extensive mathematical research on the problem of uniqueness of solution and numerical algorithms for this problem.

In geophysics a similar technique (called electrical resistivity tomography) is used using electrodes on the surface of the earth or in bore holes to locate resistivity anomalies, and in industrial process monitoring the arrays of electrodes are used for example to monitor mixtures of conductive fluids in vessels or pipes. The method is used in industrial process imaging for imaging conductive fluids. In that context the technique is usually called **electrical resistance tomography** (note the slight contrast to the name used in geophysics). Metal electrodes are generally in direct contact with the fluid but electronics and reconstruction techniques are broadly similar to the medical case. In geophysics, the idea dates from the 1930s.

Theory

In biological tissue the electrical conductivity and permittivity varies between tissue types likewise depending on temperature and physiological factors. For example lungs are less conductive when the alveoli is filled with air. In EIT adhesive electrodes applied to the skin and an electric current, typically a few milli-Amperes of alternating current at a frequency of 10–100 kHz, is applied across two or more electrodes. Other electrodes are used to measure the resulting voltage. This is repeated for numerous "stimulation patterns", such as successive pairs of adjacent electrodes.

The currents used are relatively small, and certainly below the threshold at which they would cause stimulation of nerves. The frequency of the alternating current is sufficiently high not to give rise to electrolytic effects in the body and the Ohmic power dissipated is sufficiently small and diffused over the body to be easily handled by the body's thermoregulatory system.

The current is applied using current sources, either a single current source switched between electrodes using a multiplexor or a system of Voltage-to-current converters, one for each electrode, each controlled by a digital to analog converter. The measurements again may be taken either by a single voltage measurement circuit multiplexed over the

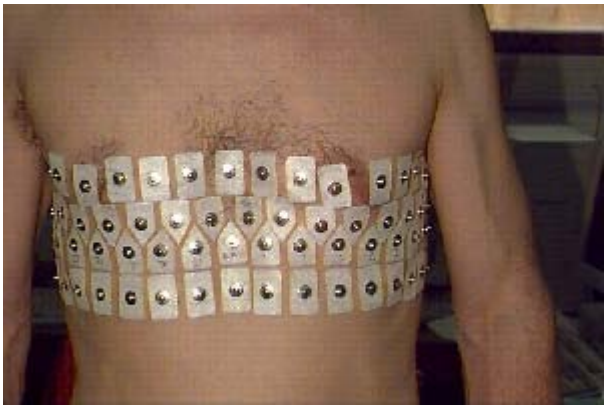
electrodes or a separate circuit for each electrode. Earlier systems typically used an analog demodulation circuit to convert the alternating voltage to a direct current level then an analog to digital converter. Many recent systems convert the alternating signal directly, the demodulation then being performed digitally. Many EIT systems are capable of working at several frequencies and can measure both the magnitude and phase of the voltage.

The voltages measured are then passed to a computer to perform the reconstruction and display of the image. If images are required in real time a typical approach is the application of some form of regularized inverse of a linearization of the forward problem. In most practical systems used in a medical setting a 'difference image' is formed. That is, the differences in voltage between two time points is left-multiplied by the regularized inverse to produce an approximate difference between the permittivity and conductivity images. Another approach is to construct a finite element model of the body and adjust the conductivities (for example using a variant of Levenburg–Marquart method) to fit the measured data. This is more challenging as it requires an accurate body shape and the exact position of the electrodes.

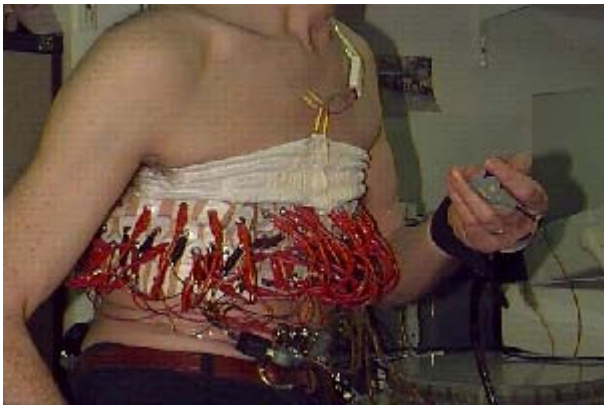
The open source project EIDORS provides a suite of programs (written in Matlab / Octave) for data reconstruction and display under the GNU/GPL license.

Lung imaging

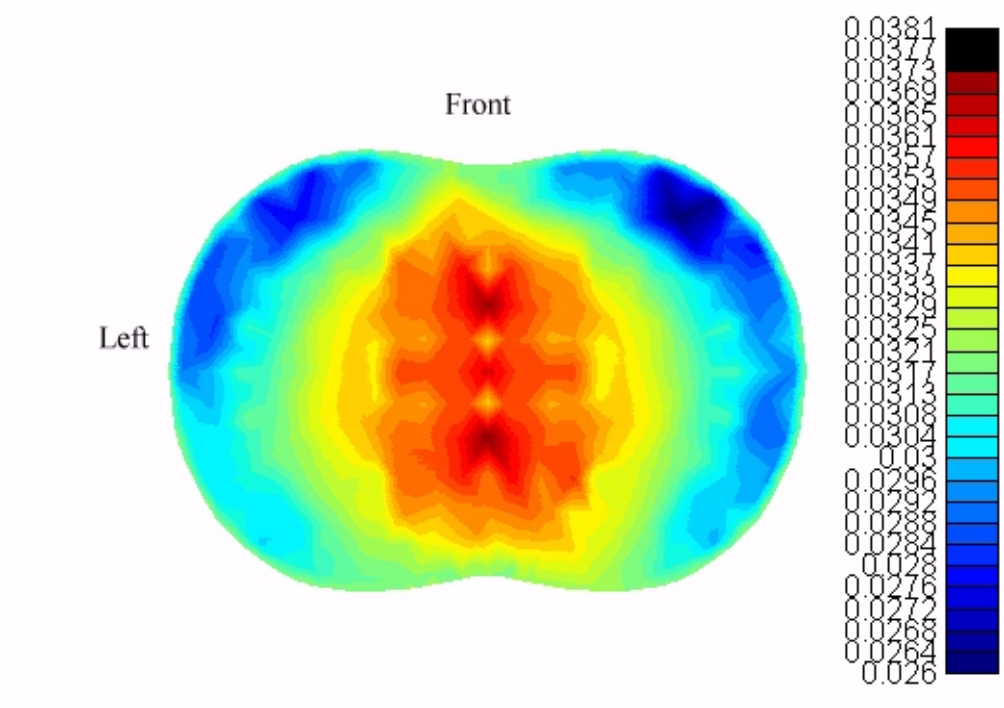
EIT is useful for monitoring patient lungs because the air has a large conductivity contrast to the other tissues in the thorax. The most promising clinical application of lung EIT measurements is for monitoring patients being treated with Mechanical ventilation. Such ventilation can often result in Ventilator-associated lung injury. EIT can resolve the changes in the distribution of lung volumes between dependent and non-dependent lung regions as ventilator parameters are changed. Thus, EIT measurements may be used to control the specific ventilator settings to maintain lung protective ventilation for each patient.



Electrodes on chest



Wires attached



Resulting image

The above images are from the EIT group at Oxford Brookes University and depict an early attempt at three dimensional EIT imaging of the chest using the OXBACT3 EIT system. The reconstructed image is a time average and shows lungs as low conductivity regions. Although an accurate chest shape was used only a 2D reconstruction algorithm was used resulting in a distorted image. The results of a similar chest study have been published.

Breast imaging

EIT is being investigated in the field of breast imaging as an alternative/complementary technique to mammography and magnetic resonance imaging (MRI) for breast cancer detection. The low specificity of mammography and of MRI result in a relatively high rate of false positive screenings, with high distress for the patient and cost for the healthcare structure. These shortcomings and concerns related to the use of ionizing radiation, for mammography, and with the nephrotoxicity of Gadolinium, the contrast agent used in breast MRI, make the development of alternative techniques highly desirable.

Literature shows that the electrical properties differ between normal and malignant breast tissues, setting the stage for cancer detection through determination of electrical properties.

A successful commercial development of non-tomographic electrical impedance imaging is the T-Scan device which has been demonstrated to improve sensitivity and specificity when used as an adjunct to screening mammography. A report to the United States Food and Drug Administration (FDA) describes a study involving 504 subjects where the sensitivity of mammography was 82%, 62% for the T-Scan alone, and 88% for the two combined. The specificity was 39% for mammography, 47% for the T-Scan alone, and 51% for the two combined.

Several research groups are across the world are actively developing the technique.

Brain imaging

EIT has been suggested as a basis for brain imaging to enable the detection and monitoring of cerebral ischemia and haemorrhage, epileptic foci localization, together with research into normal brain function and neuronal activity.

In this use EIT depends upon applying low frequency currents above the skull that are around <100 Hz since during neuronal rest at this frequency these currents remain in the extracellular space unable enter into the intracellular space within neurons. However when a neuron makes an action potential or depolarization, the resistance of its membrane preventing this reduces by a factor of 80. When this happens across large numbers of neurons a resistivity change is made of about 0.06–1.7%. This resistivity change provides a means of detecting coherent neuronal activity across large numbers of neurons and so the tomographic imaging of neural activity in the brain.

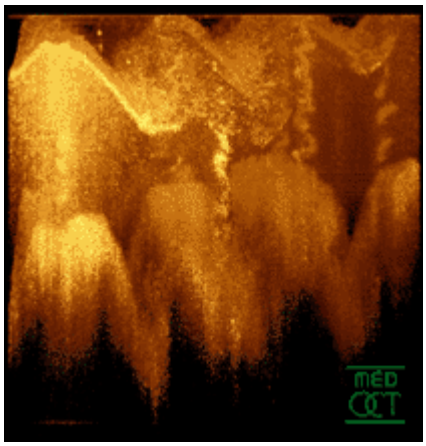
Unfortunately while such changes are detectable "they are just too small to support reliable production of images." The prospects of using this technique for imaging will depend upon improved signal processing or recording.

Commercial systems

Although medical EIT systems are not widely used several medical equipment manufactures now supply commercial versions of systems developed by university research groups. The first such system is produced by Maltron International who distribute a Sheffield Mark 3.5 system. Other manufactures include Dräger Medical, CareFusion, a respiratory monitoring company who distribute *Goe MF II* system that was developed at the University of Göttingen. Impedance Medical Technologies who manufacture systems based on designs by the Research Institute of Radioengineering and Electronics of the Russian Academy of Science in Moscow, aimed especially at breast cancer detection. Such systems typically comply with medical safety legislation and are being used by research groups in hospitals, notably in intensive care for monitoring ventilation.

Chapter 5

Optical Coherence Tomography



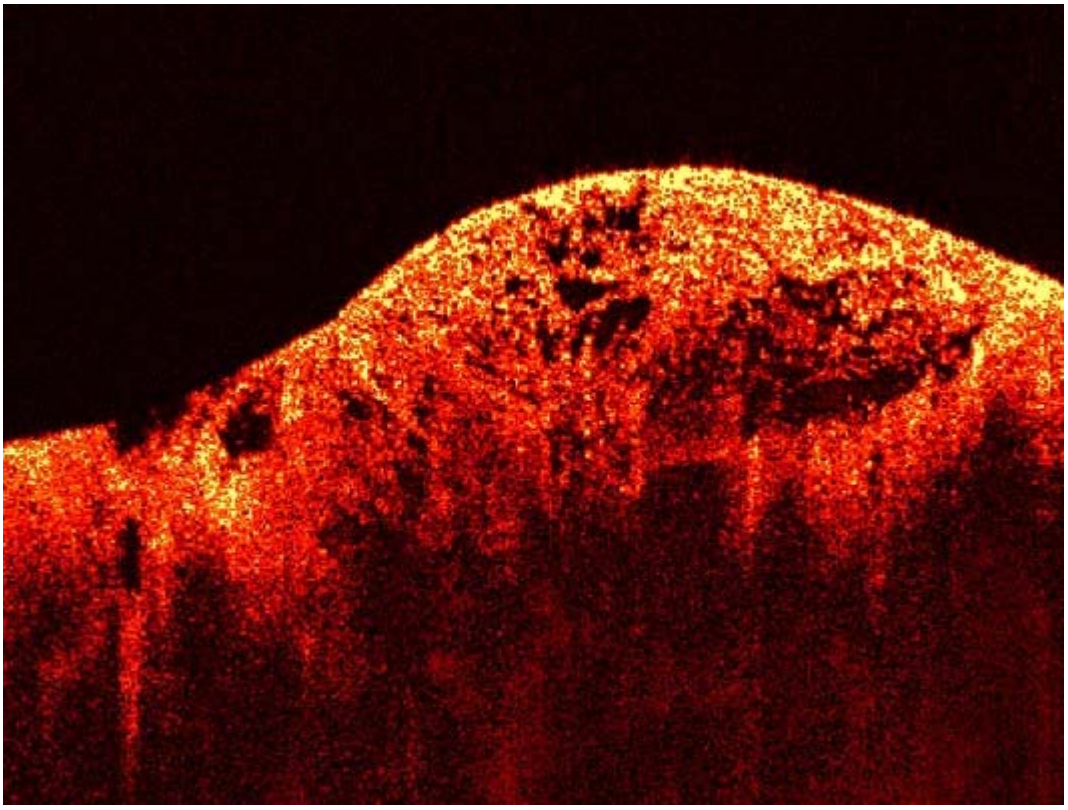
Optical coherence tomography tomogram of a fingertip

Optical coherence tomography (OCT) is an optical signal acquisition and processing method. It captures micrometer-resolution, three-dimensional images from within optical scattering media (e.g., biological tissue). Optical coherence tomography is an interferometric technique, typically employing near-infrared light. The use of relatively long wavelength light allows it to penetrate into the scattering medium. Confocal microscopy, another similar technique, typically penetrates less deeply into the sample.

Depending on the properties of the light source (superluminescent diodes and ultrashort pulsed lasers have been employed), Optical coherence tomography has achieved sub-micrometer resolution (with very wide-spectrum sources emitting over a ~100 nm wavelength range)

Optical coherence tomography is one of a class of optical tomographic techniques. A relatively recent implementation of optical coherence tomography, frequency-domain optical coherence tomography, provides advantages in signal-to-noise ratio, permitting faster signal acquisition. Commercially available optical coherence tomography systems are employed in diverse applications, including art conservation and diagnostic medicine, notably in ophthalmology where it can be used to obtain detailed images from within the retina. Recently it has also begun to be used in interventional cardiology to help diagnose coronary artery disease

Introduction



Optical Coherence Tomography (OCT) image of a sarcoma

Starting from white-light interferometry for *in vivo* ocular eye measurements imaging of biological tissue, especially of the human eye, was investigated by multiple groups worldwide. A first two-dimensional *in vivo* depiction of a human eye fundus along a horizontal meridian based on white light interferometric depth scans was presented at the ICO-15 SAT conference in 1990. Further developed in 1990 by Naohiro Tanno, then a professor at Yamagata University, and in particular since 1991 by Huang et al., optical coherence tomography (OCT) with micrometer resolution and cross-sectional imaging capabilities has become a prominent biomedical tissue-imaging technique; it is particularly suited to ophthalmic applications and other tissue imaging requiring micrometer resolution and millimeter penetration depth. First *in vivo* OCT images – displaying retinal structures – were published in 1993. OCT has also been used for various art conservation projects, where it is used to analyze different layers in a painting. OCT has critical advantages over other medical imaging systems. Medical ultrasonography, magnetic resonance imaging (MRI) and confocal microscopy are not suited to morphological tissue imaging: the first two have poor resolution; the last lacks millimeter penetration depth.

OCT bases itself upon low coherence interferometry. In conventional interferometry with long coherence length (laser interferometry), interference of light occurs over a distance of meters. In OCT, this interference is shortened to a distance of micrometers, thanks to

the use of broadband light sources (sources that can emit light over a broad range of frequencies). Light with broad bandwidths can be generated by using superluminescent diodes (superbright LEDs) or lasers with extremely short pulses (femtosecond lasers). White light is also a broadband source with lower power.

Light in an OCT system is broken into two arms—a sample arm (containing the item of interest) and a reference arm (usually a mirror). The combination of reflected light from the sample arm and reference light from the reference arm gives rise to an interference pattern, but only if light from both arms have travelled the "same" optical distance ("same" meaning a difference of less than a coherence length). By scanning the mirror in the reference arm, a reflectivity profile of the sample can be obtained (this is time domain OCT). Areas of the sample that reflect back a lot of light will create greater interference than areas that don't. Any light that is outside the short coherence length will not interfere. This reflectivity profile, called an A-scan, contains information about the spatial dimensions and location of structures within the item of interest. A cross-sectional tomograph (B-scan) may be achieved by laterally combining a series of these axial depth scans (A-scan). En face imaging (C-scan) at an acquired depth is possible depending on the imaging engine used.

Laypersons explanation

Optical Coherence Tomography, or ‘OCT’, is a technique for obtaining sub-surface images of translucent or opaque materials at a resolution equivalent to a low-power microscope. It is effectively ‘optical ultrasound’, imaging reflections from within tissue to provide cross-sectional images.

OCT is attracting interest among the medical community, because it provides tissue morphology imagery at much higher resolution (better than 10 μm) than other imaging modalities such as MRI or ultrasound.

The key benefits of OCT are:

- Live sub-surface images at near-microscopic resolution
- Instant, direct imaging of tissue morphology
- No preparation of the sample or subject
- No ionizing radiation

OCT delivers high resolution because it is based on light, rather than sound or radio frequency. An optical beam is directed at the tissue, and a small portion of this light that reflects from sub-surface features is collected. Note that most light is not reflected but, rather, scatters. The scattered light has lost its original direction and does not contribute to forming an image but rather contributes to *glare*. The glare of scattered light causes optically scattering materials (e.g., biological tissue, candle wax, or certain plastics) to appear opaque or translucent even while they do not strongly absorb light (as can be ascertained through a simple experiment — e.g., shining a red laser pointer through one's finger). Using the OCT technique, scattered light can be filtered out, completely

removing the glare. Even the very tiny proportion of reflected light that is not scattered can then be detected and used to form the image in, e.g., a scanning OCT system employing a microscope.

The physics principle allowing the filtering of scattered light is optical coherence. *Only* the reflected (non-scattered) light is coherent (i.e., retains the optical phase that causes light rays to propagate in one or another direction). In the OCT instrument, an optical interferometer is used in such a manner as to detect *only* coherent light. Essentially, the interferometer strips off scattered light from the reflected light needed to generate an image. In the process depth and intensity of light reflected from a sub-surface feature is obtained. A three-dimensional image can be built up by scanning, as in a sonar or radar system.

Within the range of noninvasive three-dimensional imaging techniques that have been introduced to the medical research community, OCT as an echo technique is similar to ultrasound imaging. Other medical imaging techniques such as computerized axial tomography, magnetic resonance imaging, or positron emission tomography do not utilize the echo-location principle.

The technique is limited to imaging 1 to 2 mm below the surface in biological tissue, because at greater depths the proportion of light that escapes without scattering is too small to be detected. No special preparation of a biological specimen is required, and images can be obtained 'non-contact' or through a transparent window or membrane. It is also important to note that the laser output from the instruments is low – eye-safe near-infra-red light is used – and no damage to the sample is therefore likely.

Theory

The principle OCT is white light or low coherence interferometry. The optical setup typically consists of an interferometer (Fig. 1, typically Michelson type) with a low coherence, broad bandwidth light source. Light is split into and recombined from reference and sample arm, respectively.

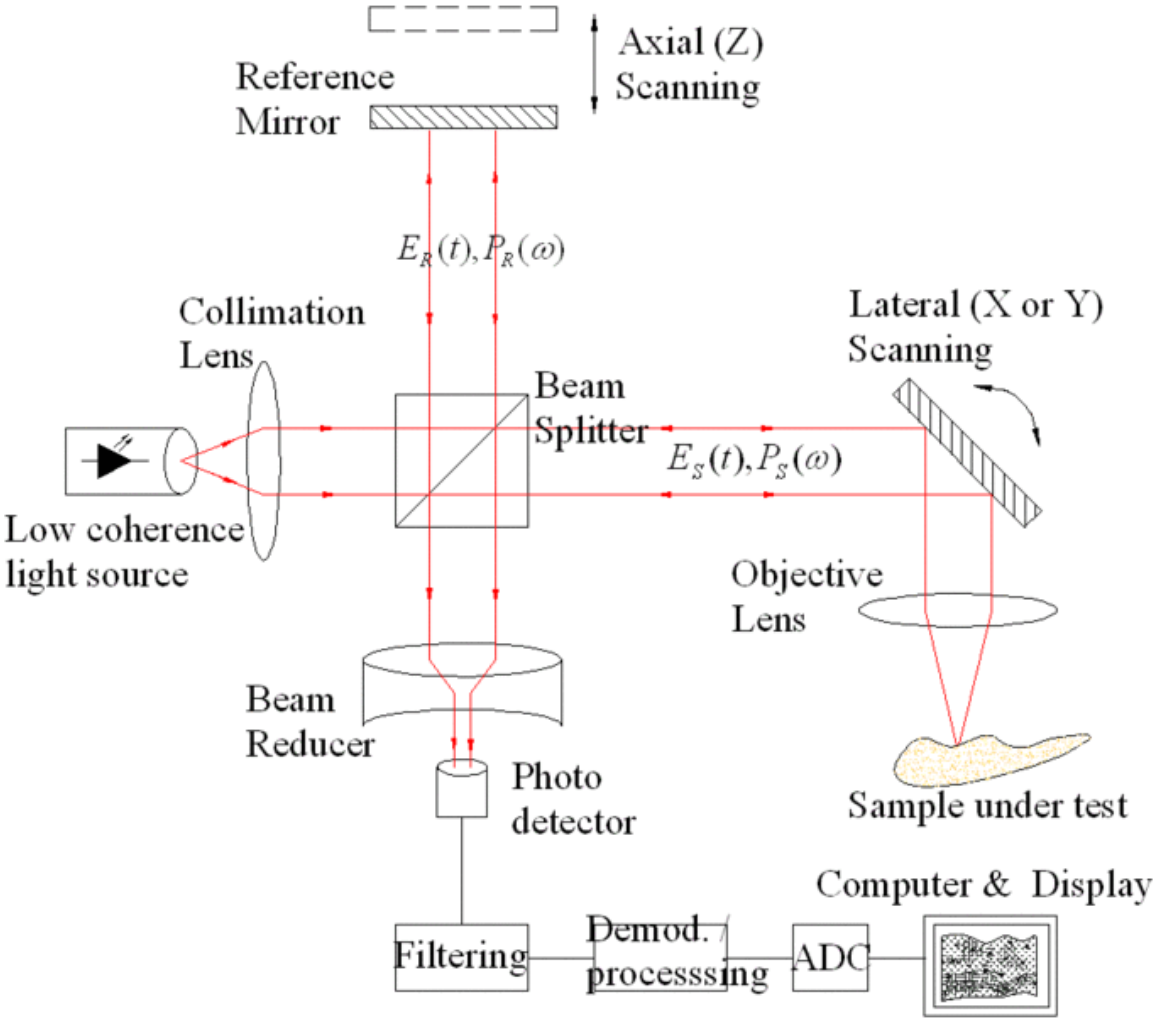


Fig. 2 Typical optical setup of single point OCT. Scanning the light beam on the sample enables non-invasive cross-sectional imaging up to 3 mm in depth with micrometer resolution.

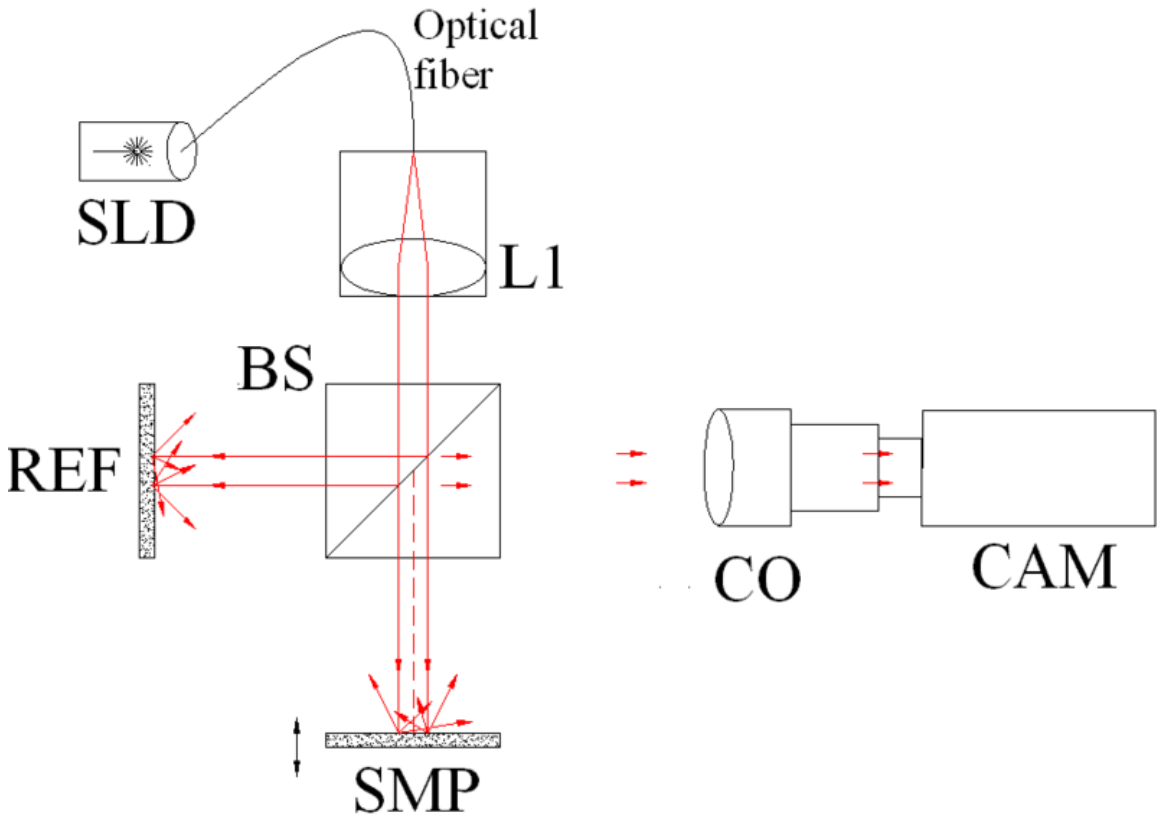


Fig. 1 Full-field OCT optical setup. Components include: super-luminescent diode (SLD), convex lens (L1), 50/50 beamsplitter (BS), camera objective (CO), CMOS-DSP camera (CAM), reference (REF) and sample (SMP). The camera functions as a two-dimensional detector array, and with the OCT technique facilitating scanning in depth, a non-invasive three dimensional imaging device is achieved.

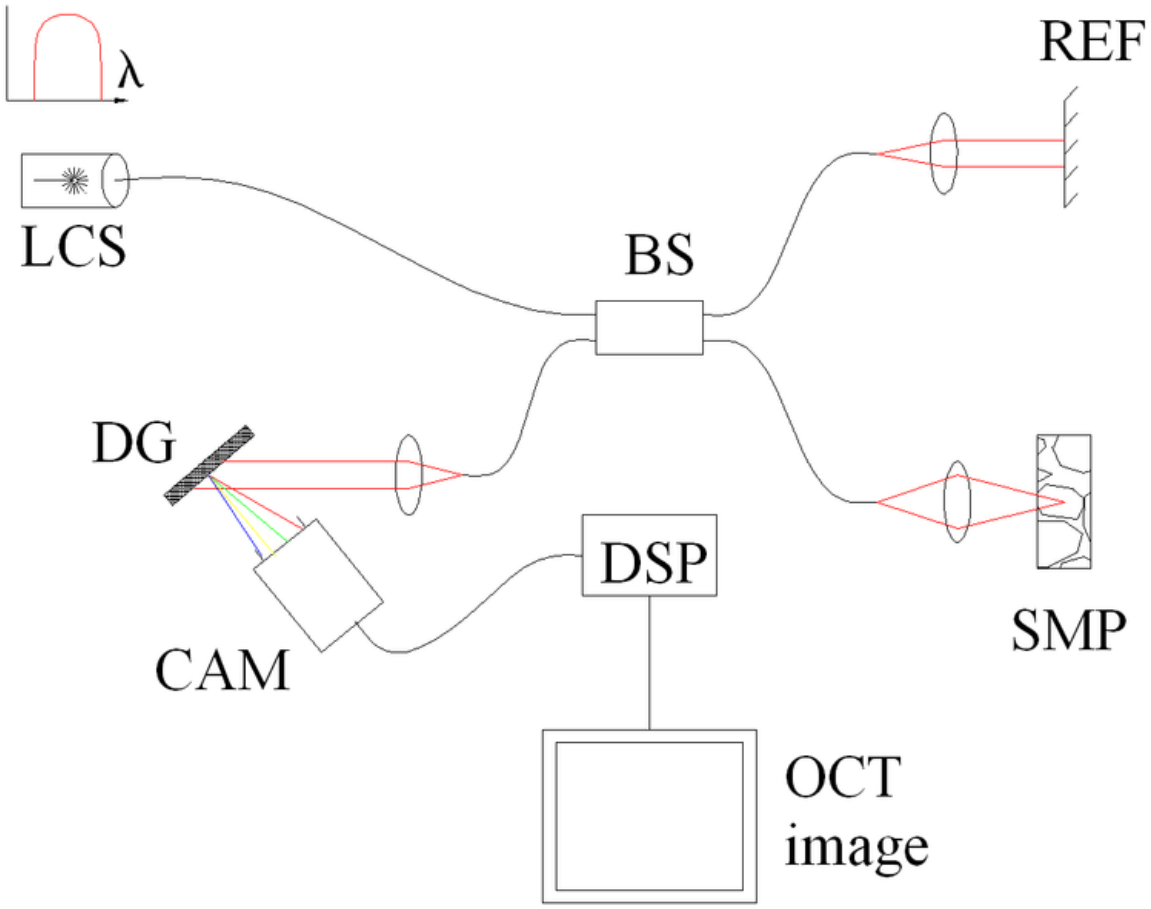


Fig. 4 Spectral discrimination by fourier-domain OCT. Components include: low coherence source (LCS), beamsplitter (BS), reference mirror (REF), sample (SMP), diffraction grating (DG) and full-field detector (CAM) act as a spectrometer, and digital signal processing (DSP)

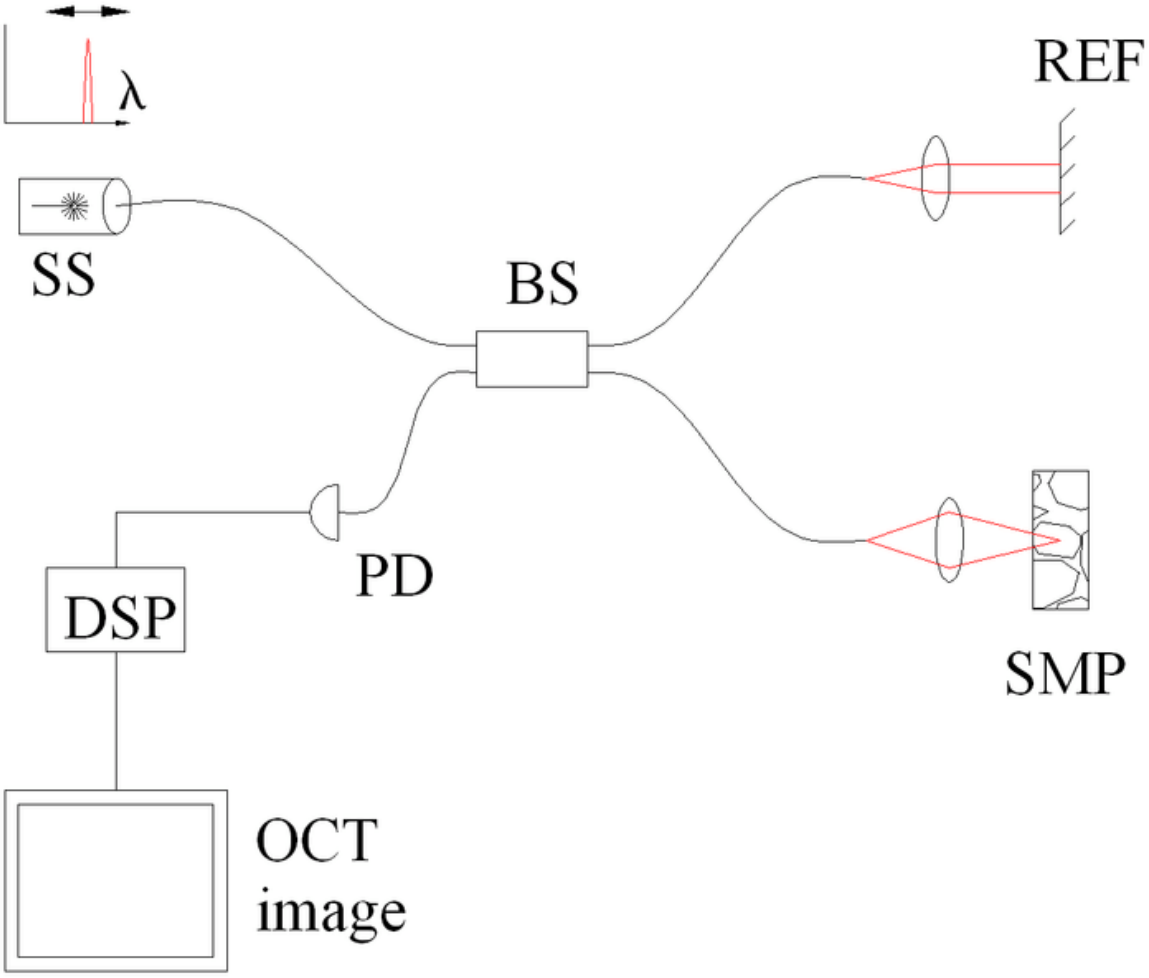


Fig. 3 Spectral discrimination by swept-source OCT. Components include: swept source or tunable laser (SS), beamsplitter (BS), reference mirror (REF), sample (SMP), photodetector (PD), digital signal processing (DSP)

Time domain OCT

In time domain OCT the pathlength of the reference arm is translated longitudinally in time. A property of low coherence interferometry is that interference, i.e. the series of dark and bright fringes, is only achieved when the path difference lies within the coherence length of the light source. This interference is called auto correlation in a symmetric interferometer (both arms have the same reflectivity), or cross-correlation in the common case. The envelope of this modulation changes as pathlength difference is varied, where the peak of the envelope corresponds to pathlength matching.

The interference of two partially coherent light beams can be expressed in terms of the source intensity, I_S, as

$$I = k_1 I_S + k_2 I_S + 2\sqrt{(k_1 I_S) \cdot (k_2 I_S)} \cdot Re\left[\gamma\left(\tau\right)\right] \qquad (1)$$

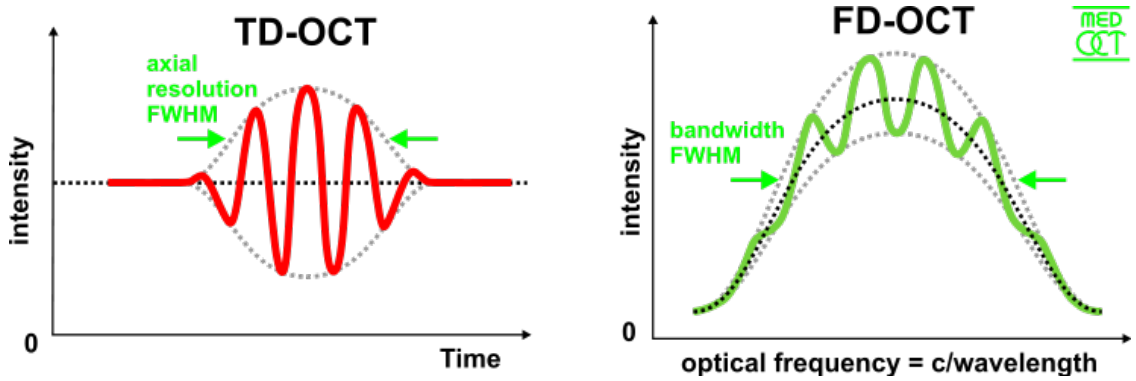
where $k_1 + k_2 < 1$ represents the interferometer beam splitting ratio, and $\gamma(\tau)$ is called the complex degree of coherence, i.e. the interference envelope and carrier dependent on reference arm scan or time delay τ, and whose recovery of interest in OCT. Due to the coherence gating effect of OCT the complex degree of coherence is represented as a Gaussian function expressed as

$$\gamma(\tau) = \exp\left[-\left(\frac{\pi \Delta\nu \tau}{2\sqrt{\ln 2}}\right)^2\right] \cdot \exp(-j2\pi\nu_0\tau) \qquad (2)$$

where $\Delta\nu$ represents the spectral width of the source in the optical frequency domain, and ν_0 is the centre optical frequency of the source. In equation (2), the Gaussian envelope is amplitude modulated by an optical carrier. The peak of this envelope represents the location of sample under test microstructure, with an amplitude dependent on the reflectivity of the surface. The optical carrier is due to the Doppler effect resulting from scanning one arm of the interferometer, and the frequency of this modulation is controlled by the speed of scanning. Therefore translating one arm of the interferometer has two functions; depth scanning and a Doppler-shifted optical carrier are accomplished by pathlength variation. In OCT, the Doppler-shifted optical carrier has a frequency expressed as

$$f_{Dopp} = \frac{2 \cdot \nu_0 \cdot v_s}{c} \qquad (3)$$

where ν_0 is the central optical frequency of the source, v_s is the scanning velocity of the pathlength variation, and c is the speed of light.



interference signals in TD vs. FD-OCT

The axial and lateral resolutions of OCT are decoupled from one another; the former being an equivalent to the coherence length of the light source and the latter being a function of the optics. The coherence length of a source and hence the axial resolution of OCT is defined as

$$l_c = \frac{2\ln 2}{\pi} \cdot \frac{\lambda_0^2}{\Delta\lambda} \approx 0.44 \cdot \frac{\lambda_0^2}{\Delta\lambda} \quad (4)$$

Frequency domain OCT (FD-OCT)

In frequency domain OCT the broadband interference is acquired with spectrally separated detectors (either by encoding the optical frequency in time with a spectrally scanning source or with a dispersive detector, like a grating and a linear detector array). Due to the Fourier relation (Wiener-Khintchine theorem between the auto correlation and the spectral power density) the depth scan can be immediately calculated by a Fourier-transform from the acquired spectra, without movement of the reference arm. This feature improves imaging speed dramatically, while the reduced losses during a single scan improve the signal to noise proportional to the number of detection elements. The parallel detection at multiple wavelength ranges limits the scanning range, while the full spectral bandwidth sets the axial resolution.

Spatially encoded frequency domain OCT (spectral domain or Fourier domain OCT)

SEFD-OCT extracts spectral information by distributing different optical frequencies onto a detector stripe (line-array CCD or CMOS) via a dispersive element (see Fig. 4). Thereby the information of the full depth scan can be acquired within a single exposure. However, the large signal to noise advantage of FD-OCT is reduced due the lower dynamic range of stripe detectors in respect to single photosensitive diodes, resulting in an SNR (signal to noise ratio) advantage of ~10 dB at much higher speeds. This is not much of a problem when working at 1300 nm, however, since dynamic range is not a serious problem at this wavelength range.

The drawbacks of this technology are found in a strong fall-off of the SNR, which is proportional to the distance from the zero delay and a sinc-type reduction of the depth dependent sensitivity because of limited detection linewidth. (One pixel detects a quasi-rectangular portion of an optical frequency range instead of a single frequency, the Fourier-transform leads to the sinc(z) behavior). Additionally the dispersive elements in the spectroscopic detector usually do not distribute the light equally spaced in frequency on the detector, but mostly have an inverse dependence. Therefore the signal has to be resampled before processing, which can not take care of the difference in local (pixelwise) bandwidth, which results in further reduction of the signal quality. However, the fall-off is not a serious problem with the development of new generation CCD or photodiode array with a larger number of pixels.

Synthetic array heterodyne detection offers another approach to this problem without the need for high dispersion.

Time encoded frequency domain OCT (also swept source OCT)

TEFD-OCT tries to combine some of the advantages of standard TD and SEFD-OCT. Here the spectral components are not encoded by spatial separation, but they are encoded in time. The spectrum either filtered or generated in single successive frequency steps and reconstructed before Fourier-transformation. By accommodation of a frequency scanning light source (i.e. frequency scanning laser) the optical setup (see Fig. 5) becomes simpler than SEFD, but the problem of scanning is essentially translated from the TD-OCT reference-arm into the TEFD-OCT light source. Here the advantage lies in the proven high SNR detection technology, while swept laser sources achieve very small instantaneous bandwidths (=linewidth) at very high frequencies (20–200 kHz). Drawbacks are the nonlinearities in the wavelength, especially at high scanning frequencies. The broadening of the linewidth at high frequencies and a high sensitivity to movements of the scanning geometry or the sample (below the range of nanometers within successive frequency steps).

Scanning schemes

Focusing the light beam to a point on the surface of the sample under test, and recombining the reflected light with the reference will yield an interferogram with sample information corresponding to a single A-scan (Z axis only). Scanning of the sample can be accomplished by either scanning the light on the sample, or by moving the sample under test. A linear scan will yield a two-dimensional data set corresponding to a cross-sectional image (X-Z axes scan), whereas an area scan achieves a three-dimensional data set corresponding to a volumetric image (X-Y-Z axes scan), also called full-field OCT.

Single point (confocal) OCT

Systems based on single point, or flying-spot time domain OCT, must scan the sample in two lateral dimensions and reconstruct a three-dimensional image using depth information obtained by coherence-gating through an axially scanning reference arm (Fig. 2). Two-dimensional lateral scanning has been electromechanically implemented by moving the sample using a translation stage, and using a novel micro-electro-mechanical system scanner.

Parallel (or full field) OCT

Parallel OCT using a charge-coupled device (CCD) camera has been used in which the sample is full-field illuminated and en face imaged with the CCD, hence eliminating the electromechanical lateral scan. By stepping the reference mirror and recording successive *en face* images a three-dimensional representation can be reconstructed. Three-dimensional OCT using a CCD camera was demonstrated in a phase-stepped technique, using geometric phase-shifting with a Linnik interferometer, utilising a pair of CCDs and heterodyne detection, and in a Linnik interferometer with an oscillating reference mirror and axial translation stage. Central to the CCD approach is the necessity for either very

fast CCDs or carrier generation separate to the stepping reference mirror to track the high frequency OCT carrier.

Smart detector array for parallel TD-OCT

A two-dimensional smart detector array, fabricated using a 2 μm complementary metal-oxide-semiconductor (CMOS) process, was used to demonstrate full-field OCT. Featuring an uncomplicated optical setup (Fig. 3), each pixel of the 58x58 pixel smart detector array acted as an individual photodiode and included its own hardware demodulation circuitry.

Selected applications

Optical coherence tomography is an established medical imaging technique. It is widely used, for example, to obtain high-resolution images of the retina and the anterior segment of the eye, which can, for example, provide a straightforward method of assessing axonal integrity in multiple sclerosis. Researchers are also seeking to develop a method that uses frequency domain OCT to image coronary arteries in order to detect vulnerable lipid-rich plaques.

Optical coherence tomography is also applicable and increasingly used in industrial applications, such as Non Destructive Testing(NDT), material thickness measurements, surface roughness characterization, surface and cross-section imaging, and volume loss measurements. OCT systems with feedback can be used to control manufacturing processes. With high speed data acquisition and sub-micron resolution, OCT is adaptable to perform both inline and off-line. Fiber-based OCT systems are particularly adaptable to industrial environments. These can access and scan interiors of hard-to-reach spaces, and are able to operate in hostile environments - whether radioactive, cryogenic or very hot.

Chapter 6

Magnetoencephalography

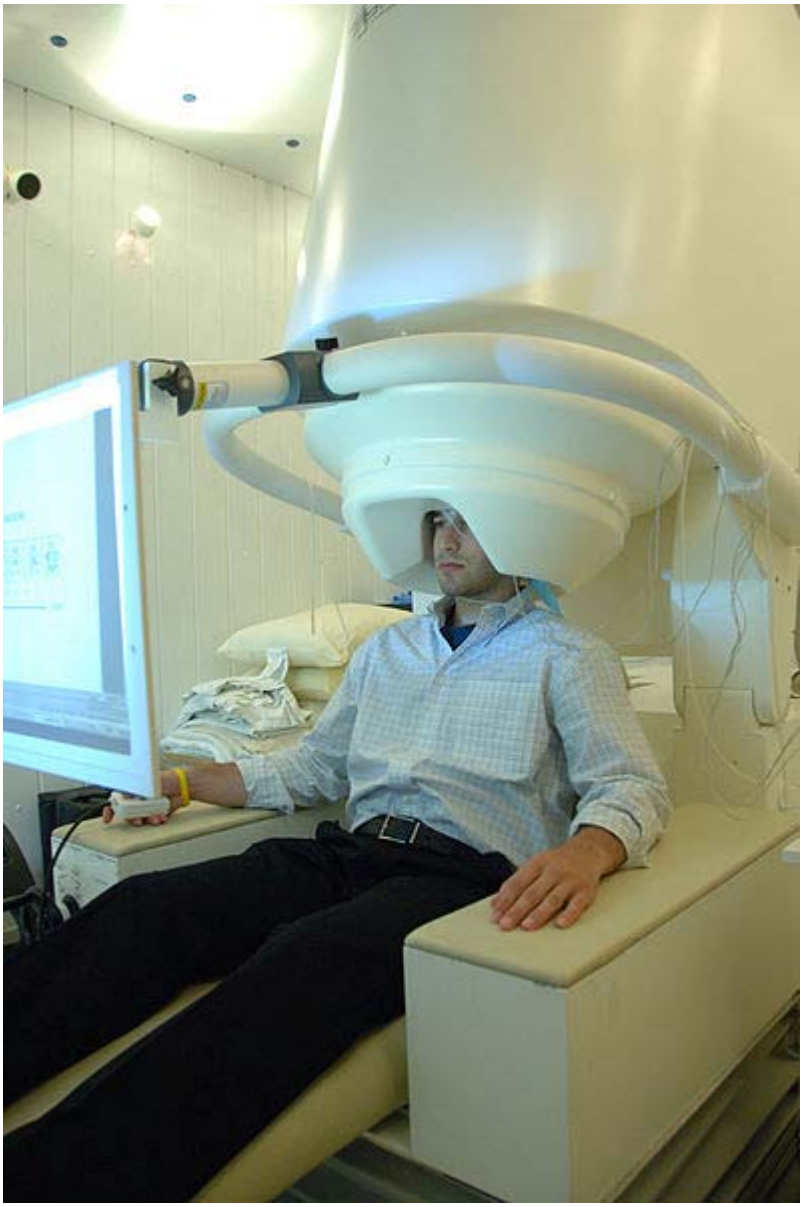
Magnetoencephalography (**MEG**) is a technique for mapping brain activity by recording magnetic fields produced by electrical currents occurring naturally in the brain, using arrays of SQUIDs (superconducting quantum interference devices). Applications of MEG include basic research into perceptual and cognitive brain processes, localizing regions affected by pathology before surgical removal, determining the function of various parts of the brain, and neurofeedback.

History of MEG

MEG signals were first measured by University of Illinois physicist David Cohen in 1968, before the availability of the SQUID, using a copper induction coil as the detector. To reduce the magnetic background noise, the measurements were made in a magnetically shielded room. The coil detector was barely sensitive enough, resulting in poor, noisy MEG measurements that were difficult to use. Later, Cohen built a better shielded room at MIT, and used one of the first SQUID detectors, just developed by James E. Zimmerman, a researcher at Ford Motor Company, to again measure MEG signals. This time the signals were almost as clear as those of EEG. This stimulated the interest of physicists who had been looking for uses of SQUIDs. Subsequently, various types of spontaneous and evoked MEGs began to be measured.

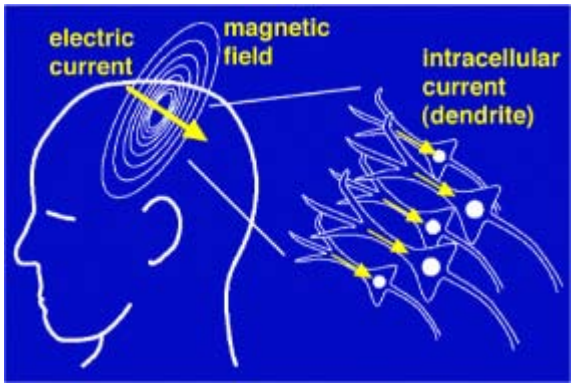
At first, a single SQUID detector was used to successively measure the magnetic field at a number of points around the subject's head. This was cumbersome, and in the 1980s, MEG manufacturers began to arrange multiple sensors into arrays to cover a larger area of the head. Present-day MEG arrays are set in helmet-shaped dewar that typically contain 300 sensors, covering most of the head. In this way, MEGs of a subject or patient can now be accumulated rapidly and efficiently.

The basis of the MEG signal



Patient undergoing an MEG

Synchronized neuronal currents induce weak magnetic fields. At 10 femtotesla (fT) for cortical activity and 10^3 fT for the human alpha rhythm, the brain's magnetic field is considerably smaller than the ambient magnetic noise in an urban environment, which is on the order of 10^8 fT or 0.1 μT. The essential problem of biomagnetism is thus the weakness of the signal relative to the sensitivity of the detectors, and to the competing environmental noise.



Origin of the brain's magnetic field. The electric current also produces the EEG signal.

The MEG (and EEG) signals derive from the net effect of ionic currents flowing in the dendrites of neurons during synaptic transmission. In accordance with Maxwell's equations, any electrical current will produce an orthogonally oriented magnetic field. It is this field which is measured. The net currents can be thought of as electric dipoles, i.e. currents with a position, orientation, and magnitude, but no spatial extent. According to the right-hand rule, a current dipole gives rise to a magnetic field that flows around the axis of its vector component.

To generate a signal that is detectable, approximately 50,000 active neurons are needed. Since current dipoles must have similar orientations to generate magnetic fields that reinforce each other, it is often the layer of pyramidal cells, which are situated perpendicular to the cortical surface, that give rise to measurable magnetic fields. Bundles of these neurons that are orientated tangentially to the scalp surface project measurable portions of their magnetic fields outside of the head, and these bundles are typically located in the sulci. Researchers are experimenting with various signal processing methods in the search for methods that detect deep brain (i.e., non-cortical) signal, but no clinically useful method is currently available.

It is worth noting that action potentials do not usually produce an observable field, mainly because the currents associated with action potentials flow in opposite directions and the magnetic fields cancel out. However, action fields have been measured from peripheral nerves.

Magnetic shielding

Since the magnetic signals emitted by the brain are on the order of a few femtoteslas, shielding from external magnetic signals, including the Earth's magnetic field, is necessary. Appropriate magnetic shielding can be obtained by constructing rooms made of aluminium and mu-metal for reducing high-frequency and low-frequency noise, respectively.

Entrance to MSR, showing the separate shielding layers

Magnetically shielded room (MSR)

A magnetically shielded room (MSR) model consists of three nested main layers. Each of these layers is made of a pure aluminium layer, plus a high permeability ferromagnetic layer, similar in composition to molybdenum permalloy. The ferromagnetic layer is supplied as 1 mm sheets, while the innermost layer is composed of four sheets in close contact, and the outer two layers are composed of three sheets each. Magnetic continuity is maintained by overlay strips. Insulating washers are used in the screw assemblies to ensure that each main layer is electrically isolated. This helps eliminate radio frequency radiation, which would degrade SQUID performance. Electrical continuity of the aluminium is also maintained by aluminium overlay strips to ensure AC eddy-current shielding, which is important at frequencies greater than 1 Hz. The junctions of the inner layer are often electroplated with silver or gold to improve conductivity of the aluminium layers.

Active shielding system

Active systems are designed for three dimensional noise cancellation. To implement an active system, low-noise fluxgate magnetometers are mounted at the center of each surface and oriented orthogonally to it. This negatively feeds a DC amplifier through a low-pass network with a slow falloff to minimize positive feedback and oscillation. Built into the system are shaking and degaussing wires. Shaking wires increase the magnetic permeability, while the permanent degaussing wires are applied to all surfaces of the inner main layer to degauss the surfaces. Moreover, noise cancellation algorithms can reduce both low-frequency and high-frequency noise. Modern systems have a noise floor of around 2–3 $fT/Hz^{0.5}$ above 1 Hz.

Source localization

The inverse problem

The challenge posed by MEG is to determine the location of electric activity within the brain from the induced magnetic fields outside the head. Problems such as this, where model parameters (the location of the activity) have to be estimated from measured data (the SQUID signals) are referred to as *inverse problems* (in contrast to *forward problems* where the model parameters (e.g. source location) are known and the data (e.g. the field at a given distance) is to be estimated.) The primary difficulty is that the inverse problem does not have a unique solution (i.e., there are infinite possible "correct" answers), and the problem of defining the "best" solution is itself the subject of intensive research. Possible solutions can be derived using models involving prior knowledge of brain activity.

The source models can be either over-determined or under-determined. An over-determined model may consist of a few point-like sources ("equivalent dipoles"), whose locations are then estimated from the data. Under-determined models may be used in cases where many different distributed areas are activated ("distributed source solutions"): there are infinitely many possible current distributions explaining the measurement results, but the most likely is selected. Localization algorithms make use of given source and head models to find a likely location for an underlying focal field generator.

Localization algorithms using overdetermined models operate by expectation-maximization: the system is initialized with a first guess. A loop is started, in which a forward model is used to simulate the magnetic field that would result from the current guess. The guess is adjusted to reduce the discrepancy between the simulated field and the measured field. This process is iterated until convergence.

The extent to which the constraint-free MEG inverse problem is ill-posed cannot be overemphasized. If one's goal is to estimate the current density within the human brain with say a 5mm resolution then it is well established that the vast majority of the information needed to perform a unique inversion must come not from the magnetic field measurement but rather from the constraints applied to the problem. Furthermore, even when a unique inversion is possible in the presence of such constraints said inversion can be unstable. These conclusions are easily deduced from published works

Magnetic source imaging

The estimated source locations can be combined with magnetic resonance imaging (MRI) images to create magnetic source images (MSI). The two sets of data are combined by measuring the location of a common set of fiducial points marked during MRI with lipid markers and marked during MEG with electrified coils of wire that give off magnetic fields. The locations of the fiducial points in each data set are then used to define a

common coordinate system so that superimposing the functional MEG data onto the structural MRI data ("coregistration") is possible.

A criticism of the use of this technique in clinical practice is that it produces colored areas with definite boundaries superimposed upon an MRI scan: the untrained viewer may not realize that the colors do not represent a physiological certainty, because of the relatively low spatial resolution of MEG, but rather a probability cloud derived from statistical processes. However, when the magnetic source image corroborates other data, it can be of clinical utility.

Dipole model source localization

A widely accepted source-modeling technique for MEG involves calculating a set of equivalent current dipoles (ECDs), which assumes the underlying neuronal sources to be focal. This dipole fitting procedure is non-linear and over-determined, since the number of unknown dipole parameters is smaller than the number of MEG measurements. Automated multiple dipole model algorithms such as MUSIC (MUltiple SIgnal Classification) and MSST (MultiStart Spatial and Temporal) modeling are applied to the analysis of MEG responses. The limitations of dipole models for characterizing neuronal responses are (1) difficulties in localizing extended sources with ECDs, (2) problems with accurately estimating the total number of dipoles in advance, and (3) dependency on dipole location, especially depth in the brain.

Distributed Source Models

Unlike multiple-dipole modeling, distributed source models divide the source space into a grid containing a large number of dipoles. The inverse problem is to obtain the dipole moments for the grid nodes. As the number of unknown dipole moments is much greater than the number of MEG sensors, the inverse solution is highly underdetermined, so additional constraints are needed to reduce ambiguity of the solution. The primary advantage of this approach is that no prior specification of the source model is necessary. However, the resulting distributions may be difficult to interpret, because they only reflect a "blurred" (or even distorted) image of the true neuronal source distribution. The matter is complicated by the fact that spatial resolution depends strongly on several parameters such as brain area, depth, orientation, number of sensors etc.

Independent component analysis (ICA)

Independent component analysis (ICA) is another signal processing solution that separates different signals that are statistically independent in time. It is primarily used to remove artifacts such as blinking, eye muscle movement, facial muscle artifacts, cardiac artifacts, etc. from MEG and EEG signals that may be contaminated with outside noise. However, ICA has poor resolution of highly correlated brain sources.

MEG use in the field

In research, MEG's primary use is the measurement of time courses of activity. MEG can resolve events with a precision of 10 milliseconds or faster, while functional MRI (fMRI), which depends on changes in blood flow, can at best resolve events with a precision of several hundred milliseconds. MEG also accurately pinpoints sources in primary auditory, somatosensory and motor areas. For creating functional maps of human cortex during more complex cognitive tasks, MEG is most often combined with fMRI, as the methods complement each other. Neuronal (MEG) and hemodynamic (fMRI) data do not necessarily agree, in spite of the tight relationship between local field potentials (LFP) and blood oxygenation level dependent (BOLD) signals. MEG and BOLD signals may originate from the same source (though the BOLD signals are filtered through the hemodynamic response).

Recent studies have reported successful classification of patients with multiple sclerosis, Alzheimer's disease, schizophrenia, Sjögren's syndrome, chronic alcoholism, and facial pain. MEG can be used to distinguish these patients from healthy control subjects, suggesting a future role of MEG in diagnostics.

Focal epilepsy

The clinical uses of MEG are in detecting and localizing pathological activity in patients with epilepsy, and in localizing eloquent cortex for surgical planning in patients with brain tumors or intractable epilepsy. The goal of epilepsy surgery is to remove the epileptogenic tissue while sparing healthy brain areas. Knowing the exact position of essential brain regions (such as the primary motor cortex and primary sensory cortex, visual cortex, and areas involved in speech production and comprehension) helps to avoid surgically induced neurological deficits. Direct cortical stimulation and somatosensory evoked potentials recorded on ECoG are considered the gold standard for localizing essential brain regions. These procedures can be performed either intraoperatively or from chronically indwelling subdural grid electrodes. Both are invasive.

Noninvasive MEG localizations of the central sulcus obtained from somatosensory evoked magnetic fields show strong agreement with these invasive recordings. MEG studies assist in clarification of the functional organization of primary somatosensory cortex and to delineate the spatial extent of hand somatosensory cortex by stimulation of the individual digits. This agreement between invasive localization of cortical tissue and MEG recordings shows the effectiveness of MEG analysis and indicates that MEG may substitute invasive procedures in the future.

Fetal MEG

MEG has been used to study cognitive processes such as vision, audition and language processing in fetuses and newborns.

Comparison with related techniques

MEG has been in development since the 1960s but has been greatly aided by recent advances in computing algorithms and hardware, and promises improved spatial resolution coupled with extremely high temporal resolution (better than 1 ms). Since the MEG signal is a direct measure of neuronal activity, its temporal resolution is comparable with that of intracranial electrodes.

MEG complements other brain activity measurement techniques such as electroencephalography (EEG), positron emission tomography (PET), and fMRI. Its strengths consist in independence of head geometry compared to EEG (unless ferromagnetic implants are present) and non-invasiveness, as opposed to PET.

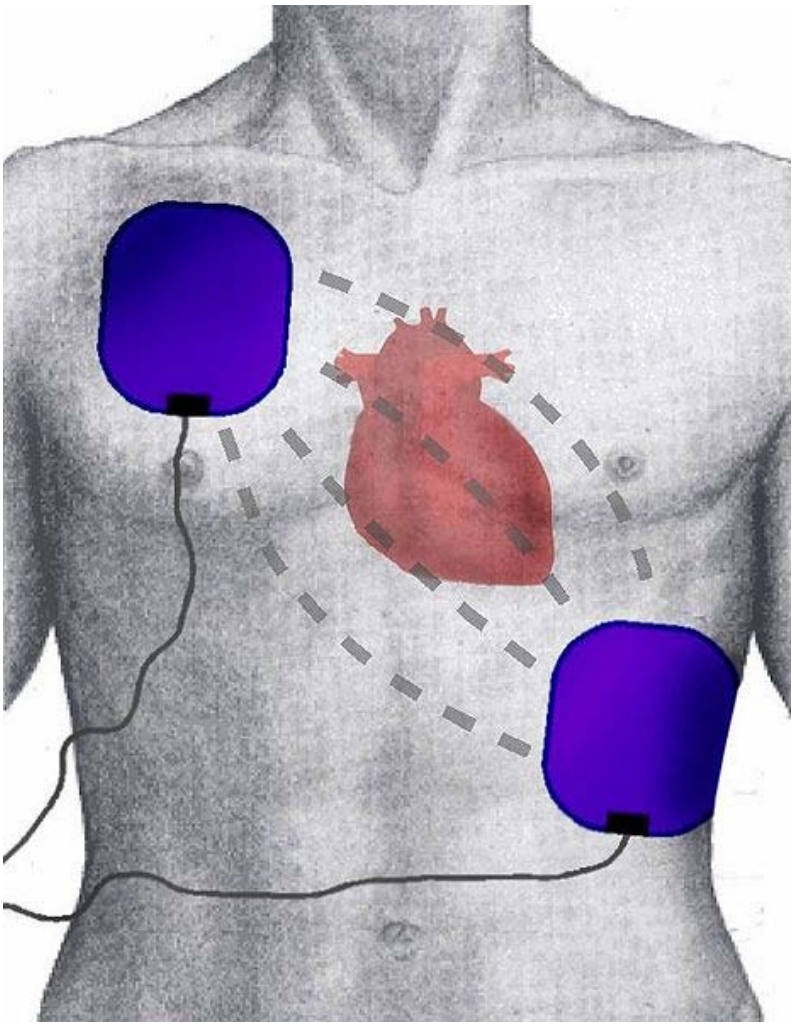
MEG vs. EEG

Although EEG and MEG signals originate from the same neurophysiological processes, there are important differences. Magnetic fields are less distorted than electric fields by the skull and scalp, which results in a better spatial resolution of the MEG. Whereas scalp EEG is sensitive to both tangential and radial components of a current source in a spherical volume conductor, MEG detects only its tangential components. MEG therefore measures activity in the sulci selectively, whereas scalp EEG measures activity both in the sulci and at the top of the cortical gyri. EEG is therefore sensitive to activity in more brain areas, but activity that is visible in MEG can also be localized with more accuracy.

Scalp EEG is sensitive to extracellular volume currents produced by postsynaptic potentials. MEG primarily detects intracellular currents associated with these synaptic potentials because the field components generated by volume currents tend to cancel out in a spherical volume conductor The decay of magnetic fields as a function of distance is more pronounced than for electric fields. MEG is therefore more sensitive to superficial cortical activity, which makes it useful for the study of neocortical epilepsy. Finally, MEG is reference-free, while scalp EEG relies on a reference that, when active, makes interpretation of the data difficult.

Chapter 7

Defibrillation



View of defibrillator position and placement, using hands free electrodes

Defibrillation is the definitive treatment for the life-threatening cardiac arrhythmias, ventricular fibrillation and pulseless ventricular tachycardia. Defibrillation consists of delivering a therapeutic dose of electrical energy to the affected heart with a device called a **defibrillator**. This depolarizes a critical mass of the heart muscle, terminates the arrhythmia, and allows normal sinus rhythm to be reestablished by the body's natural

pacemaker, in the sinoatrial node of the heart. Defibrillators can be external, transvenous, or implanted, depending on the type of device used or needed. Some external units, known as automated external defibrillators (AEDs), automate the diagnosis of treatable rhythms, meaning that lay responders or bystanders are able to use them successfully with little, or in some cases no training at all.

History

Defibrillation was first demonstrated in 1899 by Jean Louis Prevost and Frederic Batelli, two physiologists from University of Geneva, Switzerland. They discovered that small electric shocks could induce ventricular fibrillation in dogs, and that larger charges would reverse the condition.

In 1933 a Dr Albert Hyman a heart specialist at the Beth Davis Hospital of New York city and a C. Henry Hyman, an electrical engineer, looking for an alternative to injecting powerful drugs directly into the heart, came up with an invention that used an electrical shock in place of drug injection. This invention was called the *Hyman Otor* where a hollow needle is used to pass an insulated wire to the heart area to deliver the electrical shock. The hollow steel needle being one end of the circuit and the insulated wire the other end. Whether the *Hyman Otor* was a success is unknown.

The first use on a human was in 1947 by Claude Beck, professor of surgery at Case Western Reserve University. Beck's theory was that ventricular fibrillation often occurred in hearts which were fundamentally healthy, in his terms "Hearts that are too good to die", and that there must be a way of saving them. Beck first used the technique successfully on a 14 year old boy who was being operated on for a congenital chest defect. The boy's chest was surgically opened, and manual cardiac massage was undertaken for 45 minutes until the arrival of the defibrillator. Beck used internal paddles on either side of the heart, along with procainamide, an antiarrhythmic drug, and achieved return of normal sinus rhythm.

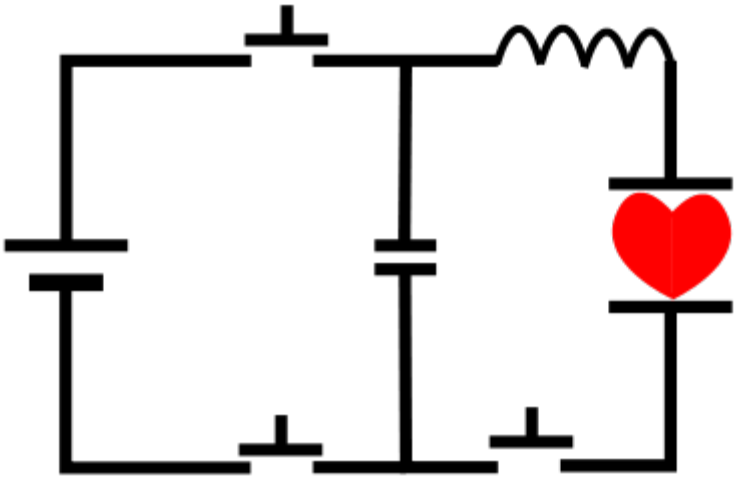
These early defibrillators used the alternating current from a power socket, transformed from the 110-240 volts available in the line, up to between 300 and 1000 volts, to the exposed heart by way of 'paddle' type electrodes. The technique was often ineffective in reverting VF while morphological studies showed damage to the cells of the heart muscle post mortem. The nature of the AC machine with a large transformer also made these units very hard to transport, and they tended to be large units on wheels.

Closed-chest method

Until the early 1950s, defibrillation of the heart was possible only when the chest cavity was open during surgery. The technique used an alternating current from a 300 or greater volt source delivered to the sides of the exposed heart by 'paddle' electrodes where each electrode was a flat or slightly concave metal plate of about 40 mm diameter. The closed-chest defibrillator device which applied an alternating current of greater than 1000 amps, conducted by means of externally applied electrodes through the chest cage to the heart,

was pioneered by Dr V. Eskin with assistance by A. Klimov in Frunze, USSR (today known as Bishkek, Kyrgyzstan) in mid 1950s.

Move to direct current



A circuit diagram showing the simplest (non-electronically controlled) defibrillator design, depending on the inductor (damping), producing a Lown, Edmark or Gurvich Waveform

In 1959 Bernard Lown commenced research into an alternative technique which involved charging of a bank of capacitors to approximately 1000 volts with an energy content of 100-200 joules then delivering the charge through an inductance such as to produce a heavily damped sinusoidal wave of finite duration (~5 milliseconds) to the heart by way of 'paddle' electrodes. The work of Lown was taken to clinical application by engineer Barouh Berkovits with his "cardioverter".

The Lown waveform, as it was known, was the standard for defibrillation until the late 1980s when numerous studies showed that a biphasic truncated waveform (BTE) was equally efficacious while requiring the delivery of lower levels of energy to produce defibrillation. A side effect was a significant reduction in weight of the machine. The BTE waveform, combined with automatic measurement of transthoracic impedance is the basis for modern defibrillators.

Portable units become available

A major breakthrough was the introduction of portable defibrillators used out of the hospital. This was pioneered in the early 1960s by Prof. Frank Pantridge in Belfast. Today portable defibrillators are among the many very important tools carried by ambulances. They are the only proven way to resuscitate a person who has had a cardiac arrest unwitnessed by EMS who is still in persistent ventricular fibrillation or ventricular tachycardia at the arrival of pre-hospital providers.

Gradual improvements in the design of defibrillators, partly based on the work developing implanted versions (see below), have led to the availability of Automated External Defibrillators. These devices can analyse the heart rhythm by themselves, diagnose the shockable rhythms, and charge to treat. This means that no clinical skill is required in their use, allowing lay people to respond to emergencies effectively.

Change to a biphasic waveform

Until the late 1980s, external defibrillators delivered a Lown type waveform which was a heavily damped sinusoidal impulse having a mainly uniphasic characteristic. Biphasic defibrillation, alternates the direction of the pulses, completing one cycle in approximately 10 milliseconds. Biphasic defibrillation was originally developed and used for implantable cardioverter-defibrillators. When applied to external defibrillators, biphasic defibrillation significantly decreases the energy level necessary for successful defibrillation, decreasing the risk of burns and myocardial damage.

Ventricular fibrillation (VF) could be returned to normal sinus rhythm in 60% of cardiac arrest patients treated with a single shock from a monophasic defibrillator. Most biphasic defibrillators have a first shock success rate of greater than 90%.

Implantable devices

A further development in defibrillation came with the invention of the implantable device, known as an implantable cardioverter-defibrillator (or ICD). This was pioneered at Sinai Hospital in Baltimore by a team that included Stephen Heilman, Alois Langer, Jack Lattuca, Morton Mower, Michel Mirowski, and Mir Imran, with the help of industrial collaborator Intec Systems of Pittsburgh. Mirowski teamed up with Mower and Staewen, and together they commenced their research in 1969 but it was 11 years before they treated their first patient. Similar developmental work was carried out by Schuder and colleagues at the University of Missouri.

The work was commenced, despite doubts amongst leading experts in the field of arrhythmias and sudden death. There was doubt that their ideas would ever become a clinical reality. In 1962 Bernard Lown introduced the external DC defibrillator. This device applied a direct current from a discharging capacitor through the chest wall into the heart to stop heart fibrillation. In 1972, Lown stated in the journal *Circulation* - "The very rare patient who has frequent bouts of ventricular fibrillation is best treated in a coronary care unit and is better served by an effective antiarrhythmic program or surgical correction of inadequate coronary blood flow or ventricular malfunction. In fact, the implanted defibrillator system represents an imperfect solution in search of a plausible and practical application."

The problems to be overcome were the design of a system which would allow detection of ventricular fibrillation or ventricular tachycardia. Despite the lack of financial backing and grants, they persisted and the first device was implanted in February 1980 at Johns

Hopkins Hospital by Dr. Levi Watkins, Jr. Modern ICDs do not require a thoracotomy and possess pacing, cardioversion, and defibrillation capabilities.

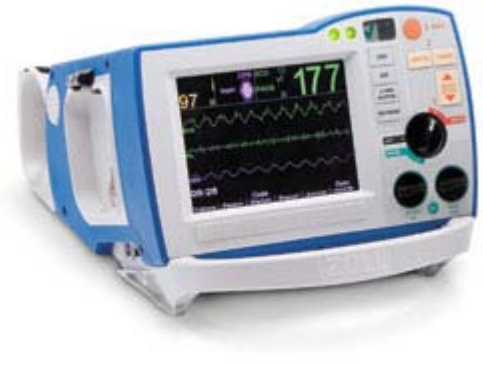
The invention of implantable units is invaluable to some regular sufferers of heart problems, although they are generally only given to those people who have already had a cardiac episode.

Types

Manual external defibrillator

External defibrillator / monitor

The units are used in conjunction with (or more often have inbuilt) electrocardiogram readers, which the healthcare provider uses to diagnose a cardiac condition (most often fibrillation or tachycardia although there are some other rhythms which can be treated by different shocks).



Manual external defibrillator monitor

The healthcare provider will then decide what charge (in joules) to use, based on proven guidelines and experience, and will deliver the shock through paddles or pads on the patient's chest. As they require detailed medical knowledge, these units are generally only found in hospitals and on some ambulances. For instance, every NHS ambulance in the United Kingdom is equipped with a manual defibrillator for use by the attending paramedics and technicians. In the United States, many advanced EMTs and all paramedics are trained to recognize lethal arrhythmias and deliver appropriate electrical therapy with a manual defibrillator when appropriate.

Manual internal defibrillator

These are the direct descendants of the work of Beck and Lown. They are virtually identical to the external version, except that the charge is delivered through internal paddles in direct contact with the heart. These are almost exclusively found in operating theatres, where the chest is likely to be open, or can be opened quickly by a surgeon.

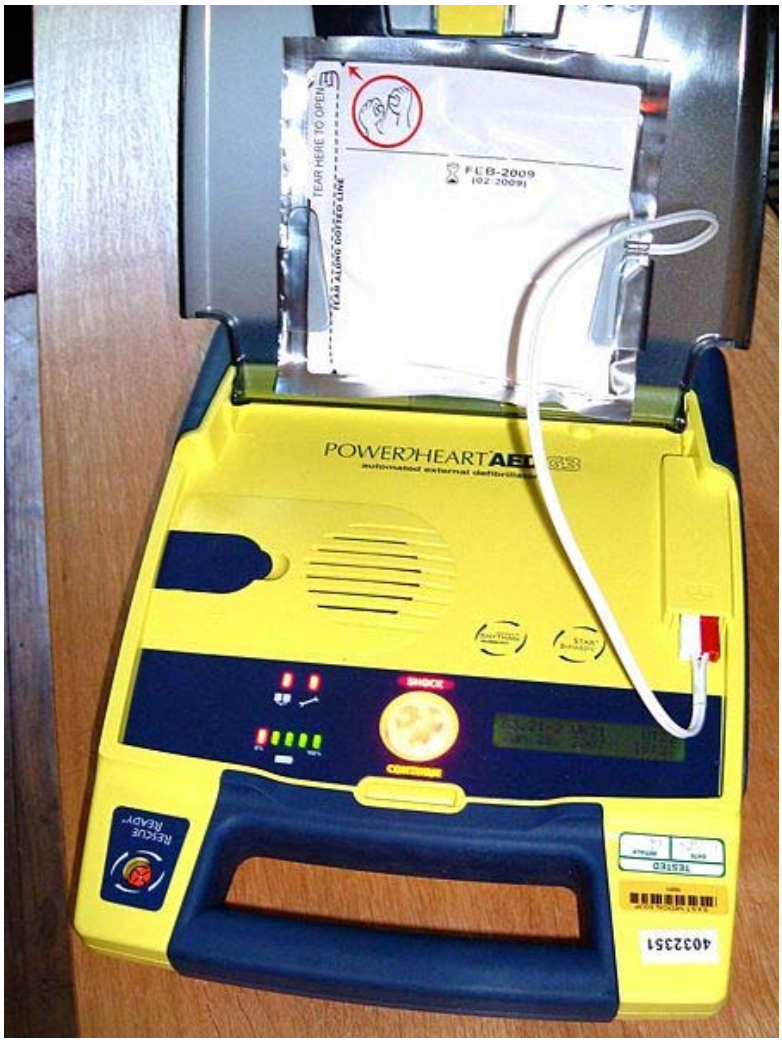
Automated external defibrillator (AED)

An AED at a railway station in Japan. The AED box has information on how to use it in Japanese, English, Chinese and Korean, and station staff are trained to use it.

These simple-to-use units are based on computer technology which is designed to analyze the heart rhythm itself, and then advise the user whether a shock is required. They are designed to be used by lay persons, who require little training to operate them correctly. They are usually limited in their interventions to delivering high joule shocks for VF (ventricular fibrillation) and VT (ventricular tachycardia) rhythms, making them generally of limited use to health professionals, who could diagnose and treat a wider range of problems with a manual or semi-automatic unit.

The automatic units also take time (generally 10–20 seconds) to diagnose the rhythm, where a professional could diagnose and treat the condition far more quickly with a manual unit. These time intervals for analysis, which require stopping chest compressions, have been shown in a number of studies to have a significant negative effect on shock success. This effect led to the recent change in the AHA defibrillation guideline (calling for two minutes of CPR after each shock without analyzing the cardiac rhythm) and some bodies recommend that AEDs should not be used when manual defibrillators and trained operators are available.

Automated external defibrillators are generally either held by trained personnel who will attend incidents, or are **public access** units which can be found in places including corporate and government offices, shopping centres, airports, restaurants, casinos, hotels, sports stadiums, schools and universities, community centers, fitness centers and health clubs.



An automated external defibrillator, open and ready for pads to be attached

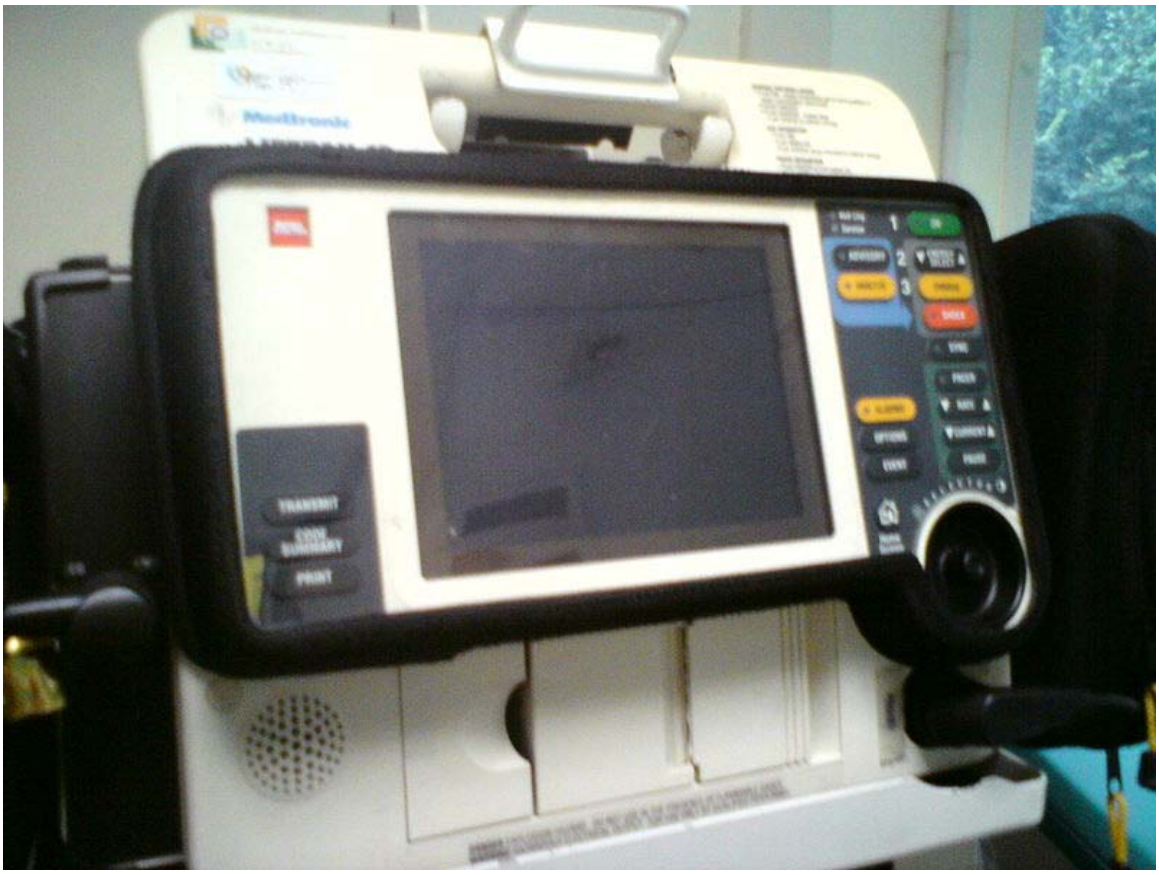
The locating of a public access AED should take in to account where large groups of people gather, and the risk category associated with these people, to ascertain whether the risk of a sudden cardiac arrest incident is high. For example, a center for teenage children is a particularly low risk category (as children very rarely enter heart rhythms such as VF (Ventricular Fibrillation) or VT (Ventricular Tachycardia), being generally young and fit, and the most common causes of pediatric cardiac arrest are respiratory arrest and trauma - where the heart is more likely to enter asystole or PEA, (where an AED is of no use). On the other hand, a large office building with a high ratio of males over 50 is a very high risk environment.

Automated-external-defibrillator

In many areas, emergency services vehicles are likely to carry AEDs. EMT-Basics in most areas are not trained in manual defibrillation, and often carry an AED instead. Some ambulances carry an AED in addition to a manual unit. In addition, some police or fire service vehicles carry an AED for first responder use. Some areas have dedicated community first responders, who are volunteers tasked with keeping an AED and taking it to any victims in their area. It is also increasingly common to find AEDs on transport such as commercial airlines and cruise ships. The presence of an AED can be a particularly decisive factor in cardiac patient survival in these scenarios, as professional medical assistance may be hours away.

In order to make them highly visible, public access AEDs often are brightly coloured, and are mounted in protective cases near the entrance of a building. When these protective cases are opened, and the defibrillator removed, some will sound a buzzer to alert nearby staff to their removal but do not necessarily summon emergency services. All trained AED operators should also know to phone for an ambulance when sending for or using an AED, as the patient will be unconscious, which always requires ambulance attendance.

Semi-automated external defibrillators



A Lifepak semi-automatic defibrillator/ECG monitor mounted in an ambulance. These units are designed for use only by healthcare professionals and are capable of measuring blood pressure and blood oxygen saturation in addition to the primary functions.

These units are a compromise between a full manual unit and an automated unit. They are mostly used by pre-hospital care professionals such as paramedics and emergency medical technicians. These units have the automated capabilities of the AED but also feature an ECG display, and a manual override, where the clinician can make their own decision, either before or instead of the computer. Some of these units are also able to act as a pacemaker if the heart rate is too slow (bradycardia) and perform other functions which require a skilled operator.

Implantable cardioverter-defibrillator (ICD)

Also known as automatic internal cardiac defibrillator (AICD). These devices are implants, similar to pacemakers (and many can also perform the pacemaking function). They constantly monitor the patient's heart rhythm, and automatically administer shocks for various life threatening arrhythmias, according to the device's programming. Many modern devices can distinguish between ventricular fibrillation, ventricular tachycardia, and more benign arrhythmias like supraventricular tachycardia and atrial fibrillation. Some devices may attempt overdrive pacing prior to synchronised cardioversion. When

the life threatening arrhythmia is ventricular fibrillation, the device is programmed to proceed immediately to an unsynchronized shock.

There are cases where the patient's ICD may fire constantly or inappropriately. This is considered a medical emergency, as it depletes the device's battery life, causes significant discomfort and anxiety to the patient, and in some cases may actually trigger life threatening arrhythmias. Some emergency medical services personnel are now equipped with a ring magnet to place over the device, which effectively disables the shock function of the device while still allowing the pacemaker to function (if the device is so equipped). If the device is shocking frequently, but appropriately, EMS personnel may administer sedation.

Wearable cardiac defibrillator

A development of the AICD is a portable external defibrillator that is worn like a vest. The unit monitors the patient 24 hours a day and will automatically deliver a biphasic shock if needed. This device is mainly indicated in patients awaiting an implantable defibrillator. Currently only one company manufactures these and they are of limited availability.

Modelling defibrillation

The efficacy of a cardiac defibrillator is highly dependent on the position of its electrodes. Most internal defibrillators are implanted in octogenarians, but a few children need the devices. Implanting defibrillators in kids is particularly difficult because children are small, will grow over time, and possess cardiac anatomy that differs from that of adults. Recently, researchers were able to create a software modeling system capable of mapping an individual’s thorax and determining the optimal position for an external or internal cardiac defibrillator.

With the help of pre-existing surgical planning applications, the software uses myocardial voltage gradients to predict the likelihood of successful defibrillation. According to the critical mass hypothesis, defibrillation is effective only if it produces a threshold voltage gradient in a large fraction of the myocardial mass. Usually, a gradient of three to five volts per centimeter is needed in 95 % of the heart. Voltage gradients of over 60 V/cm can damage tissue. The modeling software seeks to obtain safe voltage gradients above the defibrillation threshold.

Early simulations using the software suggest that small changes in electrode positioning can have large effects on defibrillation, and despite engineering hurdles that remain, the modeling system promises to help guide the placement of implanted defibrillators in children and adults.

Recent mathematical models of defibrillation are based on the bidomain model of cardiac tissue. Calculations using a realistic heart shape and fiber geometry are required to determine how cardiac tissue responds to a strong electrical shock.

Interface with the patient

The most well-known type of electrode (widely depicted in films and television) is the traditional metal paddle with an insulated (usually plastic) handle. This type must be held in place on the patient's skin while a shock or a series of shocks is delivered. Before the paddle is used, a gel must be applied to the patient's skin, in order to ensure a good connection and to minimize electrical resistance, also called chest impedance (despite the DC discharge). These are generally only found on the manual external units.

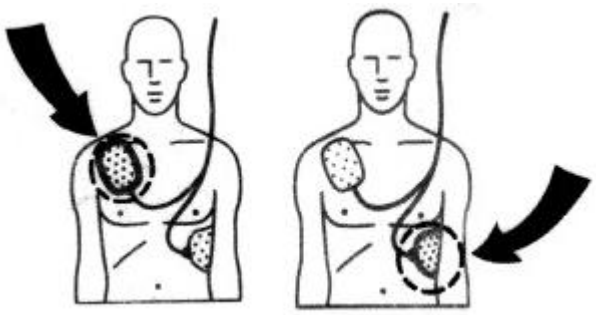
Newer types of resuscitation electrodes are designed as an adhesive pad. These are peeled off their backing and applied to the patient's chest when deemed necessary, much the same as any other sticker. These electrodes are then connected to a defibrillator. If defibrillation is required, the machine is charged, and the shock is delivered, without any need to apply any gel or to retrieve and place any paddles. These adhesive pads are found on most automated and semi-automated units, and are gradually replacing paddles entirely in non-hospital settings.

Both solid- and wet-gel adhesive electrodes are available. Solid-gel electrodes are more convenient, because there is no need to clean the patient's skin after removing the electrodes. However, the use of solid-gel electrodes presents a higher risk of burns during defibrillation, since wet-gel electrodes more evenly conduct electricity into the body.

Some adhesive electrodes are designed to be used not only for defibrillation, but also for transcutaneous pacing and synchronized electrical cardioversion.

In a hospital setting, paddles are generally preferred to pads, due to the inherent speed with which they can be placed and used. This is critical during cardiac arrest, as each second of nonperfusion means tissue loss. However, in cases in which cardiac arrest is suspected, patches placed prophalactically are superior,as they provide appropriate EKG tracing without the artifact visible from human interference with the paddles. Adhesive electrodes are also inherently safer than the paddles for the operator of the defibrillator to use, as they minimize the risk of the operator coming into physical (and thus electrical) contact with the patient as the shock is delivered, by allowing the operator to stand several feet away. Adhesive patches also require no force to remain in place and deliver the shock appropriately, whereas paddles require approximately 25 lbs of force to be applied while the shock is delivered.

Placement



Anterio-apical placement of external defibrillator electrodes (When defibrillation is unsuccessful, anterior-posterior placement is also sometimes attempted)

Resuscitation electrodes are placed according to one of two schemes. The anterior-posterior scheme (conf. image) is the preferred scheme for long-term electrode placement. One electrode is placed over the left precordium (the lower part of the chest, in front of the heart). The other electrode is placed on the back, behind the heart in the region between the scapula. This placement is preferred because it is best for non-invasive pacing.

The anterior-apex scheme can be used when the anterior-posterior scheme is inconvenient or unnecessary. In this scheme, the anterior electrode is placed on the right, below the clavicle. The apex electrode is applied to the left side of the patient, just below and to the left of the pectoral muscle. This scheme works well for defibrillation and cardioversion, as well as for monitoring an ECG.

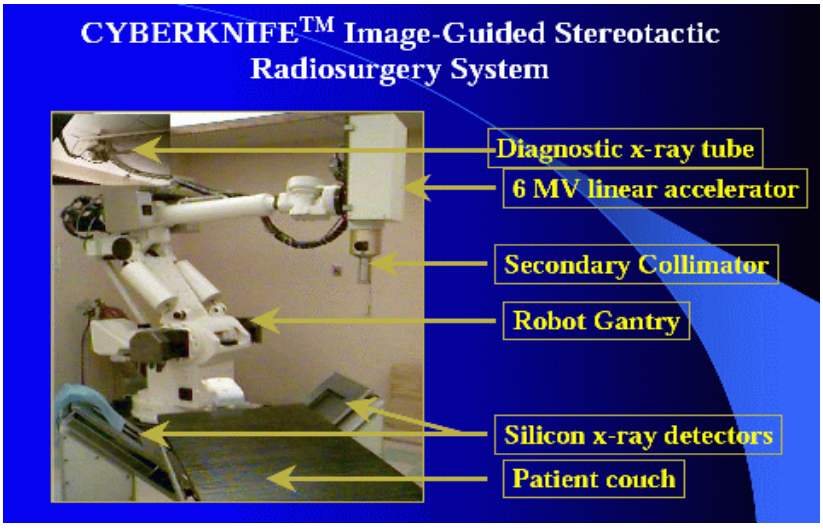
Chapter 8

Cyberknife

The **CyberKnife** is a frameless robotic radiosurgery system invented by John R. Adler, a Stanford University Professor of Neurosurgery and Radiation Oncology, and Peter and Russell Schonberg of Schonberg Research Corporation. The two main elements of the CyberKnife are (1) the radiation produced from a small linear particle accelerator and (2) a robotic arm which allows the energy to be directed at any part of the body from any direction.

The CyberKnife system is a method of delivering radiotherapy, with the intention of targeting treatment more accurately than standard radiotherapy. It is not widely available, although the number of centres offering the treatment around the world has grown in recent years to over 150, particularly centered in North America, East Asia and Europe - the first UK CyberKnife was opened at The Harley Street Clinic in February 2009.

The CyberKnife system is sold by the company Accuray, located in Sunnyvale, California. The CyberKnife system is used for treating benign tumors, malignant tumors and other medical conditions.



The main features of the CyberKnife system, shown on a Fanuc robot

Main features

Several generations of the CyberKnife system have been developed since its initial inception in 1990. There are two essential features of the CyberKnife system that set it apart from other stereotactic therapy methods.

Robotic mounting

The first is that the radiation source is mounted on a general purpose industrial robot. The original CyberKnife used a Japanese Fanuc robot, however the more modern systems use a German KUKA KR 240. Mounted on the Robot is a compact X-band linac that produces 6MV X-ray radiation. The linac is capable of delivering approximately 600 cGy of radiation each minute - a new 800 cGy / minute model was announced at ASTRO 2007. The radiation is collimated using fixed tungsten collimators (also referred to as "cones") which produce circular radiation fields. At present the radiation field sizes are: 5, 7.5, 10, 12.5, 15, 20, 25, 30, 35, 40, 50 and 60 mm. ASTRO 2007 also saw the launch of the IRIS variable-aperture collimator which uses two offset banks of six prismatic tungsten segments to form a blurred regular dodecagon field of variable size which eliminates the need for changing the fixed collimators. Mounting the radiation source on the robot allows near-complete freedom to position the source within a space about the patient. The robotic mounting allows very fast repositioning of the source, which enables the system to deliver radiation from many different directions without the need to move both the patient and source as required by current gantry configurations.

Image guidance

The image guidance system is the other essential item in the CyberKnife system. X-ray imaging cameras are located on supports around the patient allowing instantaneous X-ray images to be obtained.

6D skull

The original (and still utilized) method is called 6D or skull based tracking. The X-ray camera images are compared to a library of computer generated images of the patient anatomy. Digitally Reconstructed Radiographs (or DRR's) and a computer algorithm determines what motion corrections have to be given to the robot because of patient movement. This imaging system allows the CyberKnife to deliver radiation with an accuracy of 0.5mm without using mechanical clamps attached to the patient's skull. The use of the image guided technique is referred to as *frameless* stereotactic radiosurgery. This method is referred to as 6D because corrections are made for the 3 translational motions (X,Y and Z) and three rotational motions. It should be noted that it is necessary to use some anatomical or artificial feature to orient the robot to deliver X-ray radiation, since the tumor is never sufficiently well defined (if visible at all) on the X-ray camera images.

6D Skull tracking

Xsight

Additional image guidance methods are available for spinal tumors and for tumors located in the lung. For a tumor located in the spine, a variant of the image guidance called Xsight-Spine is used. The major difference here is that instead of taking images of the skull, images of the spinal processes are used. Whereas the skull is effectively rigid and non-deforming, the spinal vertebrae can move relative to each other, this means that image warping algorithms must be used to correct for the distortion of the X-ray camera images.

A recent enhancement to Xsight is Xsight-Lung which allows tracking of some lung tumors without the need to implant fiduciary markers.

Fiducial

For soft tissue tumors, a method known as fiducial tracking can be utilized. Small metal markers (fiducials) made out of gold for bio-compatibility and high density to give good contrast on X-ray images are surgically implanted in the patient. This is carried out by an

interventional radiologist, or neurosurgeon. The placement of the fiducials is a critical step if the fiducial tracking is to be used. If the fiducials are too far from the location of the tumor, or are not sufficiently spread out from each other it will not be possible to accurately deliver the radiation. Once these markers have been placed, they are located on a CT scan and the image guidance system is programmed with their position. When X-ray camera images are taken, the location of the tumor relative to the fiducials is determined, and the radiation can be delivered to any part of the body. Thus the fiducial tracking does not require any bony anatomy to position the radiation. Fiducials are known however to migrate and this can limit the accuracy of the treatment if sufficient time is not allowed between implantation and treatment for the fiducials to stabilize.

Synchrony

The final technology of image guidance that the CyberKnife system can use is called the Synchrony system. The Synchrony system is utilized primarily for tumors that are in motion while being treated, such as lung tumors and pancreatic tumors.

The synchrony system uses a combination of surgically placed internal fiducials, and light emitting optical fibers (markers) mounted on the patient skin. Since the tumor is moving continuously, to continuously image its location using X-ray cameras would require prohibitive amounts of radiation to be delivered to the patients skin. The Synchrony system overcomes this by periodically taking images of the internal fiducials, and predicting their location at a future time using the motion of the markers that are located on the patient's skin. The light from the markers can be tracked continuously using a CCD camera, and are placed so that their motion is correlated with the motion of the tumor.

A computer algorithm creates a correlation model that represents how the internal fiducial markers are moving compared to the external markers. The Synchrony system is therefore continuously predicting the motion of the internal fiducials, and therefore the tumor, based on the motion of the markers. The correlation model can be updated at any time if the patient breathing becomes in any way irregular. The advantage of the Synchrony system is that no assumptions about the regularity or reproducibility of the patient breathing have to be made.

To function properly, the Synchrony system requires that for any given correlation model there is a functional relationship between the markers and the internal fiducials. The external marker placement is also important, and the markers are usually placed on the patient abdomen so that their motion will reflect the internal motion of the diaphragm and the lungs.

RoboCouch

A new robotic six degree of freedom patient treatment couch called RoboCouch has been added to the CyberKnife which provides the capability for significantly improving patient positioning options for treatment.

Frameless

The frameless nature of the CyberKnife also increases the clinical efficiency. In conventional frame-based radiosurgery, the accuracy of treatment delivery is determined solely by connecting a rigid frame to the patient which is anchored to the patient's skull with invasive aluminum or titanium screws. The CyberKnife is the only radiosurgery device that does not require such a frame for precise targeting. Once the frame is connected, the relative position of the patient anatomy must be determined by making a CT or MRI scan. After the CT or MRI scan has been made, a radiation oncologist must plan the delivery of the radiation using a dedicated computer program, after which the treatment can be delivered, and the frame removed. The use of the frame therefore requires a linear sequence of events that must be carried out sequentially before another patient can be treated. Staged CyberKnife radiosurgery is of particular benefit to patients who have previously received large doses of conventional radiation therapy and patients with gliomas located near critical areas of the brain. Unlike whole brain radiotherapy, which must be administered daily over several weeks, radiosurgery treatment can usually be completed in 1-5 treatment sessions. Radiosurgery can be used alone to treat brain metastases, or in conjunction with surgery or whole brain radiotherapy, depending on the specific clinical circumstances.

By comparison, using a frameless system, a CT scan can be carried out on any day prior to treatment that is convenient. The treatment planning can also be carried out at any time prior to treatment. During the treatment the patient need only be positioned on a treatment table and the predetermined plan delivered. This allows the clinical staff to plan many patients at the same time, devoting as much time as is necessary for complicated cases without slowing down the treatment delivery. While a patient is being treated, another clinician can be considering treatment options and plans, and another can be conducting CT scans.

In addition, very young patients (pediatric cases) or patients with fragile heads because of prior brain surgery cannot be treated using a frame based system. Also, by being frameless the CyberKnife can efficiently re-treat the same patient without repeating the preparation steps that a frame-based system would require.

The delivery of a radiation treatment over several days or even weeks (referred to as fractionation) can also be beneficial from a therapeutic point of view. Tumor cells typically have poor repair mechanisms compared to healthy tissue, so by dividing the radiation dose into fractions the healthy tissue has time to repair itself between treatments. This can allow a larger dose to be delivered to the tumor compared to a single treatment.

Comparison with other stereotactic systems

Gamma Knife

One of the most widely known stereotactic radiosurgery systems is the Gamma Knife. The Gamma Knife was originally developed by Lars Leksell, remains the gold standard method for delivery of stereotactic radiosurgery to the brain and is manufactured by Elekta. John Adler, the inventor of the CyberKnife system spent time training with Lars Leksell in Stockholm at the Karolinska Institute in 1985. The GammaKnife system uses 201 Cobalt-60 sources located in a ring around a central treatment point ("isocenter"). The Gamma Knife system is equipped with a series of 4 collimators of 4mm, 8mm, 12mm and 16mm diameter, and is capable of submillimeter accuracies. The Gamma Knife system does however require a head frame to be bolted onto the skull of the patient, and is only capable of treating cranial lesions. As a result of frame placement, treatment with Gamma Knife does not require real time imaging capability as the frame does not allow movement during treatment. This is the reason that the Gamma Knife system is likely to be more accurate than Cyber Knife. The Cyberknife Society and Accuray maintain that there are no peer-reviewed published papers that establish Gamma Knife as being more accurate than CyberKnife.

Novalis

Another popular Stereotactic system is the Novalis produced by Brainlab. The Novalis radiosurgery system utilizes a small computer controlled micro Multi Leaf Collimator mMLC, that can produce many complicated shapes. The maximum radiation field size that the Novalis can produce is 98 mm x 98 mm, and the minimum is 3mm x 3mm allowing a considerable range of tumors to be treated. The Novalis system also has X-ray imaging using amorphous silicon flat panel X-ray detectors. A 2D/3D image fusion of the patient setup X-rays with digitally reconstructed radiographs from a planning CT scan quickly determines a correction vector for the patients position. Infrared fiducial markers attached to the patient then allow precise tracking of the correction vector's application to the patient's position via an infrared camera and a couch that can move in all six dimensions enables the precise positioning of the patient. Patient immobilization can also be performed framelessly using the patients internal anatomy as the frame of reference. An implanted marker based respiratory tracking option known as ExacTrac Gating is also an option. BrainLAB's Novalis has become a leading player in the world of neurosurgery.

Conventional linac

Conventional X-ray therapy linear accelerators can be utilized for radiosurgery, either by the use of additional blocking cones or by a removable or built in micro MLC system. Examples of removable micro MLC units are the Ergo from 3D line, the mMLC manufactured by Brainlab, and the AccuKnife produced by Direx., or the Novalis TX

Clinical uses

Since August 2001, the CyberKnife system has FDA clearance for treatment of tumors in any location of the body. Some of the tumors treated include: pancreas, liver, prostate, Spinal Lesions, head and neck cancers, and benign tumors.

None of these studies have shown any general survival benefit over conventional treatment methods. By increasing the accuracy with which treatment is delivered there is a potential for dose escalation, and potentially a subsequent increase in effectiveness, particularly in local control rates. However the studies cited are so far limited in scope, and more extensive research will need to be completed in order to show any effects on survival.

In 2008 actor Patrick Swayze was among the people to be treated with Cyberknife radiotherapy.

Cyberknife worldwide locations

CyberKnife systems have been installed in over 150 locations worldwide, including 100 hospitals in the United States. For example, in the US, they are installed at St Mary's-Duluth Clinic in Duluth, Minnesota, Mission Hospital of Asheville of North Carolina has been operating CyberKnife Radiosurgery since 2005, the Community Cancer Center between OSF St. Joseph Medical Center and BroMenn Regional Medical Center in Bloomington-Normal, Illinois. Stanford University Medical Center (Blake Wilbur Cyberknife Center) and the Comprehensive Cancer Center at Stanford University, Georgetown University Hospital, UCSF Medical Center, St. Mary's of Michigan, Kennestone Hospital in Georgia, Baylor University Medical Center, St. Luke's Episcopal Hospital, the University of Pittsburgh, CyberKnife Centers of San Diego in central San Diego and CyberKnife of Southern California at Vista, Apollo Specialty Hospitals, India, Healthcare Global (HCG) at Bangalore, India. Additional locations in the United States include the Denver CyberKnife in Colorado, Cyberknife Center at Capital Health in Trenton, New Jersey, Philadelphia CyberKnife, Rocky Mountain CyberKnife in Boulder, Colorado, Salt Lake CyberKnife, Reno CyberKnife, CyberKnife St. Louis - St. Louis University Hospital - St. Louis, MO, Oklahoma CyberKnife in Tulsa, Oklahoma, and North Broward Medical Center Deerfield Beach, FL. The first CyberKnife outside of Stanford University where it was developed was installed at Newport Diagnostic Center (NDC) in Newport Beach, Calif. In January, 2010, NDC installed the latest CyberKnife, the G4800 MU. The CyberKnife Institute at Mercy Hospital in Miami, Florida was installed in January, 2010 and the first patient was treated on January 14, 2010.

Stanford University has treated over 2,500 patients using the Cyberknife system, and worldwide over 40,000 patients have been treated.

Overlook Hospital in Summit, New Jersey was the first hospital in the New York metro area to offer the CyberKnife Stereotactic Radiosurgery System. Today, Overlook has performed the second most treatments of prostate cancer with the cyberknife in the world.

There are 19 centers in Japan, 5 in China, 5 in South Korea, 5 in Taiwan ROC, 3 in France, 3 in Italy, 3 in Canada (1 each in Montreal, Ottawa, and Hamilton), 2 in India(Apollo cancer speciality hospital Chennai, Banglore Institute of Oncology, Banglore) and Turkey, and 1 each in Czech Republic,Poland, Germany, Greece, Spain, Netherlands, Switzerland, United Kingdom- the first UK CyberKnife was opened at The Harley Street Clinic in February 2009. India, Malaysia, Thailand in Ramathibodi Hospital and Vietnam.*

Chapter 9

Brachytherapy

Brachytherapy (from the Greek word *brachys*, meaning "short-distance"), also known as **internal radiotherapy**, **sealed source radiotherapy**, **curietherapy** or **endocurietherapy**, is a form of radiotherapy where a radiation source is placed inside or next to the area requiring treatment. Brachytherapy is commonly used as an effective treatment for cervical, prostate, breast, and skin cancer and can also be used to treat tumours in many other body sites. Brachytherapy can be used alone or in combination with other therapies such as surgery, External Beam Radiotherapy (EBRT) and chemotherapy.

In contrast to EBRT in which high-energy x-rays are directed at the tumour from outside the body, brachytherapy involves the precise placement of radiation sources directly at the site of the cancerous tumour. A key feature of brachytherapy is that the irradiation only affects a very localized area around the radiation sources. Exposure to radiation of healthy tissues further away from the sources is therefore reduced. In addition, if the patient moves or if there is any movement of the tumour within the body during treatment, the radiation sources retain their correct position in relation to the tumour. These characteristics of brachytherapy provide advantages over EBRT - the tumour can be treated with very high doses of localised radiation, whilst reducing the probability of unnecessary damage to surrounding healthy tissues.

A course of brachytherapy can be completed in less time than other radiotherapy techniques. This can help reduce the chance of surviving cancer cells dividing and growing in the intervals between each radiotherapy dose. Patients typically have to make fewer visits to the radiotherapy clinic compared with EBRT, and the treatment is often performed on an outpatient basis. This makes treatment accessible and convenient for many patients. These features of brachytherapy reflect that most patients are able to tolerate the brachytherapy procedure very well.

Brachytherapy represents an effective treatment option for many types of cancer. Treatment results have demonstrated that the cancer cure rates of brachytherapy are either comparable to surgery and EBRT, or are improved when used in combination with these techniques. In addition, brachytherapy is associated with a low risk of serious adverse side effects.

History

Brachytherapy dates back to 1901 (shortly after the discovery of radioactivity by Becquerel in 1896) when Pierre Curie suggested to Henri-Alexandre Danlos that a radioactive source could be inserted into a tumour. It was found that the radiation caused the tumour to shrink. Independently, Alexander Graham Bell also suggested the use of radiation in this way. In the early twentieth century, techniques for the application of brachytherapy were pioneered at the Curie institute in Paris by Danlos and at St Luke's and Memorial Hospital in New York by Robert Abbe.

Following initial interest in brachytherapy in Europe and the US, its use declined in the middle of the twentieth century due to the problem of radiation exposure to operators from the manual application of the radioactive sources.

However, the development of remote afterloading systems, which allow the radiation to be delivered from a shielded safe, and the use of new radioactive sources in the 1950s and 1960s, reduced the risk of unnecessary radiation exposure to the operator and patients. This, together with more recent advancements in three dimensional imaging modalities, computerised treatment planning systems and delivery equipment has made brachytherapy a safe and effective treatment for many types of cancer today.

Types

Different types of brachytherapy can be defined according to (1) the placement of the radiation sources in the target treatment area, (2) the rate or ‘intensity’ of the irradiation dose delivered to the tumour, and (3) the duration of dose delivery.

Source placement

The two main types of brachytherapy treatment in terms of the placement of the radioactive source are **interstitial** and **contact**.

- In the case of interstitial brachytherapy, the sources are placed directly in the target tissue of the affected site, such as the prostate or breast.

- Contact brachytherapy involves placement of the radiation source in a space next to the target tissue. This space may be a body cavity (**intracavitary** brachytherapy) such as the cervix, uterus or vagina; a body lumen (**intraluminal** brachytherapy) such as the trachea or oesophagus; or externally (**surface** brachytherapy) such as the skin. A radiation source can also be placed in blood vessels (**intravascular** brachytherapy) for the treatment of coronary in-stent restenosis.

Dose rate

The dose rate of brachytherapy refers to the level or ‘intensity’ with which the radiation is delivered to the surrounding medium and is expressed in Grays per hour (Gy/h).

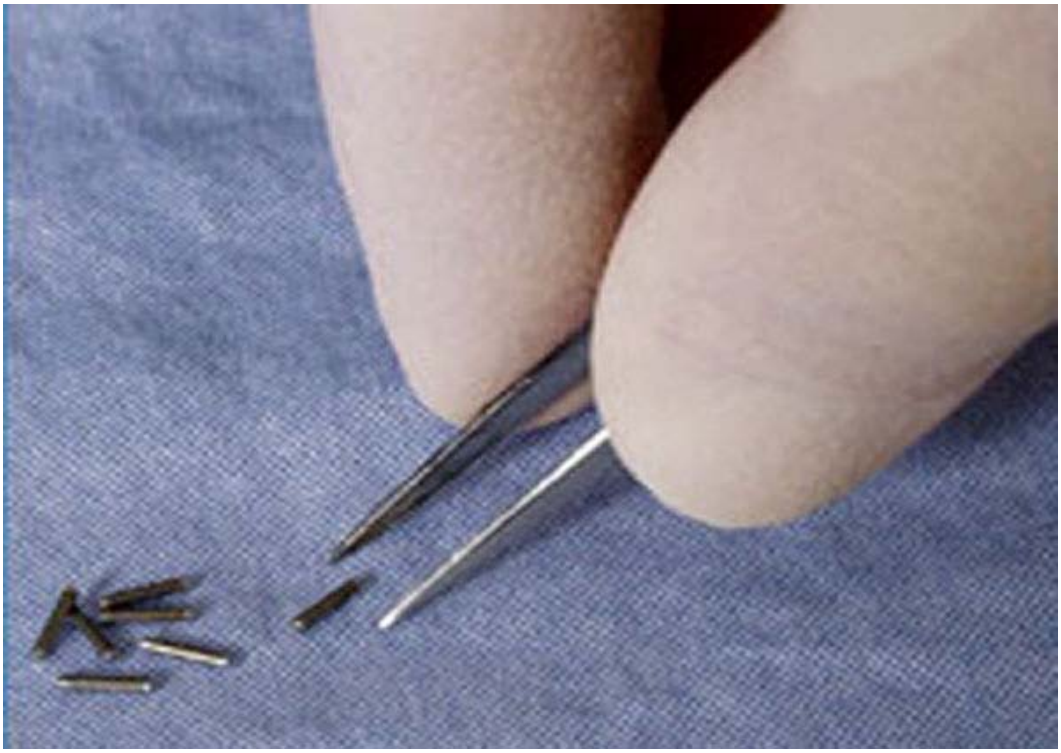
- **Low-dose rate(LDR)** brachytherapy involves implanting radiation sources that emit radiation at a rate of up to 2 Gy.hr-1. LDR brachytherapy is commonly used for cancers of the oral cavity, oropharynx, sarcomas and prostate cancer

- **Medium-dose rate (MDR)** brachytherapy is characterized by a medium rate of dose delivery, ranging between 2 Gy.hr-1 to 12 Gy.hr-1.

- **High-dose rate (HDR)** brachytherapy is when the rate of dose delivery exceeds 12 Gy.hr-1. The most common applications of HDR brachytherapy are in tumours of the cervix, oesophagus, lungs, breasts and prostate. Most HDR treatments are performed on an outpatient basis, but this is dependent on the treatment site.

- **Pulsed-dose rate (PDR)** brachytherapy involves short pulses of radiation, typically once an hour, to simulate the overall rate and effectiveness of LDR treatment. Typical tumour sites treated by PDR brachytherapy are gynaecological and head and neck cancers.

Duration of dose delivery



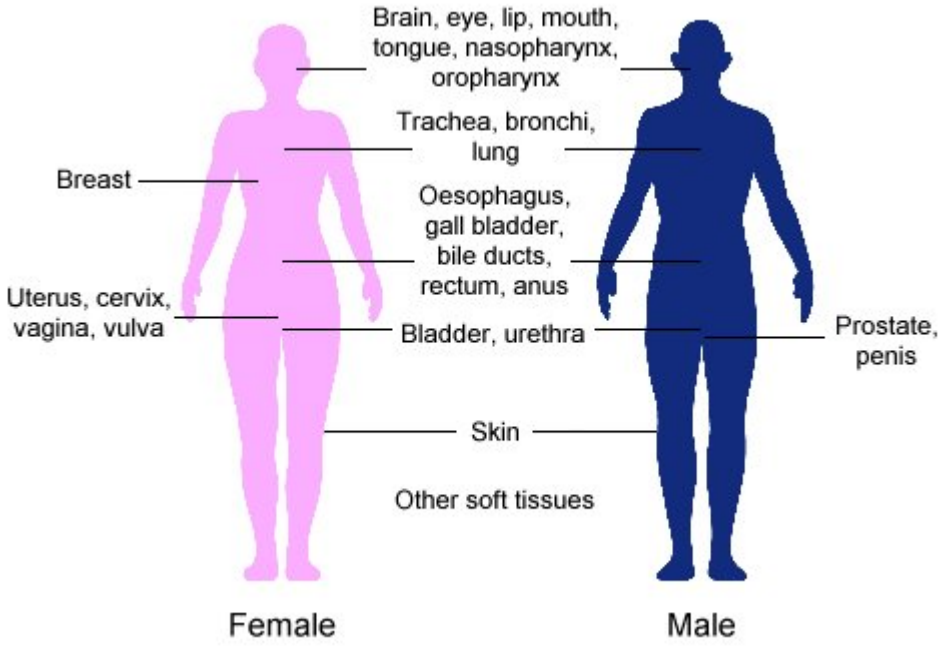
Permanent brachytherapy is often performed for prostate cancer using "seeds" - small radioactive rods implanted directly into the tumour.

The placement of radiation sources in the target area can be **temporary** or **permanent**.

- **Temporary brachytherapy** involves placement of radiation sources for a set duration (usually a number of minutes or hours) before being withdrawn. The specific treatment duration will depend on many different factors, including the required rate of dose delivery and the type, size and location of the cancer. In LDR and PDR brachytherapy, the source typically stays in place up to 24 hours before being removed, while in HDR brachytherapy this time is typically a few minutes.

- **Permanent brachytherapy**, also known as seed implantation, involves placing small LDR radioactive seeds or pellets (about the size of a grain of rice) in the tumour or treatment site and leaving them there permanently to gradually decay. Over a period of weeks or months, the level of radiation emitted by the sources will decline to almost zero. The inactive seeds then remain in the treatment site with no lasting effect. Permanent brachytherapy is most commonly used in the treatment of prostate cancer.

Clinical applications



Body sites in which brachytherapy can be used to treat cancer

Brachytherapy is commonly used to treat cancers of the cervix, prostate, breast, and skin.

Brachytherapy can also be used in the treatment of tumours of the brain, eye, head and neck region (lip, floor of mouth, tongue, nasopharynx and oropharynx), respiratory tract (trachea and bronchi), digestive tract (oesophagus, gall bladder, bile-ducts, rectum, anus),

urinary tract (bladder, urethra, penis), female reproductive tract (uterus, vagina, vulva), and soft tissues.

As the radiation sources can be precisely positioned at the tumour treatment site, brachytherapy enables a high dose of radiation to be applied to a small area. Furthermore, because the radiation sources are placed in or next to the target tumour, the sources maintain their position in relation to the tumour when the patient moves of if there is any movement of the tumour within the body. Therefore, the radiation sources remain accurately targeted. This enables clinicians to achieve a high level of dose conformity – i.e. ensuring the whole of the tumour receives an optimal level of radiation. It also reduces the risk of damage to healthy tissue, organs or structures around the tumour, thus enhancing the chance of cure and preservation of organ function.

The use of HDR brachytherapy enables overall treatment times to be reduced compared with EBRT. Patients receiving brachytherapy generally have to make fewer visits for radiotherapy compared with EBRT, and overall radiotherapy treatment plans can be completed in less time. Many brachytherapy procedures are performed on an outpatient basis. This convenience may be particularly relevant for patients who have to work, older patients, or patients who live some distance from treatment centres, to ensure that they have access to radiotherapy treatment and adhere to treatment plans. Shorter treatment times and outpatient procedures can also help improve the efficiency of radiotherapy clinics.

Brachytherapy can be used with the aim of curing the cancer in cases of small or locally advanced tumours, provided the cancer has not metastasized (spread to other parts of the body). In appropriately selected cases, brachytherapy for primary tumours often represents a comparable approach to surgery, achieving the same probability of cure and with similar side effects. However, in locally advanced tumours, surgery may not routinely provide the best chance of cure and is often not technically feasible to perform. In these cases radiotherapy, including brachytherapy, offers the only chance of cure. In more advanced disease stages, brachytherapy can be used as palliative treatment for symptom relief from pain and bleeding.

In cases where the tumour is not easily accessible or is too large to ensure an optimal distribution of irradiation to the treatment area, brachytherapy can be combined with other treatments, such as EBRT and/or surgery. Combination therapy of brachytherapy exclusively with chemotherapy is rare.

Cervical cancer

Brachytherapy is commonly used in the treatment of early or locally confined cervical cancer and is a standard of care in many countries. Cervical cancer can be treated with either LDR, PDR or HDR brachytherapy. Used in combination with EBRT, brachytherapy can provide better outcomes than EBRT alone. The precision of brachytherapy enables a high dose of targeted radiation to be delivered to the cervix, while minimising radiation exposure to adjacent tissues and organs.

The chances of staying free of disease (disease-free survival) and of staying alive (overall survival) are similar for LDR, PDR and HDR treatments. However, a key advantage of HDR treatment is that each dose can be delivered on an outpatient basis with a short administration time providing greater convenience for many patients.

Prostate cancer

Brachytherapy to treat prostate cancer can be given either as permanent LDR seed implantation or as temporary HDR brachytherapy.

Permanent seed implantation is suitable for patients with a localised tumour and good prognosis and has been shown to be a highly effective treatment to prevent the cancer from returning. The survival rate is similar to that found with EBRT or surgery (radical prostatectomy), but with fewer side effects such as impotence and incontinence. The procedure can be completed quickly and patients are usually able to go home on the same day of treatment and return to normal activities after 1 to 2 days. Permanent seed implantation is often a less invasive treatment option compared to the surgical removal of the prostate.

Temporary HDR brachytherapy is a newer approach to treating prostate cancer, but is currently less common than seed implantation. It is predominately used as to provide an extra dose in addition to EBRT (known as ‘”boost” therapy) as it offers an alternative method to deliver a high dose of radiation therapy that conforms to the shape of the tumour within the prostate, while sparing radiation exposure to surrounding tissues. HDR brachytherapy as a boost for prostate cancer also means that the EBRT course can be shorter than when EBRT is used alone.

Breast cancer

Radiation therapy is standard of care for women who have undergone lumpectomy or mastectomy surgery, and is an integral component of breast-conserving therapy. Brachytherapy can be used after surgery, before chemotherapy or palliatively in the case of advanced disease. Brachytherapy to treat breast cancer is usually performed with HDR temporary brachytherapy. Post surgery, breast brachytherapy can be used as a “boost” following irradiation of the whole breast using EBRT. More recently, brachytherapy alone is applied in a technique called APBI (accelerated partial breast irradiation), involving delivery of radiation to only the immediate region surrounding the original tumour.

The main benefit of breast brachytherapy compared to EBRT is that a high dose of radiation can be precisely applied to the tumour while sparing radiation to healthy breast tissues and underlying structures such as the ribs and lungs. APBI can typically be completed over the course of a week. The option of brachytherapy may be particularly important in ensuring that working women, the elderly or women without easy access to a treatment centre, are able to benefit from breast-conserving therapy due to the short treatment course compared with EBRT (which often requires more visits over the course

of 1–2 months). Brachytherapy has demonstrated excellent local control of breast cancer at follow-up of up to 6 years post treatment. A study is underway to compare patient outcomes of APBI in comparison to EBRT at up to 10 years after treatment.

There are two methods that can be used to deliver breast brachytherapy:

- **Interstitial breast brachytherapy** using multiple catheters
- **Intracavitary breast brachytherapy** using a balloon catheter

Interstitial breast brachytherapy involves the temporary placement of several flexible plastic catheters in the breast tissue. These are carefully positioned to allow optimal targeting of radiation to the treatment area while sparing the surrounding breast tissue. The catheters are connected to an afterloader, which delivers the planned radiation dose to the treatment area. Interstitial breast brachytherapy can be used as "boost" after EBRT, or as APBI.

Intracavitary breast brachytherapy (also known as "balloon brachytherapy") involves the placement of a single catheter into the breast cavity left after the removal of the tumour (lumpectomy). The catheter can be placed at the time of the lumpectomy or postoperatively. Via the catheter, a balloon is then inflated in the cavity. The catheter is then connected to an afterloader, which delivers the radiation dose through the catheter and into the balloon. Currently, intracavitary breast brachytherapy is only routinely used for APBI.

There are also devices that combine the features of interstitial and intracavitary breast brachytherapy (e.g. SAVI). These devices use multiple catheters but are inserted through a single-entry point in the breast. Studies suggest the use of multiple catheters enables physicians to target the radiation more precisely.

Skin cancer

HDR brachytherapy for nonmelanomatous skin cancer, such as basal cell carcinoma and squamous cell carcinoma, provides an alternative treatment option to surgery. This is especially relevant for cancers on the nose, ears, eyelids or lips, where surgery may cause disfigurement or require extensive reconstruction. Various applicators can be used to ensure close contact between the radiation source(s) and the skin, which conform to the curvature of the skin and help ensure precision delivery of the optimal irradiation dose.

Brachytherapy for skin cancer provides good cosmetic results and clinical efficacy; studies with up to 5 years follow-up have shown that brachytherapy is highly effective in terms local control, and is comparable to EBRT. Treatment times are typically short, providing convenience for patients. It has been suggested that brachytherapy may become a standard of treatment for skin cancer in the near future.

Other applications

Brachytherapy can be used in the treatment of coronary in-stent restenosis, in which a catheter is placed inside blood vessels, through which sources are inserted and removed. The therapy has also been investigated for use in the treatment of peripheral vasculature stenosis and considered for the treatment of atrial fibrillation.

Side effects

The likelihood and nature of potential acute, sub-acute or long-term side-effects associated with brachytherapy depends on the location of the tumour being treated and the type of brachytherapy being used.

Acute

Acute side effects associated with brachytherapy include localised bruising, swelling, bleeding, discharge or discomfort within the implanted region. These usually resolve within a few days following completion of treatment. Patients may also feel fatigued for a short period following treatment.

Brachytherapy treatment for cervical or prostate cancer can cause acute and transient urinary symptoms such as urinary retention, urinary incontinence or painful urination (dysuria). Transient increased bowel frequency, diarrhoea, constipation or minor rectal bleeding, may also occur. Acute and subacute side effects usually resolve over a matter of days or a few weeks. In the case of permanent (seed) brachytherapy for prostate cancer, there is a small chance that some seeds may migrate out of the treatment region into the bladder or urethra and be passed in the urine.

Brachytherapy for skin cancer may result in a shedding of the outer layers of skin (desquamation) around the area of treatment in the weeks following therapy, which typically heals in 5–8 weeks. If the cancer is located on the lip, ulceration may occur as a result of brachytherapy, but usually resolves after 4–6 weeks.

Most of the acute side effects associated with brachytherapy can be treated with medication or through dietary changes, and usually disappear over time (typically a matter of weeks), once the treatment is completed. The acute side effects of HDR brachytherapy are broadly similar to EBRT.

Long-term

In a small number of people, brachytherapy may cause long-term side effects due to damage or disruption of adjacent tissues or organs. Long-term side effects are usually mild or moderate in nature. For example, urinary and digestive problems may persist as a result of brachytherapy for cervical or prostate cancer, and may require ongoing management.

Brachytherapy for prostate cancer may cause erectile dysfunction in approximately 15-30% of patients. However, the risk of erectile dysfunction is related to age (older men are at a greater risk than younger men) and also the level of erectile function prior to receiving brachytherapy. In patients who do experience erectile dysfunction, the majority of cases can successfully be treated with drugs such as Viagra. Importantly, the risk of erectile dysfunction after brachytherapy is less than after radical prostatectomy.

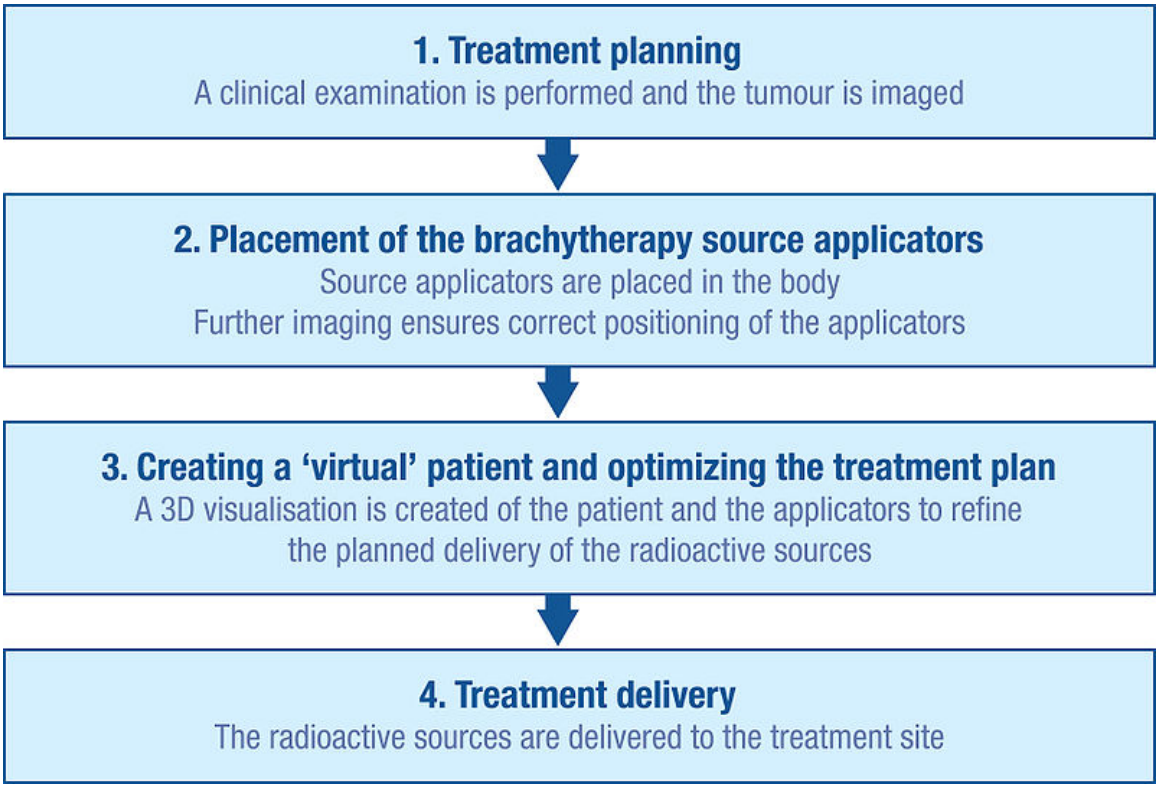
Brachytherapy for breast or skin cancer may cause scar tissue to form around the treatment area. In the case of breast brachytherapy, fat necrosis may occur as a result of fatty acids entering the breast tissues. This can cause the breast tissue to become swollen and tender. Fat necrosis is a benign condition and typically occurs 4–12 months after treatment and affects about 2% of patients.

Safety around others

Patients often ask if they need to have special safety precautions around family and friends after receiving brachytherapy. If temporary brachytherapy is used, no radioactive sources remain in the body after treatment. Therefore, there is no radiation risk to friends or family from being in close proximity with them.

If permanent brachytherapy is used, low dose radioactive sources (seeds) are left in the body after treatment - the radiation levels are very low and decrease over time. In addition, the irradiation only affects tissues within a few millimeters of the radioactive sources (i.e. the tumour being treated). As a precaution, some people receiving permanent brachytherapy may be advised to not hold any small children or be too close to pregnant women for a short time after treatment. Radiation oncologists or nurses can provide specific instructions to patients and advise for how long they need to be careful.

Procedure



Typical stages of a brachytherapy procedure

Initial planning

In order to accurately plan the brachytherapy procedure, a thorough clinical examination is performed to understand the characteristics of the tumour. In addition, a range of imaging modalities can be used to visualise the shape and size of the tumour and its relation to surrounding tissues and organs. These include x-ray radiography, ultrasound, computed axial tomography (CT or CAT) scans and magnetic resonance imaging (MRI). The data from many of these sources can be used to create a 3D visualisation of the tumour and the surrounding tissues.

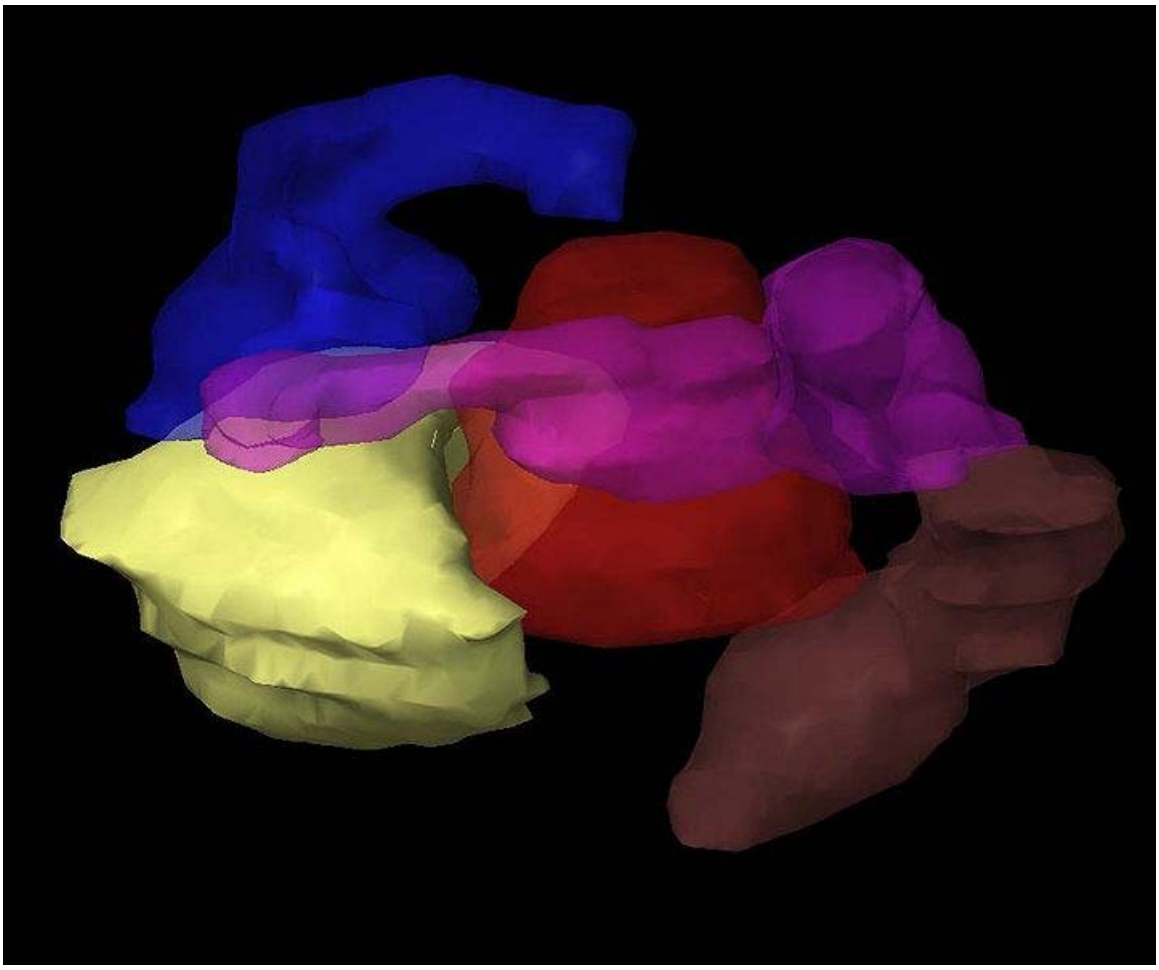
Using this information, a plan of the optimal distribution of the radiation sources can be developed. This includes consideration of how the source carriers (applicators), which are used to deliver the radiation to the treatment site, should be placed and positioned. Applicators are non-radioactive and are typically needles or plastic catheters. The specific type of applicator used will depend on the type of cancer being treated and the characteristics of the target tumour.

This initial planning helps to ensure that 'cold spots' (too little irradiation) and 'hot spots' (too much irradiation) are avoided during treatment, as these can respectively result in treatment failure and side-effects.

Insertion and imaging of the applicator(s)

Before radioactive sources can be delivered to the tumour site, the applicators have to be inserted and correctly positioned in line with the initial planning.

Imaging techniques, such as x-ray, fluoroscopy and ultrasound are typically used to help guide the placement of the applicators to their correct positions and to further refine the treatment plan. CAT scans and MRI can also be used. Once the applicators are inserted, they are held in place against the skin using sutures or adhesive tape to prevent them from moving. Once the applicators are confirmed as being in the correct position, further imaging can be performed to guide detailed treatment planning.



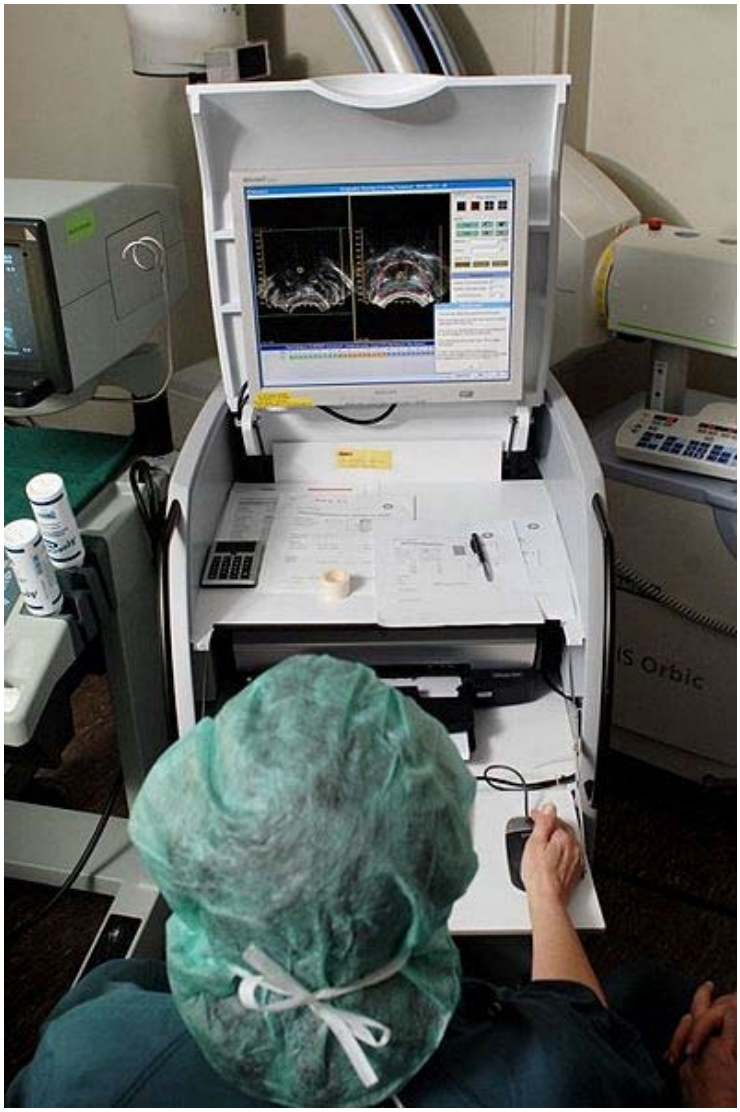
Creation of the 'virtual' patient to plan the delivery of brachytherapy

Creation of a virtual patient

The images of the patient with the applicators in situ are imported into treatment planning software and the patient is brought into a dedicated shielded room for treatment. The treatment planning software enables multiple 2D images of the treatment site to be

translated into a 3D ‘virtual patient’, within which the position of the applicators can be defined. The spatial relationships between the applicators, the treatment site and the surrounding healthy tissues within this ‘virtual patient’ are a copy of the relationships in the actual patient.

Optimizing the irradiation plan



Refinement of the treatment plan during the brachytherapy procedure

To identify the optimal spatial and temporal distribution of radiation sources within the applicators of the implanted tissue or cavity, the treatment planning software allows virtual radiation sources to be placed within the virtual patient. The software shows a graphical representation of the distribution of the irradiation. This serves as a guide for the brachytherapy team to refine the distribution of the sources and provide a treatment plan that is optimally tailored to the anatomy of each patient before actual delivery of the irradiation begins. This approach is sometimes called ‘dose-painting’.

Treatment delivery

The radiation sources used for brachytherapy are always enclosed within a non-radioactive capsule. The sources can be delivered manually, but are more commonly delivered through a technique known as 'afterloading'.

Manual delivery of brachytherapy is limited to a few LDR applications, due to risk of radiation exposure to clinical staff.

In contrast, afterloading involves the accurate positioning of non-radioactive applicators in the treatment site, which are subsequently loaded with the radiation sources. In manual afterloading, the source is delivered into the applicator by the operator.

Remote afterloading systems provide protection from radiation exposure to healthcare professionals by securing the radiation source in a shielded safe. Once the applicators are correctly positioned in the patient, they are connected to an 'afterloader' machine (containing the radioactive sources) through a series of connecting guide tubes. The treatment plan is sent to the afterloader, which then controls the delivery of the sources along the guide tubes into the pre-specified positions within the applicator. This process is only engaged once staff are removed from the treatment room. The sources remain in place for a pre-specified length of time, again following the treatment plan, following which they are returned along the tubes to the afterloader.

On completion of delivery of the radioactive sources, the applicators are carefully removed from the body. Patients typically recover quickly from the brachytherapy procedure, enabling it to often be performed on an outpatient basis.

Radiation sources

Commonly used radiation sources (radionuclides) for brachytherapy

Radionuclide	Type	Half-life	Energy
Caesium-137 (^{137}Cs)	γ-ray	30.17 years	0.662 MeV
Cobalt-60 (^{60}Co)	γ-rays	5.26 years	1.17, 1.33 MeV
Iridium-192 (^{192}Ir)	γ-ray	74.0 days	0.38 MeV (mean)
Iodine-125 (^{125}I)	X-rays	59.6 days	27.4, 31.4 and 35.5 keV
Palladium-103 (^{103}Pd)	X-ray	17.0 days	21 keV (mean)
Ruthenium-106 (^{106}Ru)	β-particles	1.02 years	3.54 MeV

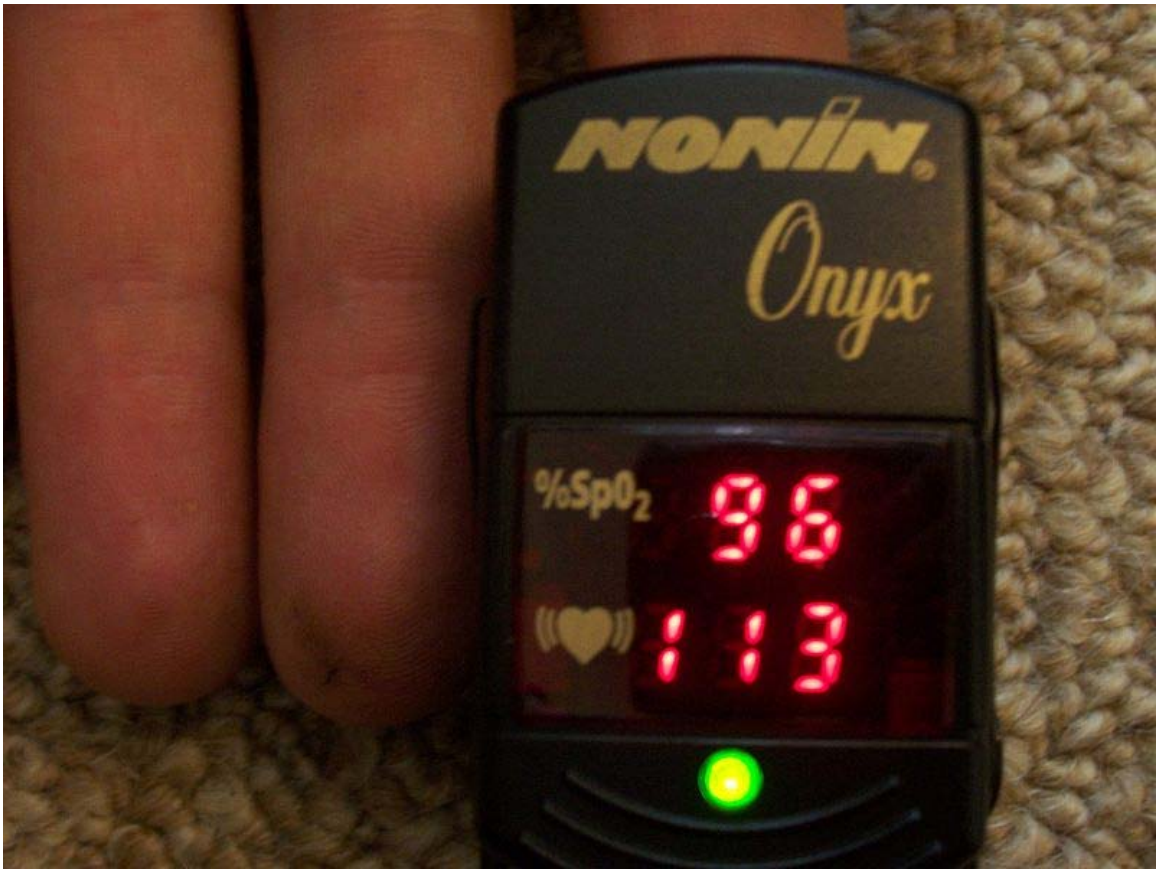
Electronic brachytherapy

Electronic brachytherapy involves placement of miniature low energy x-ray tube sources into a pre-positioned applicator within body/tumour cavities to rapidly deliver high doses to target tissues while maintaining low doses to distant non-target tissues.

Chapter 10

Pulse Oximetry and Sphygmomanometer

Pulse oximetry



Pulse Oximeter

Pulse oximetry (or **pulse oxymetry** in the UK) is a non-invasive method allowing the monitoring of the oxygenation of a patient's hemoglobin.

A sensor is placed on a thin part of the patient's body, usually a fingertip or earlobe, or in the case of an infant, across a foot. Light with red wavelengths and light with infrared wavelengths is sequentially passed from one side to a photodetector on the other side.

Changing absorbance of each of the two wavelengths is measured, allowing determination of the absorbances due to the pulsing arterial blood alone, excluding venous blood, skin, bone, muscle, fat, and (in most cases) fingernail polish. Based upon the ratio of changing absorbance of the red and infrared light caused by the difference in color between oxygen-bound (bright red) and oxygen-unbound (dark red or blue, in severe cases) blood hemoglobin, a measure of oxygenation (the per cent of hemoglobin molecules bound with oxygen molecules) can be made.

Indication

Pulse oximetry data is necessary whenever a patient's oxygenation may be unstable, as in intensive care, critical care, and emergency department areas of a hospital. Data can also be obtained from pilots in unpressurized aircraft, and for assessment of any patient's oxygenation in primary care. A patient's need for oxygen is essential to life; no human life thrives in the absence of oxygen (cellular or gross). Although pulse oximetry is used to monitor oxygenation, it cannot determine the metabolism of oxygen, or the amount of oxygen being used by a patient. For this purpose, it is necessary to also measure carbon dioxide (CO_2) levels. It is possible that pulse oximetry can also be used to detect abnormalities in ventilation. However, detection of hypoventilation is impaired by the use of supplemental oxygen, as it is only when patients breathe room air that abnormalities in respiratory function can be detected reliably. Therefore, the routine administration of supplemental oxygen may be unwarranted if the patient is able to maintain adequate oxygenation in room air, since it can result in hypoventilation going undetected.

History

In 1935 Matthes developed the first 2-wavelength ear O_2 saturation meter with red and green filters, later switched to red and infrared filters. This was the first device to measure O_2 saturation.

In 1949 Wood added a pressure capsule to squeeze blood out of ear to obtain zero setting in an effort to obtain absolute O_2 saturation value when blood was readmitted. The concept is similar to today's conventional pulse oximetry but was hard to implement because of unstable photocells and light sources. This method is not used clinically. In 1964 Shaw assembled the first absolute reading ear oximeter by using eight wavelengths of light. Commercialized by Hewlett Packard, its use was limited to pulmonary functions and sleep laboratories due to cost and size.

Pulse oximetry was developed in 1974, by Takuo Aoyagi and Michio Kishi, bioengineers, at Nihon Kohden using the ratio of red to infrared light absorption of pulsating components at the measuring site. Susumu Nakajima, a surgeon, and his associates first tested the device in patients, reporting it in 1975. It was commercialized by Biox in 1981 and Nellcor in 1983. Biox was founded in 1979, and introduced the first pulse oximeter to commercial distribution in 1981. Biox initially focused on respiratory care, but when the company discovered that their pulse oximeters were being used in operating rooms to monitor oxygen levels, Biox expanded its marketing resources to

focus on operating rooms in late 1982. A competitor, Nellcor (now part of Covidien, Ltd.), began to compete with Biox for the US operating room market in 1983. Prior to its introduction, a patient's oxygenation could only be determined by arterial blood gas, a single-point measurement that takes a few minutes of processing by a laboratory. (In the absence of oxygenation, damage to the brain starts within 5 minutes with brain death ensuing within another 10–15 minutes). In the US alone, approximately $2 billion was spent annually on this measurement. With the introduction of pulse oximetry, a non-invasive, continuous measure of patient's oxygenation was possible, revolutionizing the practice of anesthesia and greatly improving patient safety. Prior to its introduction, studies in anesthesia journals estimated US patient mortality as a consequence of undetected hypoxemia at 2,000 to 10,000 deaths per year, with no known estimate of patient morbidity.

By 1987, the standard of care for the administration of a general anesthetic in the US included pulse oximetry. From the operating room, the use of pulse oximetry rapidly spread throughout the hospital, first to the recovery room, and then into the various intensive care units. Pulse oximetry was of particular value in the neonatal unit where the patients do not thrive with inadequate oxygenation, but also can be blinded with too much oxygen. Furthermore, obtaining an arterial blood gas from a neonatal patient is extremely difficult.

By 2008, the accuracy and capability of pulse oximetry had further improved, and had allowed for the adoption of the term high resolution pulse oximetry (HRPO) by MASIMO and Dolphin Medical. One area of particular interest is the use of pulse oximetry in conducting portable and in-home sleep apnea screening and testing.

In 2009, the world's first Bluetooth-enabled fingertip pulse oximeter was introduced by Nonin Medical, enabling clinicians to remotely monitor patients' pulses and oxygen saturation levels. It also allows patients to monitor their own health through online patient health records and home telemedicine system.

Limitations

Pulse oximetry measures solely of oxygenation, not ventilation, and it is not a substitute for blood gases checked in a laboratory because it gives no indication of base deficit, carbon dioxide levels, blood pH, or bicarbonate HCO3- concentration. The metabolism of oxygen can be readily measured by monitoring expired CO_2. Saturation figures also give no information about blood oxygen content. Most of the oxygen in the blood is carried by hemoglobin. In severe anemia, the blood will carry less total oxygen, despite the hemoglobin being 100% saturated.

Falsely low readings may be caused by hypoperfusion of the extremity being used for monitoring (often due to the part being cold or from vasoconstriction secondary to the use of vasopressor agents); incorrect sensor application; highly calloused skin; and movement (such as shivering), especially during hypoperfusion. To ensure accuracy, the sensor should return a steady pulse and/or pulse waveform. Falsely high or falsely low readings

will occur when hemoglobin is bound to something other than oxygen. In cases of carbon monoxide poisoning, the falsely high reading may delay the recognition of hypoxemia (low blood oxygen level). Methemoglobinemia characteristically causes pulse oximetry readings in the mid-80s. Cyanide poisoning can also give a high reading because it reduces oxygen extraction from arterial blood (the reading is not false, as arterial blood oxygen is indeed high in early cyanide poisoning).

Pulse oximetry only reads the percentage of bound hemoglobin. Hemoglobin can be bound to other gases such as carbon monoxide and still read high even though the patient is hypoxemic. The only noninvasive methodology that allows for the continuous and noninvasive measurement of the dyshemoglobins is a pulse co-oximeter. Pulse co-oximetry was invented in 2005 by Masimo and currently allows clinicians to measure total hemoglobin levels in addition to carboxyhemoglobin, methemoglobin and PVI, which initial clinical studies have shown may provide clinicians with a new method for noninvasive and automatic assessment of patient fluid volume status. Appropriate fluid levels are vital to reducing postoperative risks and improving patient outcomes as fluid volumes that are too low (under hydration) or too high (over hydration) have been shown to decrease wound healing, increase risk of infection and cardiac complications.

Sphygmomanometer

Clinical mercury Manometer

Aneroid sphygmomanometer dial, bulb, and air valve

Aneroid sphygmomanometer with an adult cuff

BP 126/70 mmHg as result on electronic sphygmomanometer

A **sphygmomanometer** or **blood pressure meter** is a device used to measure blood pressure, comprising an inflatable cuff to restrict blood flow, and a mercury or mechanical manometer to measure the pressure. It is always used in conjunction with a means to determine at what pressure blood flow is just starting, and at what pressure it is unimpeded. Manual sphygmomanometers are used in conjunction with a stethoscope.

The word comes from the Greek *sphygmós* (pulse), plus the scientific term manometer (pressure meter). The device was invented by Samuel Siegfried Karl Ritter von Basch in 1881. Scipione Riva-Rocci introduced a more easily used version in 1896. Harvey Cushing discovered this device in 1901 and popularized it.

A sphygmomanometer consists of an inflatable cuff, a measuring unit (the mercury manometer, or aneroid gauge), and inflation bulb and valve, for manual instruments.

Operation

In humans, the cuff is normally placed smoothly and snugly around an upper arm, at roughly the same vertical height as the heart while the subject is seated with the arm supported. Other sites of placement depend on species, and may include the tongue, flipper, tail or teat. It is essential that the correct size of cuff is selected for the patient. Too small a cuff results in too high a pressure, while too large a cuff results in too low a

pressure. The cuff is inflated until the artery is completely occluded. Listening with a stethoscope to the brachial artery at the elbow, the examiner slowly releases the pressure in the cuff. As the pressure in the cuffs falls, a "whooshing" or pounding sound is heard when blood flow first starts again in the artery. The pressure at which this sound began is noted and recorded as the systolic blood pressure. The cuff pressure is further released until the sound can no longer be heard. This is recorded as the diastolic blood pressure. In noisy environments where auscultation is impossible (such as the scenes often encountered in emergency medicine), systolic blood pressure alone may be read by releasing the pressure until a radial pulse is palpated (felt). In veterinary medicine, auscultation is rarely of use, and palpation or visualization of pulse distal to the sphygmomanometer is used to detect systolic pressure.

Significance

By observing the mercury in the column while releasing the air pressure with a control valve, one can read the values of the blood pressure in mm Hg. The peak pressure in the arteries during the cardiac cycle is the systolic pressure, and the lowest pressure (at the resting phase of the cardiac cycle) is the diastolic pressure. A stethoscope is used in the auscultatory method. Systolic pressure (first phase) is identified with the first of the continuous Korotkoff sounds. Diastolic is identified at the moment the Korotkoff sounds disappear (fifth phase).

Types

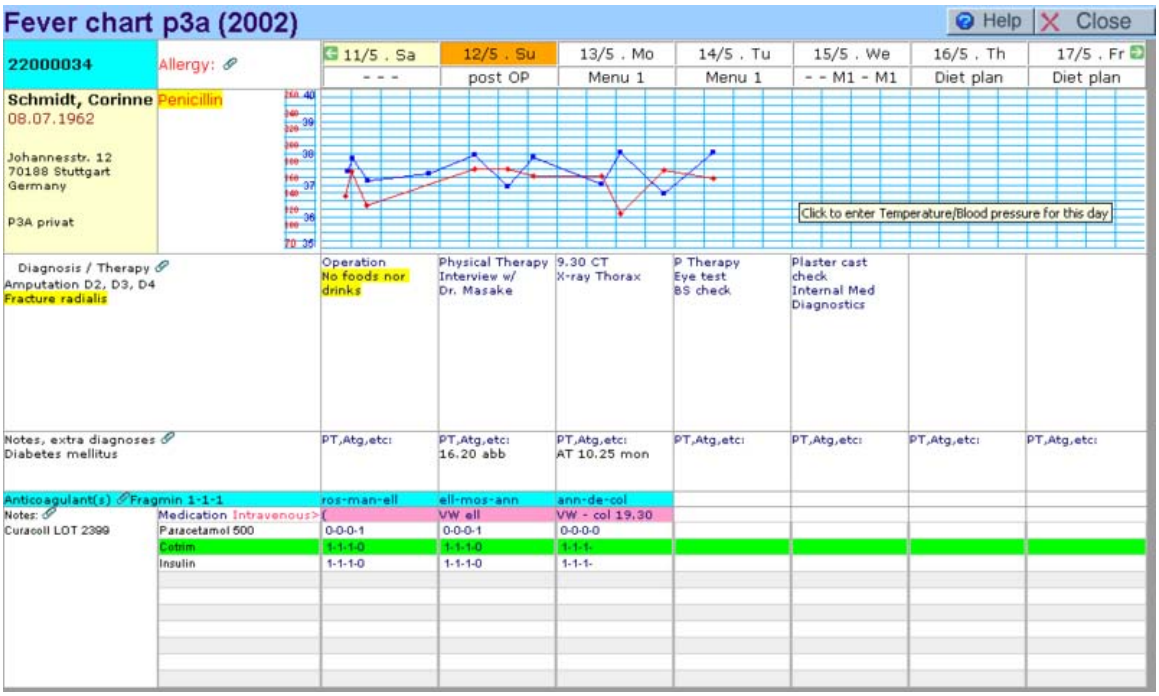
There are three types of sphygmomanometers:

- Digital with manual or automatic inflation. These are electronic, easy to operate, and practical in noisy environments. They measure mean arterial pressure (MAP) and use oscillometric detection to calculate systolic and diastolic values. In this sense, they do not actually measure the blood pressure, but rather derive the readings. Digital oscillometric monitors are also confronted with "special conditions" for which they are not designed to be used: arteriosclerosis; arrhythmia; preeclampsia; *pulsus alternans*; and *pulsus paradoxus*. Some wrist cuff blood pressure monitors have been found to be quite inaccurate, and the monitor has to be at the level of the heart when the reading is taken.
- Digital portable finger blood pressure monitors with automatic inflation. These are more portable and easy to operate, although less accurate. They are the smallest blood pressure monitors.
- Manual. Ideally operated by a trained person, mercury manometers are considered to be the gold standard and cannot be decalibrated, they are consistently accurate. Due to their accuracy, they are often required in clinical trials of pharmaceuticals and for clinical evaluations of determining blood pressure for high risk patients including pregnant women. Aneroid, (mechanical types with a dial) are in common use but they require regular calibration checks, unlike a mercury manometer. The prime reason for such maintenance is their susceptibility to bumps which can alter their accuracy. Wall mounted and mobile aneroids avoid

this shortcoming. The aneroid sphygmomanometer should be checked for accuracy (usually every 6 months)by using a mercury manometer, as the gold standard. The unit of measurement of blood pressure is millimeters of mercury (mmHg) and are usually given as an even number. Manual sphygmomanometers require a stethoscope for auscultation. Although it is possible to obtain a basic reading through palpation, this only yields the systolic number.

Chapter 11

Health Informatics



Electronic patient chart from a health information system

Health informatics (also called **health care informatics**, **healthcare informatics**, **medical informatics**, **nursing informatics**, or **biomedical informatics**) is a discipline at the intersection of information science, computer science, and health care. It deals with the resources, devices, and methods required to optimize the acquisition, storage, retrieval, and use of information in health and biomedicine. Health informatics tools include not only computers but also clinical guidelines, formal medical terminologies, and information and communication systems. It is applied to the areas of nursing, clinical care, dentistry, pharmacy, public health, occupational therapy, and (bio)medical research.

Aspects of the field

- architectures for electronic medical records and other health information systems used for billing, scheduling, and research

- decision support systems in healthcare, including clinical decision support systems and information workflows
- standards (e.g. DICOM, HL7) and integration profiles (e.g. Integrating the Healthcare Enterprise) to facilitate the exchange of information between healthcare information systems—these specifically define the *means* to exchange data, not the content
- controlled medical vocabularies (CMVs) such as the Systematized Nomenclature of Medicine, Clinical Terms (SNOMED CT), MEDCIN, Logical Observation Identifiers Names and Codes (LOINC), OpenGALEN Common Reference Model or the highly complex UMLS—used to allow a standard, accurate exchange of data content between systems and providers
- use of hand-held or portable devices to assist providers with data entry/retrieval or medical decision-making, sometimes called mHealth.
- The international standards on the subject are covered by ICS 35.240.80 in which ISO 27799:2008 is one of the core components.
- Molecular bioinformatics and clinical informatics have converged into the field of translational bioinformatics.

History

World wide use of technology in medicine began in the early 1950s with the rise of the computers. In 1949, Gustav Wager established the first professional organization for informatics in Germany. The prehistory, history, and future of medical information and health information technology are discussed in reference. Specialized university departments and Informatics training programs began during the 1960s in France, Germany, Belgium and The Netherlands. Medical informatics research units began to appear during the 1970s in Poland and in the U.S. Since then the development of high-quality health informatics research, education and infrastructure has been the goal of the U.S. and the European Union.

Early names for health informatics included medical computing, medical computer science, computer medicine, medical electronic data processing, medical automatic data processing, medical information processing, medical information science, medical software engineering, and medical computer technology.

The health informatics community is still growing, it is by no means a mature profession, but work in the UK by the voluntary registration body, the UK Council of Health Informatics Professions has suggested eight key constituencies within the domain - information management, knowledge management, portfolio/programme/project management, ICT, education and research, clinical informatics, health records(service and business-related), health informatics service management. These constituencies accommodate professionals in and for the NHS, in academia and commercial service and solution providers.

Since the 1970s the most prominent international coordinating body has been the [[International Medical Informatics Association]] (IMIA).

Medical informatics in the United States

Even though there was talk about using computers in medicine as technology advanced in the early twentieth century, it was not until the 1950s that informatics really took off in the United States.

The earliest use of computation for medicine was for dental projects in the 1950s at the United States National Bureau of Standards by Robert Ledley.

The next step in the mid 1950s were the development of expert systems such as MYCIN and Internist-I. In 1965, the National Library of Medicine started to use MEDLINE and MEDLARS. At this time, Neil Pappalardo, Curtis Marble, and Robert Greenes developed MUMPS (Massachusetts General Hospital Utility Multi-Programming System) in Octo Barnett's Laboratory of Computer Science at Massachusetts General Hospital in Boston. In the 1970s and 1980s it was the most commonly used programming language for clinical applications. The MUMPS operating system was used to support MUMPS language specifications. As of 2004, a descendent of this system is being used in the United States Veterans Affairs hospital system. The VA has the largest enterprise-wide health information system that includes an electronic medical record, known as the Veterans Health Information Systems and Technology Architecture (VistA). A graphical user interface known as the Computerized Patient Record System (CPRS) allows health care providers to review and update a patient’s electronic medical record at any of the VA's over 1,000 health care facilities.

In the 1970s a growing number of commercial vendors began to market practice management and electronic medical records systems. Although many products exist, only a small number of health practitioners use fully featured electronic health care records systems.

Homer R. Warner, one of the fathers of medical informatics, founded the Department of Medical Informatics at the University of Utah in 1968. The American Medical Informatics Association (AMIA) has an award named after him on application of informatics to medicine.

Current state of health informatics and policy initiatives

Americas

Argentina

Since 1997, the Buenos Aires Biomedical Informatics Group, a nonprofit group, represents the interests of a broad range of clinical and non-clinical professionals working within the Health Informatics sphere. Its purposes are:

- Promote the implementation of the computer tool in the healthcare activity, scientific research, health administration and in all areas related to health sciences and biomedical research.
- Support, promote and disseminate content related activities with the management of health information and tools they used to do under the name of Biomedical informatics.
- Promote cooperation and exchange of actions generated in the field of biomedical informatics, both in the public and private, national and international level.
- Interact with all scientists, recognized academic stimulating the creation of new instances that have the same goal and be inspired by the same purpose.
- To promote, organize, sponsor and participate in events and activities for training in computer and information and disseminating developments in this area that might be useful for team members and health related activities.

The Argentinian health system is very heterogeneous, because of that the informatics developments shows an heterogeneous stage. Lot of private Health Care center has develop system, as the German Hospital of Buenos Aires who was one of the first in develop the electronic health records system.

Brazil

The first applications of computers to medicine and healthcare in Brazil started around 1968, with the installation of the first mainframes in public university hospitals, and the use of programmable calculators in scientific research applications. Minicomputers, such as the IBM 1130 were installed in several universities, and the first applications were developed for them, such as the hospital census in the School of Medicine of Ribeirão Preto and patient master files, in the Hospital das Clínicas da Universidade de São Paulo, respectively at the cities of Ribeirão Preto and São Paulo campi of the University of São Paulo. In the 1970s, several Digital Corporation and Hewlett Packard minicomputers were acquired for public and Armed Forces hospitals, and more intensively used for intensive-care unit, cardiology diagnostics, patient monitoring amd other applications. In the early 1980s, with the arrival of cheaper microcomputers, a great upsurge of computer applications in health ensued, and in 1986 the Brazilian Society of Health Informatics was founded, the first Brazilian Congress of Health Informatics was held, and the first *Brazilian Journal of Health Informatics* was published.

Canada

Health Informatics projects in Canada are implemented provincially, with different provinces creating different systems. A national, federally-funded, not-for-profit organization called Canada Health Infoway was created in 2001 to foster the development and adoption of electronic health records across Canada. As of December 31, 2008 there were 276 EHR projects under way in Canadian hospitals, other health-care facilities, pharmacies and laboratories, with an investment value of $1.5-billion from Canada Health Infoway.

Provincial and territorial programmes include the following:

- **eHealth Ontario** was created as an Ontario provincial government agency in September 2008. It has been plagued by delays and its CEO was fired over a multimillion-dollar contracts scandal in 2009.
- **Alberta Netcare** was created in 2003 by the Government of Alberta. Today the netCARE portal is used daily by thousands of clinicians. It provides access to demographic data, prescribed/dispensed drugs, known allergies/intolerances, immunizations, laboratory test results, diagnostic imaging reports, the diabetes registry and other medical reports. netCARE interface capabilities are being included in electronic medical record products which are being funded by the provincial government.

United States

In 2004 the U.S. Department of Health and Human Services (HHS) formed the Office of the National Coordinator for Health Information Technology (ONCHIT). The mission of this office is widespread adoption of interoperable electronic health records (EHRs) in the US within 10 years.

The Certification Commission for Healthcare Information Technology (CCHIT), a private nonprofit group, was funded in 2005 by the U.S. Department of Health and Human Services to develop a set of standards for electronic health records (EHR) and supporting networks, and certify vendors who meet them. In July, 2006 CCHIT released its first list of 22 certified ambulatory EHR products, in two different announcements.

Europe

The European Union's Member States are committed to sharing their best practices and experiences to create a European eHealth Area, thereby improving access to and quality health care at the same time as stimulating growth in a promising new industrial sector. The European eHealth Action Plan plays a fundamental role in the European Union's strategy. Work on this initiative involves a collaborative approach among several parts of the Commission services. The European Institute for Health Records is involved in the promotion of high quality electronic health record systems in the European Union.

The NHS in England has contracted out to several vendors for a National Medical Informatics system 'NPFIT' that divides the country into five regions and is to be united by a central electronic medical record system nicknamed "the spine". The project, in 2010, is seriously behind schedule and its scope and design are being revised in real time. The degree of computerisation in NHS secondary was quite high before NPfIT and that programme has had the unfortunate effect of largely stalling further development of the installed base.

Almost all general practices in England and Wales are computerised and patients have relatively extensive computerised primary care clinical records. Computerisation is the

responsibility of individual practices and there is no single, standardised GP system. Interoperation between primary and secondary care systems is rather primitive.

Scotland has an approach to central connection under way which is more advanced than the English one in some ways. Scotland has the GPASS system whose source code is owned by the State, and controlled and developed by NHS Scotland. It has been provided free to all GPs in Scotland but has developed poorly. Discussion of open sourcing it as a remedy is occurring.

The European Commission's preference, as exemplified in the 5th Framework as well as currently pursued pilot projects, is for Free/Libre and Open Source Software (FLOSS) for healthcare.

Asia and Oceania

In Asia and Australia-New Zealand, the regional group called the Asia Pacific Association for Medical Informatics (APAMI) was established in 1994 and now consists of more than 15 member regions in the Asia Pacific Region.

Australia

The Australasian College of Health Informatics (ACHI) is the professional association for health informatics in the Asia-Pacific region. It represents the interests of a broad range of clinical and non-clinical professionals working within the health informatics sphere through a commitment to quality, standards and ethical practice. Founded in 2002, ACHI is increasingly valued for its thought leadership, its trusted advisors and national and international experts in Health Informatics. ACHI is an academic institutional member of the International Medical Informatics Association (IMIA) and a full member of the Australian Council of Professions. ACHI is a sponsor of the "e-Journal for Health Informatics", an indexed and peer-reviewed professional journal. ACHI has also supported the "Australian Health Informatics Education Council" (AHIEC) since its founding in 2009.

Although there are a number of health informatics organisations in Australia, the Health Informatics Society of Australia (HISA) is regarded as the major umbrella group and is a member of the International Medical Informatics Association (IMIA). Nursing informaticians were the driving force behind the formation of HISA, which is now a company limited by guarantee of the members. The membership comes from across the informatics spectrum that is from students to corporate affiliates. HISA has a number of branches (Queensland, New South Wales, Victoria and Western Australia) as well as special interest groups such as nursing (NIA), pathology, aged and community care, industry and medical imaging (Conrick, 2006).

China

Hong Kong

In Hong Kong a computerized patient record system called the Clinical Management System (CMS) has been developed by the Hospital Authority since 1994. This system has been deployed at all the sites of the Authority (40 hospitals and 120 clinics), and is used by all 30,000 clinical staff on a daily basis, with a daily transaction of up to 2 millions. The comprehensive records of 7 million patients are available on-line in the Electronic Patient Record (ePR), with data integrated from all sites. Since 2004 radiology image viewing has been added to the ePR, with radiography images from any HA site being available as part of the ePR.

The Hong Kong Hospital Authority placed particular attention to the governance of clinical systems development, with input from hundreds of clinicians being incorporated through a structured process. The Health Informatics Section in Hong Kong Hospital Authority has close relationship with Information Technology Department and clinicians to develop healthcare systems for the organization to support the service to all public hospitals and clinics in the region.

The Hong Kong Society of Medical Informatics (HKSMI) was established in 1987 to promote the use of information technology in healthcare. The eHealth Consortium has been formed to bring together clinicians from both the private and public sectors, medical informatics professionals and the IT industry to further promote IT in healthcare in Hong Kong.

India

Religare Technova IT solutions is attempting a new service to improve the healthcare information system in India

New Zealand

Health Informatics is taught at five New Zealand universities. The most mature and established is the Otago programme which has been offered for over a decade. Health Informatics New Zealand (HINZ), is the national organisation that advocates for Health Informatics. HINZ organises a conference every year.

Saudi Arabia

The Saudi Association for Health Information (SAHI) was established in 2006 to work under direct supervision of King Saud University for Health Sciences to practice public activities, develop theoretical and applicable knowledge, and provide scientific and applicable studies.

Health informatics law

Health informatics law deals with evolving and sometimes complex legal principles as they apply to information technology in health-related fields. It addresses the privacy, ethical and operational issues that invariably arise when electronic tools, information and media are used in health care delivery. Health Informatics Law also applies to all matters that involve information technology, health care and the interaction of information. It deals with the circumstances under which data and records are shared with other fields or areas that support and enhance patient care.

Clinical Informatics

Clinical Informatics is concerned with use information in health care by clinicians.

Clinical informaticians transform health care by analyzing, designing, implementing, and evaluating information and communication systems that enhance individual and population health outcomes, improve [patient] care, and strengthen the clinician-patient relationship. Clinical informaticians use their knowledge of patient care combined with their understanding of informatics concepts, methods, and health informatics tools to:

- assess information and knowledge needs of health care professionals and patients,
- characterize, evaluate, and refine clinical processes,
- develop, implement, and refine clinical decision support systems, and
- lead or participate in the procurement, customization, development, implementation, management, evaluation, and continuous improvement of clinical information systems.

Clinicians collaborate with other health care and information technology professionals to develop health informatics tools which promote patient care that is safe, efficient, effective, timely, patient-centered, and equitable.

Translational bioinformatics

With the completion of the human genome and the recent advent of high throughput sequencing and genome-wise association studies of single nucleotide polymorphisms, the fields of molecular bioinformatics, biostatistiques, statistical genetics and clinical informatics are converging into the emerging field of translational bioinformatics.

Chapter 12

Telemedicine

Telemedicine is a rapidly developing application of clinical medicine where medical information is transferred through interactive audiovisual media for the purpose of consulting, and sometimes remote medical procedures or examinations.

Telemedicine may be as simple as two health professionals discussing a case over the telephone, or as complex as using satellite technology and videoconferencing equipment to conduct a real-time consultation between medical specialists in two different countries. Telemedicine generally refers to the use of communications and information technologies for the delivery of clinical care.

Care at a distance (also called *in absentia* care), an old practice which was often conducted via post. There has been a long and successful history of in absentia health care which, thanks to modern communication technology, has evolved into what we know as modern telemedicine.

In its early manifestations, African villagers used smoke signals to warn people to stay away from the village in case of serious disease. In the early 1900s, people living in remote areas of Australia used two-way radios, powered by a dynamo driven by a set of bicycle pedals, to communicate with the Royal Flying Doctor Service of Australia.

The terms eHealth and telehealth are at times incorrectly interchanged with telemedicine. Like the terms "medicine" and "health care", telemedicine often refers only to the provision of clinical services while the term telehealth can refer to clinical and non-clinical services such as medical education, administration, and research. The term eHealth is often, particularly in the U.K. and Europe, used as an umbrella term that includes telehealth, electronic medical records, and other components of health IT.

Types of telemedicine

Telemedicine can be broken into three main categories: **store-and-forward**, **remote monitoring** and **interactive** services.

Store-and-forward telemedicine involves acquiring medical data (like medical images, biosignals etc) and then transmitting this data to a doctor or medical specialist at a convenient time for assessment offline. It does not require the presence of both parties at

the same time. Dermatology (cf: teledermatology), radiology, and pathology are common specialties that are conducive to asynchronous telemedicine. A properly structured medical record preferably in electronic form should be a component of this transfer. A key difference between traditional in-person patient meetings and telemedicine encounters is the omission of an actual physical examination and history. The 'store-and-forward' process requires the clinician to rely on a history report and audio/video information in lieu of a physical examination.

Remote monitoring, also known as self-monitoring or testing, enables medical professionals to monitor a patient remotely using various technological devices. This method is primarily used for managing chronic diseases or specific conditions, such as heart disease, diabetes mellitus, or asthma. These services can provide comparable health outcomes to traditional in-person patient encounters, supply greater satisfaction to patients, and may be cost-effective.

Interactive telemedicine services provide real-time interactions between patient and provider, to include phone conversations, online communication and home visits. Many activities such as history review, physical examination, psychiatric evaluations and ophthalmology assessments can be conducted comparably to those done in traditional face-to-face visits. In addition, “clinician-interactive” telemedicine services may be less costly than in-person clinical visits.

Benefits and uses

Telemedicine can be extremely beneficial for people living in isolated communities and remote regions and is currently being applied in virtually all medical domains. Patients who live in such areas can be seen by a doctor or specialist, who can provide an accurate and complete examination, while the patient may not have to travel or wait the normal distances or times like those from conventional hospital or GP visits.

Specialties that use telemedicine often use a 'tele-' prefix; for example, telemedicine as applied by radiologists is called 'teleradiology'. Similarly telemedicine as applied by cardiologists is termed as 'telecardiology', etc...

Telemedicine is also useful as a communication tool between a general practitioner and a specialist available at a remote location. Telemedicine can be used as a teaching tool, by which experienced medical staff can observe, show and instruct medical staff in another location, more effective or faster examination techniques. It improved access to healthcare for patients in remote locations. "Telemedicine has been shown to reduce the cost of healthcare and increase efficiency through better management of chronic diseases,shared health professional staffing, reduced travel times, and fewer or shorter hospital stays." Several studies have documented increase patient satisfaction of telemedicine over past fifteen years.

The first interactive telemedicine system, operating over standard telephone lines, for remotely diagnosing and treating patients requiring cardiac resuscitation (defibrillation)

was developed and marketed by MedPhone Corporation Telemonitoring is a medical practice that involves remotely monitoring patients who are not at the same location as the health care provider. In general, a patient will have a number of monitoring devices at home, and the results of these devices will be transmitted via telephone to the health care provider. Telemonitoring is a convenient way for patients to avoid travel and to perform some of the more basic work of healthcare for themselves.

In addition to objective technological monitoring, most telemonitoring programs include subjective questioning regarding the patient's health and comfort. This questioning can take place automatically over the phone, or telemonitoring software can help keep the patient in touch with the health care provider. The provider can then make decisions about the patient's treatment based on a combination of subjective and objective information similar to what would be revealed during an on-site appointment.

Some of the more common things that telemonitoring devices keep track of include blood pressure, heart rate, weight, blood glucose, and hemoglobin. Telemonitoring is capable of providing information about any vital signs, as long as the patient has the necessary monitoring equipment at his or her location. Depending on the severity of the patient's condition, the provider may check these statistics on a daily or weekly basis to determine the best course of treatment.

Cardiac MonitorRemote Patient MonitoringVital Signs MonitorTelemedicine SystemPortable Heart MonitorHolter MonitorPortable Ekg Monitor in 1989 under the leadership of its president and founder, S.Eric Wachtel. A year later the company introduced a mobile cellular version, the MDphone. Twelve hospitals in the U.S. served as receiving and treatment centers.

The first Ayurvedic telemedicine center was established in India in 2007 by Partap Chauhan, a well-known Indian Ayurvedic doctor.

Monitoring a patient at home using known devices like blood pressure monitors and transferring the information to a caregiver is a fast growing emerging service. These remote monitoring solutions have a focus on current high morbidity chronic diseases and are mainly deployed for the First World. In developing countries a new way of practicing telemedicine is emerging better known as Primary Remote Diagnostic Visits, whereby a doctor uses devices to remotely examine and treat a patient. This new technology and principle of practicing medicine holds significant promise of improving on major health care delivery problems, in for instance, Southern Africa, because Primary Remote Diagnostic Consultations not only monitors an already diagnosed chronic disease, but has the promise to diagnose and manage the diseases a patient will typically visit a general practitioner for.

Telecardiology

ECGs, or electrocardiographs, can be transmitted using telephone and wireless. Willem Einthoven, the inventor of the ECG, actually did tests with transmission of ECG via

telephone lines. This was because the hospital did not allow him to move patients outside the hospital to his laboratory for testing of his new device. In 1906 Einthoven came up with a way to transmit the data from the hospital directly to his lab.

Teletransmission of ECG using indigenous methods. One of the oldest known telecardiology system (teletransmission of ECG) was established in Gwalior, India in 1975 at GR Medical college by Dr. Ajai Shanker, Dr. S. Makhija, P.K. Mantri using indegenous technique for the first time in India.

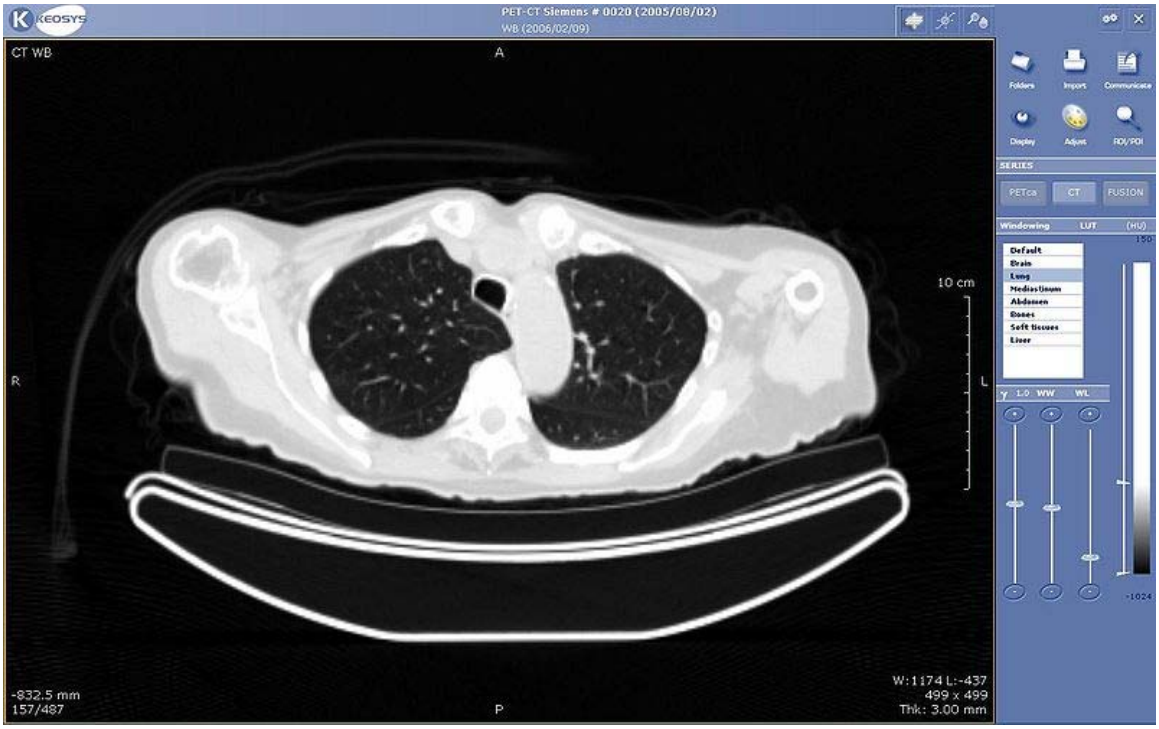
This system enabled wireless transmission of ECG from the moving ICU van or the patients home to the central station in ICU of the department of Medicine. Transmission using wireless was done using frequency modulation which eliminated noise. Transmission was also done through telephone lines. The ECG output was connected to the telephone input using a modulator which converted ECG into high frequency sound. At the other end a demodulator reconverted the sound into ECG with a good gain accuracy. The ECG was converted to sound waves with a frequency varying from 500 Hz to 2500 Hz with 1500 Hz at baseline.

This system was also used to monitor patients with pacemakers in remote areas. The central control unit at the ICU was able to correctly interpret arrhythmia. This technique helped medical aid reach in remote areas.

In addition, Electronic stethoscopes can be used as recording devices, which is helpful for purposes of telecardiology.

In Pakistan a pilot project in telemedicine was initiated by the Electronic Government Directorate in collaboration with Oratier Technologies (a pioneer company within Pakistan dealing with healthcare and HMIS) and PakDataCom (a bandwidth provider). Three hub stations through were linked with VSat and four districts were linked with another hub. A 312 Kb link was also established with remote sites and 1 Mbps bandwidth was provided at each hub. Three Hubs, i.e. Mayo Hospital (the largest hospital in Asia), JPMC Karachi and Holy Family Rawalpindi were established. These 12 remote sites were connected and on average 2,000 patient were being treated per month by a single hub. The project is still running smoothly after two years.

Teleradiology



A CT exam displayed through teleradiology

Teleradiology is the ability to send radiographic images (x-rays, CT, MR, PET/CT, SPECT/CT, MG, US...) from one location to another. For this process to be implemented, three essential components are required, an image sending station, a transmission network, and a receiving-image review station. The most typical implementation are two computers connected via the Internet. The computer at the receiving end will need to have a high-quality display screen that has been tested and cleared for clinical purposes. Sometimes the receiving computer will have a printer so that images can be printed for convenience.

The teleradiology process begins at the image sending station. The radiographic image and a modem or other connection are required for this first step. The image is scanned and then sent via the network connection to the receiving computer.

Today's high-speed broadband based Internet enables the use of new technologies for teleradiology : the image reviewer can now have access to distant servers in order to view an exam. Therefore, they do not need particular workstations to view the images ; a standard Personal Computer (PC) and Digital Subscriber Line (DSL) connection is enough to reach keosys central server. No particular software is necessary on the PC and the images can be reached from wherever in the world.

Teleradiology is the most popular use for telemedicine and accounts for at least 50% of all telemedicine usage.

Telepsychiatry

Telepsychiatry, another aspect of telemedicine, also utilizes videoconferencing for patients residing in underserved areas to access psychiatric services. It offers wide range of services to the patients and providers, such as consultation between the psychiatrists, educational clinical program, diagnosis and assessment, medication therapy management, etc.

The following are some of the model programs and projects which are undergoing for implementation of telepsychiatry in rural areas in the US.

1. University of Colorado Health Sciences Center (UCHSC) supports two programs for American Indian and Alaskan Native populations

    a. The Center for Native American Telehealth and Tele-education (CNATT) and
    b. Telemental Health Treatment for American Indian Veterans with Posttraumatic Stress Disorder (PTSD)

2. Military Psychiatry, Walter Reed Army Medical Center.

Links for several sites related to telemedicine, telepsychiatry policy, guidelines, and networking are available at the website for the American Psychiatric Association.

Telepharmacy

Telepharmacy is another growing trend for providing pharmaceutical care to the patients at remote locations where they may not have physical contact with pharmacists. It encompasses drug therapy monitoring, patient counseling, prior authorization, refill authorization, monitoring formulary compliance with the aid of teleconferencing or videoconferencing. In addition, video-conferencing is vastly utilized in pharmacy for other purposes, such as providing education, training, and performing several management functions.

A notable telepharmacy program in the United States conducted at a federally qualified community health center, Community Health Association of Spokane (CHAS) in 2001, which allowed the low cost medication dispensing under federal government's program. This program utilized videotelephony for dispensing medication and patient counseling at six urban and rural clinics. There were one base pharmacy and five remote clinics in several areas of Spokane, Washington under the telepharmacy program at CHAS. "The base pharmacy provided traditional pharmacy study to the clients at Valley clinic and served as the hub pharmacy for the other remote clinics."

The remote site dispensing and patient education process was described as follows: once the prescription is sent from the remote clinics to the base pharmacy, the pharmacist verifies the hard copy and enters the order. The label is also generated simultaneously, and the label queue is transmitted to the remote site. When the label queue appears on the

medication dispensing cabinet known as ADDS, the authorized person can access the medicine from ADDS followed by medication barcode scanning, and the printing and scanning of labels. Once those steps are done, the remote site personnel are connected to the pharmacist at base pharmacy via videoconferencing for medication verification and patient counseling.

In recent time, the U.S. Navy Bureau of Medicine took a significant step in advancing telepharmacy worldwide. The telepharmacy program was piloted in 2006 "in the regions served by Naval Hospital Pensacola, Florida, and Naval Hospital Bremerton, Washington." Starting from March 2010, the Navy expanded its telepharmacy system to more sites throughout the world. According to Navy Lieutenant Justin Eubanks at Navy Hospital Pensacola, Florida, telepharmacy would be initiated at more than 100 Navy sites covering four continents by the end of 2010.

Licensing, regulatory issues & telemedicine

Restrictive licensure laws in the United States require a practitioner to obtain a full license to deliver telemedicine care across state lines. Typically, states with restrictive licensure laws also have several exceptions (varying from state to state) that may release an out-of-state practitioner from the additional burden of obtaining such a license. A number of States require practitioners who seek compensation to frequently deliver interstate care to acquire a full license. If a practitioner serves several states, obtaining this license in each state could be an expensive and time-consuming proposition. Even if the practitioner never practices medicine face-to-face with a patient in another state, he/she still must meet a variety of other individual state requirements, including paying substantial licensure fees, passing additional oral and written examinations, and traveling for interviews. Regulations concerning the practice of Telemedicine vary from state to state. Physicians who will be prescribing over the Internet to patients should mandate strict controls on their practice to insure that they stay compliant with the various State Medical Board Regulations concerning Internet Prescribing.

Chapter 13

Assisted Reproductive Technology

Assisted reproductive technology (**ART**) is a general term referring to methods used to achieve pregnancy by artificial or partially artificial means. It is reproductive technology used primarily in infertility treatments. Some forms of *ART* are also used in fertile couples for genetic reasons. *ART* is also used in couples who are discordant for certain communicable diseases, i.e. AIDS, to reduce the risk of infection when a pregnancy is desired. The term includes any reproductive technique involving a third party e.g. a sperm donor. There is yet no strict definition of the term. Usage of the ART mainly belongs in the field of reproductive endocrinology and infertility.

Definitions

While there is no consensus on the definition, generally the process of intercourse is bypassed either by insemination (for example, artificial insemination) or fertilization of the oocytes in the laboratory environment (i.e., in vitro fertilization).

- The Centers for Disease Control and Prevention (CDC)—which is required as a result of the 1992 Fertility Clinic Success Rate and Certification Act to publish the annual ART success rates at U.S. fertility clinics—defines ART to include "all fertility treatments in which both eggs and sperm are handled. In general, ART procedures involve surgically removing eggs from a woman's ovaries, combining them with sperm in the laboratory, and returning them to the woman's body or donating them to another woman." According to CDC, "they do not include treatments in which only sperm are handled (i.e., intrauterine—or artificial—insemination) or procedures in which a woman takes medicine only to stimulate egg production without the intention of having eggs retrieved."

Procedures

Procedures are mainly fertility medication, as well as ART techniques that use more substantial and forceful interventions, of which in vitro fertilization (IVF) and expansions of it (e.g. OCR, AZH, ICSI, ZIFT) are the most prevalent. However, there are also other manual ART, not necessarily dependent on IVF (e.g. PGD, GIFT, SSR).

Medication

Most fertility medication are agents that stimulate the development of follicles in the ovary. Examples are gonadotropins and gonadotropin releasing hormone.

In vitro fertilization

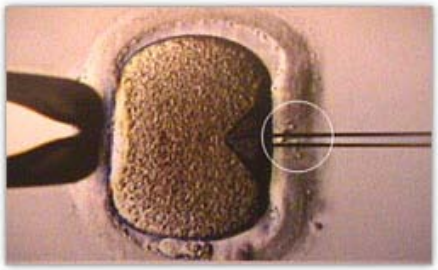
In vitro fertilization (IVF) is the technique of letting fertilization of the male and female gametes (sperm and egg) occur outside the female body.

Embryo transfer is the step in the process whereby one or several embryos are placed into the uterus of the female with the intent to establish a pregnancy.

Expansions of IVF

The following are techniques involved in, or requiring, in vitro fertilisation. In vitro fertilization does not necessarily involve each technique.

- Transvaginal ovum retrieval (OCR) is the process whereby a small needle is inserted through the back of the vagina and guided via ultrasound into the ovarian follicles to collect the fluid that contains the eggs.
- Assisted zona hatching (AZH) is performed shortly before the embryo is transferred to the uterus. A small opening is made in the outer layer surrounding the egg in order to help the embryo hatch out and aid in the implantation process of the growing embryo.



Intracytoplasmic Sperm Injection (ICSI)

Intracytoplasmic sperm injection (ICSI) is beneficial in the case of male factor infertility where sperm counts are very low or failed fertilization occurred with previous IVF attempt(s). The ICSI procedure involves a single sperm carefully injected into the center of an egg using a microneedle. This method is also sometimes employed when donor sperm is used.

- Autologous endometrial coculture is a possible treatment for patients who have failed previous IVF attempts or who have poor embryo quality. The patient's

fertilized eggs are placed on top of a layer of cells from the patient's own uterine lining, creating a more natural environment for embryo development.
- In zygote intrafallopian transfer (ZIFT), egg cells are removed from the woman's ovaries and fertilized in the laboratory; the resulting zygote is then placed into the fallopian tube.
- Cytoplasmic transfer is the technique in which the contents of a fertile egg from a donor are injected into the infertile egg of the patient along with the sperm.
- Egg donors are resources for women with no eggs due to surgery, chemotherapy, or genetic causes; or with poor egg quality, previously unsuccessful IVF cycles or advanced maternal age. In the egg donor process, eggs are retrieved from a donor's ovaries, fertilized in the laboratory with the sperm from the recipient's partner, and the resulting healthy embryos are returned to the recipient's uterus.
- A gestational carrier is an option when a patient's medical condition prevents a safe pregnancy, when a patient has ovaries but no uterus due to congenital absence or previous surgical removal, and where a patient has no ovaries and is also unable to carry a pregnancy to full term.
- Preimplantation genetic diagnosis (PGD) involves the use of genetic screening mechanisms such as Fluorescent In Situ Hybridization (FISH) or Comparative Genomic Hybridization (CGH) to help identify genetically abnormal embryos and improve healthy outcomes.
- Embryo splitting can be used for twinning to increase the number of available embryos.

Others

The following Assisted Reproduction techniques don't necessarily involve IVF.

- In gamete intrafallopian transfer (GIFT) a mixture of sperm and eggs is placed directly into a woman's fallopian tubes using laparoscopy following a transvaginal ovum retrieval.
- Sex selection is the attempt to control the sex of offspring to achieve a desired sex. It can be accomplished in several ways, both pre- and post-implantation of an embryo, as well as at birth. Pre-implantation techniques include PGD, but also sperm sorting.
- Artificial insemination (AI) is when sperm is placed into a female's uterus (intrauterine) or cervix (intracervical) using artificial means rather than by natural copulation. N.B. This can be a very low-tech process, performed at home by the woman alone or with her partner.
    - Conception devices, such as a conception cap are used to aid conception by enhancing the natural process. Conception caps are used by placing semen into a small conception cap, then placing the cap onto the cervix. This holds the semen at the cervical os, protecting the semen from the acidic vaginal secretions and keeping it in contact with the cervical mucus.
    - Artificial insemination by donor is used in situations where the woman doesn't have a partner with functional sperm. Instead, a sperm donor supplies the sperm.

- Surrogacy, where a woman agrees to become pregnant and deliver a child for a contracted party. It may be her own genetic child, or a child conceived through in vitro fertilization or embryo transfer using another woman's ova.
- Reproductive surgery, treating e.g. fallopian tube obstruction and vas deferens obstruction, or reversing a vasectomy by a reverse vasectomy.
    - In surgical sperm retrieval (SSR) the reproductive urologist obtains sperm from the vas deferens, epididymis or directly from the testis in a short outpatient procedure.
- By cryopreservation, eggs, sperm and reproductive tissue can be preserved for later IVF.

Risks

The majority of IVF-conceived infants do not have birth defects. However, some studies have suggested that assisted reproductive technology is associated with an increased risk of birth defects. In the largest U.S. study, which used data from a statewide registry of birth defects, 6.2% of IVF-conceived children had major defects, as compared with 4.4% of naturally conceived children matched for maternal age and other factors (odds ratio, 1.3; 95% confidence interval, 1.00 to 1.67).

The main risks are:

- Genetic disorders. DNA damage increases in e.g. IVF and ICSI, which is reflected e.g. by upregulation of the gene expression of HNRNPC in the placenta.
- Low birth weight. In IVF and ICSI, a risk factor is the decreased expression of proteins in energy metabolism; Ferritin light chain and ATP5A1.
- Preterm birth. Low birth weight and preterm birth are strongly associated with many health problems, such as visual impairment and cerebral palsy, and children born after IVF are roughly twice as likely to have cerebral palsy.

Other risk factors are:

- Membrane damage, which is contributed to or reflected by increased expression of the membrane fusion proteins NAPA and Annexin A3.

Sperm donation is an exception, with a birth defect rate of almost a fifth compared to the general population. It may be explained by that sperm banks accept only people with high sperm count.

Current data indicate little or no increased risk for postpartum depression among women who use ART.

Usage

Assisted reproductive technology procedures performed in the U.S. has more than doubled since 10 years ago, with 140.000 procedures in 2006, resulting in 55.000 infants born.

In Australia, 3.1 percent of babies now born are a result of ART.

Costs

United States of America

Not everyone in the U.S. has insurance coverage for fertility investigations and treatments. Many states are starting to mandate coverage, and the rate of utilization is 277% higher in states with complete coverage.

There are some health insurance companies that cover diagnosis of infertility but frequently once diagnosed will not cover any treatment costs.

2005 approximate treatment/diagnosis costs (United States, costs in US$):

- Initial workup: hysteroscopy, hysterosalpingogram, blood tests ~$2,000
- Intrauterine Insemination (IUI) aka Artificial insemination ~ $200– 900 per. trial
- Sonohysterogram (SHG) ~ $600 – 1,000
- Clomiphene citrate cycle ~ $ 200 - 500
- IVF cycle ~ $10,000 -30,000
- Use of a surrogate mother to carry the child - dependent on arrangements

Another way to look at costs is to determine the cost of establishing a pregnancy. Thus if a clomiphene treatment has a chance to establish a pregnancy in 8% of cycles and costs $500, it will cost ~ $6,000 to establish a pregnancy, compared to an IVF cycle (cycle fecundity 40%) with a corresponding cost of ($12,000/40%) $30,000

For the community as a whole, the cost of IVF on average pays back by 700% by tax from future employment by the conceived human being.

United Kingdom

In the UK all patients have the right to preliminary testing, provided free of charge by the National Health Service. However, treatment is not widely available on the NHS and there can be long waiting lists. Many patients therefore pay for immediate treatment within the NHS or seek help from private clinics.

Sweden

In Sweden, official fertility clinics provide most necessary treatments and initial workup, but there are long waiting lists, especially for egg donations, since the donor gets just as low reward as the receiving couple are charged. However, there are private fertility clinics.

Canada

Some treatments are covered by OHIP (public health insurance) in Ontario and others are not. If you are undergoing artificial insemination or if you have bilaterally blocked fallopian tubes and are under 40, the treatment is covered but you are still required to pay lab fees which are around $3,000-4,000. Coverage would vary in other provinces. Most other patients are required to pay for treatments themselves.

Israel

Israel's National Health Insurance, which is mandatory for all Israeli citizens, covers nearly all fertility treatments. In-Vitro-Fertilization costs are fully subsidized up to the birth of two children for all Israeli women, including single women and lesbian couples. Embryo transfers for purposes of gestational surrogacy are also covered.

New Zealand

The national public health system of New Zealand covers IVF treatment in specific circumstances only, based on a 'points for conception challenges' equation. Publicly funded IVF treatments are limited (between one and three treatments dependent on criteria) and are subject to substantial wait-lists, dependent on local health funding region, which raises potential inequity of ART support across the country. Infertility testing through blood tests can be covered by public funding, however in the absence of explicit gynecological complications, additional investigations are may not be covered publicly. Investigation such as a hysterosalpingogram may be covered, but the wait-list could be in excess of six weeks, whereas a privately sourced HSG can cost $NZ900 but is readily available. Many New Zealanders select self-funded IVF cycles, at approximately $NZ10,000 per cycle, and other forms of ART, such as IUI, at approximately $NZ1200, using the services of private fertility clinics, which in itself is a growing local industry. Individuals using private services are generally not covered under personal health insurance policies in New Zealand.

Ethics

Some couples find it difficult to stop treatment despite very bad prognosis, resulting in futile therapies. This may give ART providers a difficult decision of whether to continue or refuse treatment.

Fictional representation

Films and other fiction depicting emotional struggles of assisted reproductive technology have had an upswing in the latter part of the 2000s decade, although the techniques have been available for decades. Yet, the amount of people that can relate to it by personal experience in one way or another is ever growing, and the variety of trials and struggles are huge.

Chapter 14

Computer-Aided Diagnosis

Computer-aided detection (CADe) and computer-aided diagnosis (CADx) are procedures in medicine that assist doctors in the interpretation of medical images. Imaging techniques in X-ray, MRI, and Ultrasound diagnostics yield a great deal of information, which the radiologist has to analyze and evaluate comprehensively in a short time. CAD systems help scan digital images, *e.g.* from computed tomography, for typical appearances and to highlight conspicuous sections, such as possible diseases.

CAD is a relatively young interdisciplinary technology combining elements of artificial intelligence and digital image processing with radiological image processing. A typical application is the detection of a tumor. For instance, some hospitals use CAD to support preventive medical check-ups in mammography (diagnosis of breast cancer), the detection of polyps in the colon, and lung cancer.

Overview

CADe systems are usually confined to marking conspicuous structures and sections. Computer Aided Diagnosis (CADx) systems evaluate the conspicuous structures. For example, in mammography CAD highlights micro calcification clusters and hyperdense structures in the soft tissue. This allows the radiologist to draw conclusions about the condition of the pathology. Another application is CADq, which quantifies, e.g., the size of a tumor or the tumor's behavior in contrast medium uptake. At the present stage of the technology, CAD cannot and may not substitute the doctor, but rather plays a supporting role. The doctor (generally a radiologist) is always responsible for the final interpretation of a medical image.

Computer-aided diagnosis topics

Methodology

CAD is fundamentally based on highly complex pattern recognition. X-ray images are scanned for suspicious structures. Normally a few thousand images are required to optimize the algorithm. Digital image data are copied to a CAD server in a DICOM-format and are prepared and analyzed in several steps.

1. Preprocessing for

- Reduction of artifacts (bugs in images)
- Image noise reduction
- Leveling (harmonization) of image quality for clearing the image's different basic conditions e.g. different exposure parameter.

2. Segmentation for

- Differentiation of different structures in the image, e.g. heart, lung, ribcage , possible round lesions
- Matching with anatomic databank

3. Structure/ROI (Region of Interest) Analyze Every detected region is analyzed individually for special characteristics:

- Compactness
- Form, size and location
- Reference to close-by structures / ROIs
- Average greylevel value analyze within a ROI
- Proportion of greylevels to border of the structure inside the ROI

4. Evaluation / classification After the structure is analyzed, every ROI is evaluated individually (scoring) for the probability of a TP. Therefore the procedures are:

- Nearest-Neighbor Rule
- Minimum distance classifier
- Cascade Classifier
- Bayesian Classifier
- Multilayer perception
- Radial basis function network (RBF)
- SVM

If the detected structures have reached a certain threshold level, they are highlighted in the image for the radiologist. Depending on the CAD system these markings can be permanently or temporary saved. The latter's advantage is that only the markings which are approved by the radiologist are saved. False hits should not be saved, because an examination at a later date becomes more difficult then.

Sensitivity and specificity

CAD systems seek to highlight suspicious structures. Today's CAD systems cannot detect 100% of pathological changes. The hit rate (sensitivity) can be up to 90% depending on system and application. A correct hit is termed a True Positive (TP), while the incorrect marking of healthy sections constitutes a False Positive (FP). The less FPs indicated, the higher the specificity is. A low specificity reduces the acceptance of the CAD system

because the user has to identify all of these wrong hits. The FP-rate in lung overview examinations (CAD Chest) could be reduced to 2 per examination. In other segments (*e.g.* CT lung examinations) the FP-rate could be 25 or more.

Absolute detection rate

The absolute detection rate of the radiologist is an alternative metric to sensitivity and specificity. Overall, results of clinical trials about sensitivity, specificity, and the absolute detection rate can vary markedly. Each study result depends on its basic conditions and has to be evaluated on those terms. The following facts have a strong influence:

- Retrospective or prospective design
- Quality of the used images
- Condition of the x-ray examination
- Radiologist's experience and education
- Type of tumor
- Size of the considered tumor

Applications

CAD is used in the diagnosis of breast cancer, lung cancer, colon cancer, prostate cancer, bone metastases and coronary artery disease.

Breast cancer

CAD is used in screening mammography (X-ray examination of the female breast). Screening mammography is used for the early detection of breast cancer. CAD is especially established in US and the Netherlands and is used in addition to human evaluation, usually by a radiologist. The first CAD system for mammography was developed in a research project at the University of Chicago. Today it is commercially offered by iCAD and Hologic. There are currently some non-commercial projects being developed, such as Ashita Project, a gradient-based screening software by Alan Hshieh, as well. However, while achieving high sensitivities, CAD systems tend to have very low specificity and the benefits of using CAD remain uncertain. Some studies suggest a positive impact on mammography screening programs, but others show no improvement. A 2008 systematic review on computer-aided detection in screening mammography concluded that CAD does not have a significant effect on cancer detection rate, but does undesirably increase recall rate (*i.e.* the rate of false positives). However, it noted considerable heterogeneity in the impact on recall rate across studies.

Procedures to evaluate mammography based on magnetic resonance imaging exist too.

Lung cancer (bronchial carcinoma)

In the diagnosis of lung cancer, computed tomography with special three-dimensional CAD systems are established and considered as gold standard. At this a volumetric

dataset with up to 3.000 single images is prepared and analyzed. Round lesions (lung cancer, metastases and benign changes) from 1 mm are detectable. Today all well-known vendors of medical systems offer corresponding solutions.

Early detection of lung cancer is valuable. The 5-year-survival-rate of lung cancer has stagnated in the last 30 years and is now at approximately just 15%. Lung cancer takes more victims than breast cancer, prostate cancer and colon cancer together. This is due to the asymptomatic growth of this cancer. In the majority of cases it is too late for a successful therapy if the patient develops first symptoms (*e.g.* chronic croakiness or hemoptysis). But if the lung cancer is detected early (mostly by chance), there is a survival rate at 47% according to the American Cancer Society. At the same time the standard x-ray-examination of the lung is the most frequently x-ray examination with a 50% share. Indeed the random detection of lung cancer in the early stage (stage 1) in the x-ray image is difficult. It is a fact that round lesions vary from 5–10 mm are easily overlooked. The routine application of CAD Chest Systems may help to detect small changes without initial suspicion. Philips was the first vendor to present a CAD for early detection of round lung lesions on x-ray images.

Colon cancer

CAD is available for detection of colorectal polyps in the colon. Polyps are small growths that arise from the inner lining of the Colon (anatomy). CAD detects the polyps by identifying their characteristic "bump-like" shape. To avoid excessive false positives, CAD ignores the normal colon wall, including the haustral folds. In early clinical trials, CAD helped radiologists find more polyps in the colon than they found prior to using CAD.

Coronary artery disease

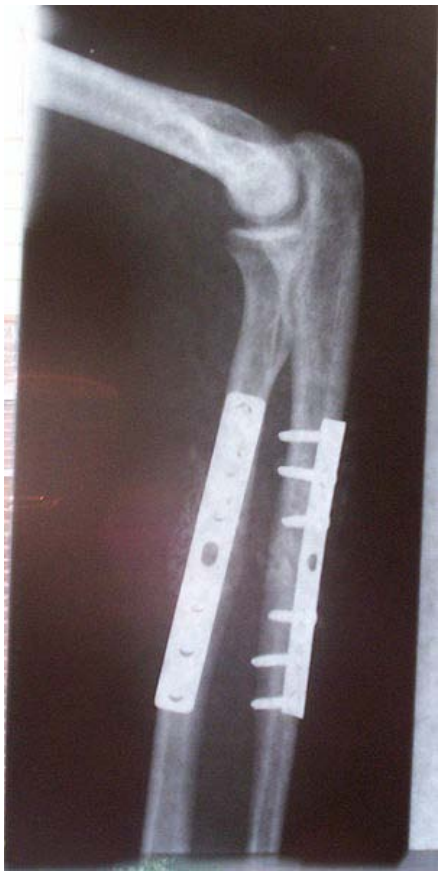
CAD is available for the automatic detection of significant (causing more than 50% stenosis) coronary artery disease in coronary CT angiography (CCTA) studies. A low false positives rate (60-70% specificity per patient)) allows using CAD as a screening device distinguishing between positive and negative studies and yielding a preliminary report. This, for example, can be used for chest pain patients' triage in an emergency setting.

Nuclear medicine

CADx is available for nuclear medicine images. Commercial CADx systems for the diagnosis of bone metastases in whole-body bone scans and coronary artery disease in myocardial perfusion images exist.

Chapter 15

Implant (Medicine)



Orthopedic implants to repair fractures to the radius and ulna. Note the visible break in the ulna. (right forearm)

An **implant** is a medical device manufactured to replace a missing biological structure, support a damaged biological structure, or enhance an existing biological structure. Medical implants are man-made devices, in contrast to a transplant, which is a transplanted biomedical tissue. The surface of implants that contact the body might be made of a biomedical material such as titanium, silicone or apatite depending on what is the most functional. In some cases implants contain electronics e.g. artificial pacemaker and cochlear implants. Some implants are bioactive, such as subcutaneous drug delivery devices in the form of implantable pills or drug-eluting stents.

Applications

Among the most common types of medical implants are the pins, rods, screws and plates used to anchor fractured bones while they heal.

Electrically-powered implants

Active implants require electricity for their operation. Artificial pacemaker is an example of such devices that is used for treatment of Bradycardia in which the heart beats too slowly. Pacemakers can help raise the heart beat to a more normal rate through electrical stimulation of heart. Active implants could be powered up using batteries, transcutaneous energy transmission, or scavenging energy from the environment .

Bio-implants

A **bio-implant** may be defined as a biomaterial surgically implanted in a person's body to replace damaged tissue. Common areas of application include orthopedic (especially maxillofacial) re-constructive prosthesis, cardiac prostheses (artificial heart valves like the Chitra heart valve), skin and cornea.

Dental implants

Dental implants are one of the few medical devices which permanently cross the boundary between the inside and the outside of the body, since the base of the implant is osseointegrated in the bone of the mandible or maxilla and the top of the implant is in the mouth, where it can be crowned with an artificial tooth.

Orthopedic implants

In orthopedic surgery, *implants* may refer to devices that are placed over or within bones to hold a fracture reduction while *prosthesis* would be the more appropriate term for devices that replace a part or whole of a defunct joint. (In this context *implants* may be placed within or outside the body.)

Types of orthopedic implants

There are many types of orthopedic implants and each orthopedic implant is designed to correct the affected joint so that it withstands the associated movement and stress and to enhance mobility and decrease pain. Broadly speaking, Orthopedic implants are available for the hip, knee, shoulder and elbow. Safety Locking Plates

- Interlocking Nail
- Nails, Wires & Pins
- Cranio Maxillofacial Implants
- Mini Fragment Implants
- Small Fragment Implants

- Large Fragment Implants
- Cannulated Screws
- DHS/DCS & Angled Blade Plates
- Hip Prosthesis
- ACL/PCL Reconstruction System
- Spine Surgery
- External Fixators...

Complications

The process of implantation of medical devices is subject to the same complications as any other invasive medical procedure, including infection, inflammation, and pain. Implants also run the risk of rejection if they ellicit a reaction from the host immune system.

Failures

There have been many examples of implant failures, including rupture of silicone breast implants, hip replacement joints and artificial heart valves, such as the Bjork–Shiley valve, all of which have caused FDA intervention. The consequences of implant failure depend on the critical nature of the implant, and its position in the body. Thus heart valve failure is likely to threaten the life of the individual, while breast implant or hip joint failure is less likely to be life-threatening.

Chapter 16

Medical Laboratory

Clinical laboratory in a Hospital setting showing several automated analysers

A **medical laboratory** or **clinical laboratory** is a laboratory where tests are done on clinical specimens in order to get information about the health of a patient as pertaining to the diagnosis, treatment, and prevention of disease.

Departments

Laboratory medicine is generally divided into two sections, and each of which is further divided into a number of units. These two sections are:

- Anatomic Pathology: units included here are histopathology, cytopathology, and electron microscopy. Academically, each unit is studied alone in one course. Other courses pertaining to this section include anatomy, physiology, histology, pathology, and pathophysiology.

- Clinical pathology, including :
    - Clinical Microbiology: This is the largest section in laboratory medicine; it encompasses five different sciences (units). These include bacteriology, virology, parasitology, immunology, and mycology.
    - Clinical Chemistry: Units under this busy section are instrumental analysis, enzymology, toxicology and endocrinology.
    - Hematology: This small, yet busy, section consists of two units, which are coagulation and blood bank.
    - Genetics is also studied along with a subspecialty known as cytogenetics.
    - Reproduction biology : Semen analysis, Sperm bank and assisted reproductive technology.

Distribution of clinical laboratories in health institutions varies greatly from one place to another. Take for example microbiology, some health facilities have a single laboratory for microbiology, while others have a separate lab for each unit, with nothing called a "microbiology" lab.

Laboratory equipment for hematology (black analyser) and urinalysis (left of the open centrifuge).

Here's a detailed breakdown of the responsibilities of each unit:

- Microbiology receives almost any clinical specimen, including swabs, feces, urine, blood, sputum, cerebrospinal fluid, synovial fluid, as well as possible infected tissue. The work here is mainly concerned with cultures, to look for suspected pathogens which, if found, are further identified based on biochemical tests. Also, sensitivity testing is carried out to determine whether the pathogen is sensitive or resistant to a suggested medicine. Results are reported with the identified organism(s) and the type and amount of drug(s) that should be prescribed for the patient.
- Parasitology is a microbiology unit that investigates parasites. The most frequently encountered specimen here is faeces. However, blood, urine, sputum, and other samples may also contain parasites.
- Virology is concerned with identification of viruses in specimens such as blood, urine, and cerebrospinal fluid.
- Hematology works with whole blood to do full blood counts, and blood films as well as many other specialised tests.
- Coagulation requires citrated blood samples to analyze blood clotting times and coagulation factors.
- Clinical Biochemistry usually receives serum or plasma. They test the serum for chemicals present in blood. These include a wide array of substances, such as lipids, blood sugar, enzymes, and hormones.
- Toxicology mainly tests for pharmaceutical and recreational drugs. Urine and blood samples are submitted to this lab.
- Immunology/Serology uses the concept of antigen-antibody interaction as a diagnostic tool. Compatibility of transplanted organs is also determined.
- Immunohaematology, or Blood bank determines blood groups, and performs compatibility testing on donor blood and recipients. It also prepares blood components, derivatives, and products for transfusion. Regulated by the FDA since giving blood is considered a drug, this unit determines a patient's blood type and Rh status, checks for antibodies to common antigens found on red blood cells, and cross matches units that are negative for the antigen.
- Urinalysis tests urine for many analytes. Some health care providers have a urinalysis laboratory, while others don't. Instead, each component of the urinalysis is performed at the corresponding unit. If measuring urine chemicals is required, the specimen is processed in the clinical biochemistry lab, but if cell studies are indicated, the specimen should be submitted to the cytopathology lab, and so on.
- Histopathology processes solid tissue removed from the body (biopsies) for evaluation at the microscopic level.
- Cytopathology examines smears of cells from all over the body (such as from the cervix) for evidence of inflammation, cancer, and other conditions.
- Electron microscopy prepares specimens and takes micrographs of very fine details by means of TEM and SEM.
- Genetics mainly performs DNA analysis.

- Cytogenetics involves using blood and other cells to get a karyotype. This can be helpful in prenatal diagnosis (e.g. Down's syndrome) as well as in cancer (some cancers have abnormal chromosomes).
- Surgical pathology examines organs, limbs, tumors, fetuses, and other tissues biopsied in surgery such as breast mastectomys.

Medical laboratory staff

Clinical laboratory in a Hospital setting with two technicians shown

The following is the hierarchy of the clinical laboratory staff from highest authority to lowest:

- Medical Director
- Pathologist, Clinical biologist
- Resident in Pathology, Anatomical pathology or Clinical biology
- Pathologist Assistant,
- Laboratory Manager,
- Department Supervisor,
- Chief/Lead Technologist,
- Cytotechnologist, Medical Laboratory Scientist, Histotechnologist,
- Medical Laboratory Technician, Histotechnician
- Medical Laboratory Assistant (Lab Aide),

- Phlebotomist,
- Transcriptionist,
- Specimen processor, Secretary).

Some of these titles don't exist in some countries. Sometimes technologists and technicians do the same work. In France, clinical biologists may also be Medical director and laboratory manager.

Types of laboratory

In many countries, there are two main types of labs that process the majority of medical specimens. **Hospital laboratories** are attached to a hospital, and perform tests on patients. **Private** (or **community**) **laboratories** receive samples from general practitioners, insurance companies, and other health clinics for analysis. These can also be called reference laboratories where more unusual and obscure tests are performed. For extremely specialised tests, samples may go to a research laboratory. A lot of samples are sent between different labs for uncommon tests. It is more cost effective if a particular laboratory specializes in a rare test, receiving specimens (and money) from other labs, while sending away tests it cannot do.

In many countries there are mainly three types of Medical Laboratories as per the types of investigations carried out. 1. Clinical Pathology 2. Clinical Microbiology & 3. Clinical Biochemistry laboratories. 1. Clinical Pathology: Haematology, Histopathology, Cytology, Routine Pathology2. Clinical Microbiology: Bacteriology, Mycobacteriology, Virology, Mycology, Parasitology, Immunology, Serology.3. Clinical Biochemistry: Biochemical analysis, Hormonal assays etc.Blood Banks:- Blood bank is a separate body. Its laboratory need Microbiological analysis for infectious diseases that may be found in blood. Pathology to observe Blood grouping, Haematology & cross matching reactions. It also involves PRO department for the communication & contact for blood donations etc..

Specimen processing and work flow

Sample processing will usually start with a set of samples and a request form.

Typically a set of vacutainer tubes containing blood, or any other specimen, will arrive to the laboratory in a small plastic bag, along with the form.

The form and the specimens are given a laboratory number. The specimens will usually all receive the same number, often as a sticker that can be placed on the tubes and form. This label has a barcode that can be scanned by automated analyzers and test requests uploaded from the LIS. Entry of requests onto a laboratory management system involves typing, or scanning (where barcodes are used) in the laboratory number, and entering the patient identification, as well as any tests requested. This allows laboratory machines, computers and staff to know what tests are pending, and also gives a place (such as a hospital department, doctor or other customer) for results to go.

For biochemistry samples, blood is usually centrifuged and serum is separated. If the serum needs to go on more than one machine, it can be divided into separate tubes.

Many specimens end up in one or more sophisticated automated analysers, that process a fraction of the sample and return one or more "results". Some laboratories use robotic sample handlers (Laboratory automation) to optimize the workflow and reduce contamination risk and sample handling of the staff.

The work flow in a lab is usually heavy from 2:00 am to 10:00 am. Nurses and doctors generally have their patients tested at least once a day with general complete blood counts and chemistry profiles. These orders are then drawn during a morning run by phlebotomists for results to be available in the patient's charts for the attending physicians to consult during their morning rounds. Another busy time for the lab is after 3:00 pm when private practice physician offices are closing. Couriers will pick up specimens that have been drawn throughout the day and deliver them to the lab. Also, couriers will stop at outpatient drawing centers and pick up specimens. These specimens will be processed in the evening and overnight to ensure results will be available the following day.

Laboratory informatics

Laboratories today are held together by a system of software programs and computers that exchange data about patients, test requests, and test results known as a Laboratory information system or LIS. The LIS is interfaced with the hospital information system.

This system enables hospitals and labs to order the correct test requests for each patient, keep track of individual patient or specimen histories, and help guarantee a better quality of results as well as printing hard copies of the results for patient charts and doctors to check.

Result analysis, validation and interpretation

According to ISO 15189 norm, all pathological results must be verified by a competent professional. In some countries staff like clinical scientists do the majority of this work inside the laboratory with abnormal results referred to the relevant pathologist. In others, only medical staff (pathologist or clinical biologist) is concerned by this phase. It can be assisted by some software in order to validate normal or non modified results. Medical staff are sometimes also required in order to explain pathology results to physicians. For a simple result given by phone or for a technical problem it's a medical technologist explaining it to a registered nurse.

Departments in some countries are exclusively directed by a specialized Pathologist, in others a consultant, medical or non-medical, may be the Head of Department. Clinical Scientists have the right to interpret and discuss pathology results in their discipline in many countries, in Europe they are qualified to at least Masters level, may have a PhD and can have an exit qualification equivalent to medical staff e.g. FRCPath in the UK. In France only medical staff (Pharm.D. and M.D. specialized in Anatomical pathology or

Clinical biology) can discuss pathological results, clinical scientists are not considered as a part of medical staff.

Scandal in the clinical lab industry

As medical technology advanced doctors were able to get more and more tests done in shorter and shorter amounts of time. Where in the past a doctor might order a potassium and glucose and it would take hours for the results, now a doctor can order a full chemistry panel of 20 or more different analytes and get the results in under an hour. The results are also much more accurate and reliable now than in the past. Thus, into the 1970s and 1980s the lab became a source of profit within the hospital structure.

Some commercial labs began taking illegal and nefarious actions to increase their income. These practices included Medicare and Medicaid fraud by performing and billing for tests that the ordering physician never ordered, paying kickbacks to private doctor offices for sending their specimens to these reference labs, and other complicated criminal activity. These kickbacks included donuts, free computers, fax machines, and more. These events culminated mostly in the mid-1990s with the SmithKline Beecham Clinical Laboratory (SBCL) scandal. It is believed SBCL paid at least $325 million in penalties and the industry as a whole paid over $1 billion to insurance and government agencies that were defrauded. Ever since this time, the lab has become a source of expense and loss in the hospital budget (commercial labs have nothing to do with hospitals) and lab medicine's reputation was given a black eye. Now many labs have a compliance officer with mandatory annual meetings about compliance for all employees.

Medical laboratory accreditation

Credibility of medical laboratories is paramount to the health and safety of the patients relying on the testing services provided by these labs. The international standard in use today for the accreditation of medical laboratories is ISO 15189 - Medical laboratories - particular requirements for quality and competence.

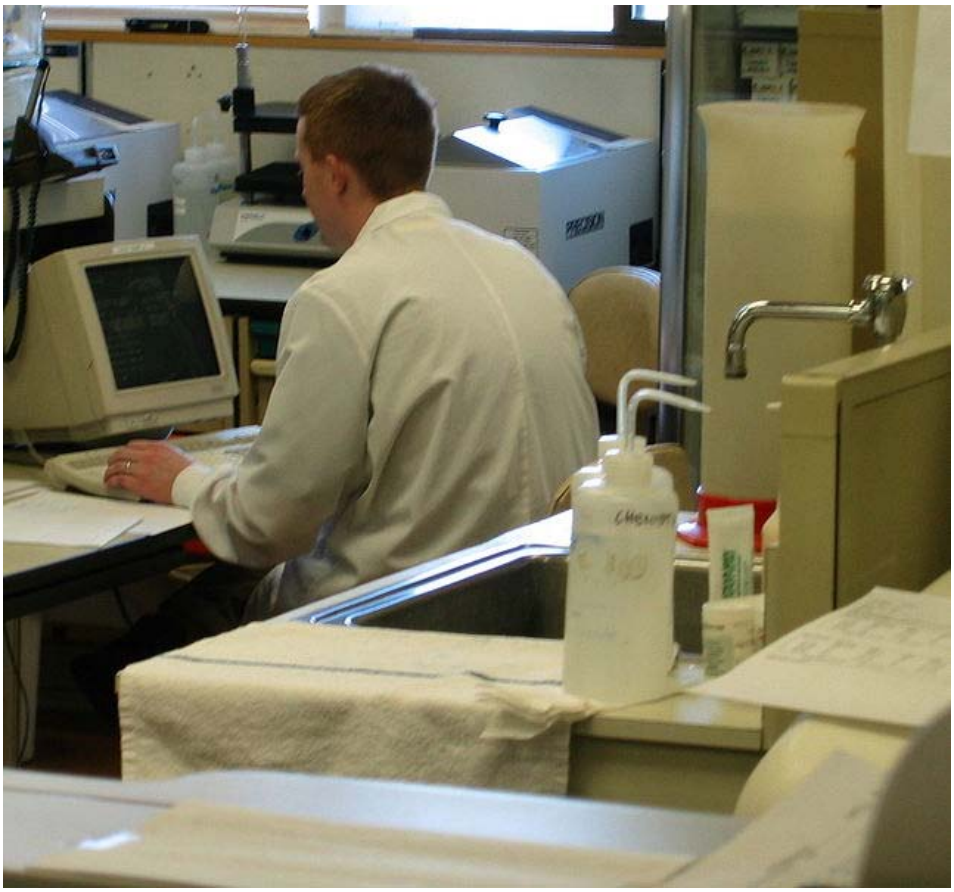
Accreditation is done by the Joint Commission, College of American Pathologists, AABB, and other state and federal agencies. CLIA 88 or the Clinical Laboratory Improvement Amendments also dictate testing and personnel.

The accrediting body in Australia is NATA, all laboratories must be NATA accredited to receive payment from Medicare.

In France, where accrediting body is COFRAC, in 2010, modification of legislation established ISO 15189 accreditation as an obligation for all clinical laboratories.

Chapter 17

Medical Laboratory Scientist



MLS in his work environment

A **Medical Laboratory Scientist** (MLS) is a healthcare professional who performs chemical, hematological, immunologic, microscopic, and bacteriological diagnostic analyses on body fluids such as blood, urine, sputum, stool, cerebrospinal fluid (CSF), peritoneal fluid, pericardial fluid, and synovial fluid, as well as other specimens. Medical Laboratory Scientists work in clinical laboratories at hospitals, doctor's offices, reference labs, and biotechnology labs.

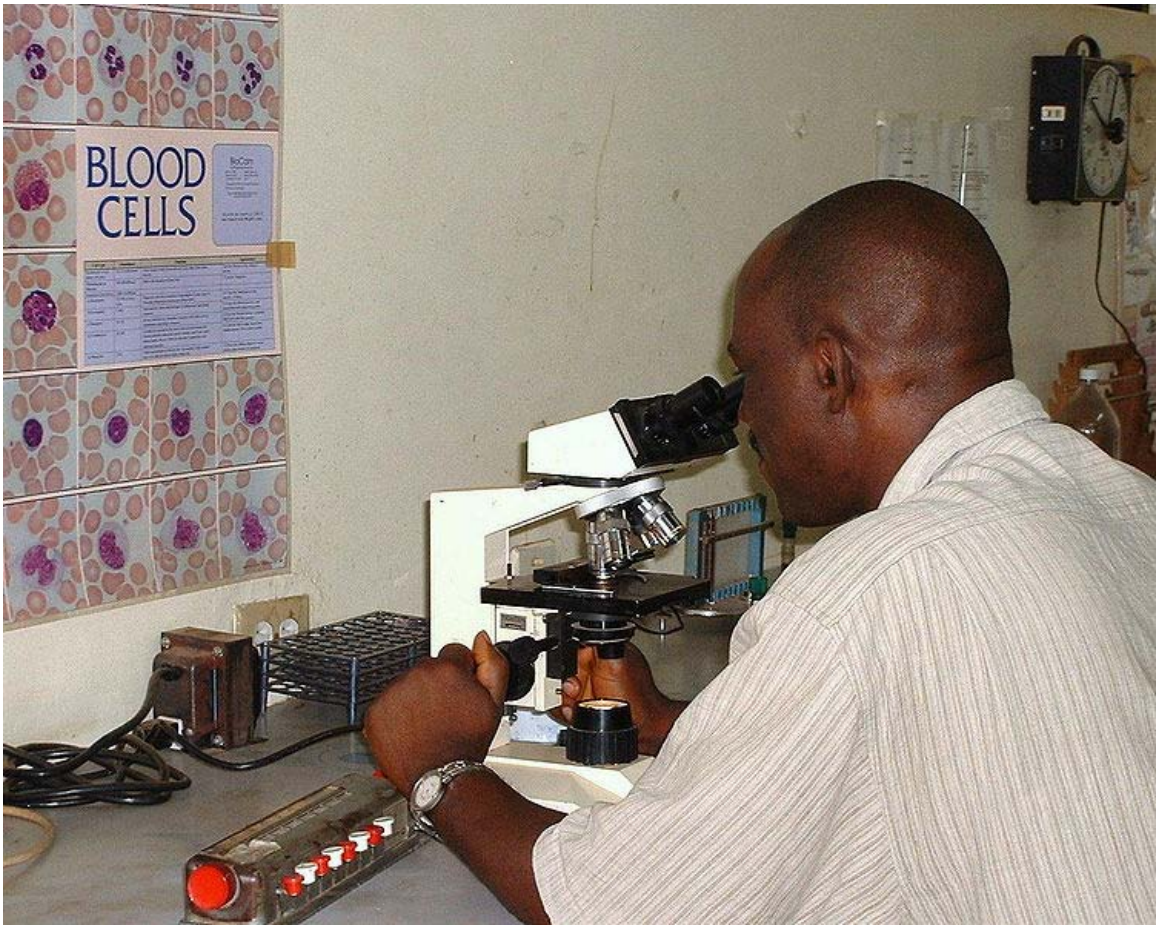
Educational requirements

A Medical Laboratory Scientist typically earns a bachelor's degree in medical laboratory science, clinical laboratory science, medical technology or in a life / biological science (biology, biochemistry, etc.), in which case certification from an accredited training program is also required. In most four-year medical laboratory degree programs, the student attends classroom courses for three years and clinical rotations are completed in their final year of study. This combination is called a 3+1 program. There are also 2+2 programs which specialize in accepting students who have completed their lower division coursework and completing their last two years of study in the CLS program. A 4+1 program would typically be completed after a student has completed a bachelor's degree and usually takes place primarily in a clinical site rather than a college. In clinical rotations, the student experiences hands-on learning in each discipline of the laboratory and, under supervision, performs diagnostic testing in a functioning laboratory. Although not compensated, a student in the clinical phase of training usually works 40 hours per week for 20 to 52 weeks, experiencing work as a full-time employee. In addition, some universities now offer graduate level programs to allow students who have undergraduate degrees in disciplines unrelated to science to enter the field.

In the United States, a similar two-year degree qualifies the graduate to work as a medical laboratory technician (MLT). Depending on the state where employment is granted, the job duties are very similar, but MLTs receive training more exclusively in laboratory sciences. The shorter training time is attractive to many students, but there are disadvantages to this route. For example, CLSs usually earn higher salaries than MLTs, and some institutions do not employ MLTs at all.

In Canada, three-year college programs are offered that include seven semesters, two of them comprising an unpaid internship. The student graduates before taking a standard examination (such as the Canadian Society for Medical Laboratory Science, or CSMLS, exam) to be qualified as a medical laboratory technologist. Many MLTs go on to receive a bachelor of science degree after they are certified, but a few university programs affiliate with a college MLT program to allow students to graduate with both MLT certification and a degree.

Certification and licensing



MLS examining a slide

Medical Laboratory Scientists who are certified and in good standing with the American Society for Clinical Pathology (ASCP) are entitled to use the credential "MLS" after their names. Formerly before the merger between ASCP and the National Credentialing Agency for Laboratory Personnel (NCA), Medical Laboratory Scientists certified by (ASCP) were entitled to use the credential "MT" (for Medical Technologist) and if credentialed by (NCA), the credential "CLS" (Clinical Laboratory Scientist) was used. Those certified by the Department of Health Services (HHS formally HEW), the American Association of Bioanalysts (AAB) and the American Medical Technologists (AMT) are still entitled to use the credential "MT." Additional certifying agencies include the National Healthcareer Association, National Phlebotomy Association, the National Center for Competency Testing, and the Accrediting Bureau of Health Education Schools. However the NCA and ASCP have now merged into the major certification agency.

In the United States, the Clinical Laboratory Improvement Amendments (CLIA '88) define the level of qualification required to perform tests of various complexity. Clinical Laboratory Scientists is the highest level of qualification, and CLSs are generally

qualified to perform the most complex clinical testing including HLA testing (also known as tissue typing) and blood type reference testing.

In addition to the national certification, 12 states (California, Florida, Georgia, Hawaii, Louisiana, Montana, Nevada, North Dakota, Rhode Island, Tennessee, West Virginia and New York) and Puerto Rico also require a state license. Minnesota, Texas, Illinois, Massachusetts, Michigan, Vermont, Washington, New Jersey, Iowa, Utah, Ohio, South Carolina, Wyoming, Pennsylvania, Virginia, South Dakota, Delaware, Missouri, Georgia and Alaska are currently attempting to obtain licensure. All states require documentation from a professional certification agency before issuing state certification. A person applying for state certification may also be expected to submit fingerprints, education and training records, and competency certification. Some states also require completion of a specified number of continuing education contact hours prior to issuing or renewing a license.

Some states recognize another state's license if it is equal or more stringent, but currently California does not recognize any other state license.

In the UK Medical Laboratory Scientists are known as Biomedical Scientists and must hold an honours degree from a university accredited by the Institute of Biomedical Science before they can embark upon a period of in-house training of at least 1 year before being assessed by the IBMS for state registration purposes. The title "Biomedical Scientist" is a protected title and can only be used by a person registered on the Health Professions Council register.

Specialty areas

Most Medical Laboratory Scientists are *generalists*, skilled in all areas of the clinical laboratory. However some CLSs are specialists, qualified by unique undergraduate education or additional training to perform more complex analyses than usual within a specific field. Specialties include clinical biochemistry, hematology, coagulation, microbiology, bacteriology, virology, parasitology, mycology, immunology, immunohematology (blood bank), histopathology, histocompatibility, cytopathology, genetics, cytogenetics, electron microscopy, and IVF labs. Medical Technologists specialty may use additional credentials, such as "SBB" (Specialist in Blood Banking) from the American Association of Blood Banks, or "SH" (Specialist in Hematology) from the ASCP. These additional notations may be appended to the base credential, for example, "MLS(ASCP)SBB".

Job duties

Medical Laboratory Scientists work in all areas of the clinical laboratory including blood banking, chemistry, hematology, immunology, histology and microbiology. They perform a full range of laboratory tests – from simple prenatal blood tests, to more complex tests to uncover diseases such as HIV/AIDS, diabetes, and cancer. They are also responsible for confirming the accuracy of test results, and reporting laboratory findings

to pathologists and other physicians. The information that a Medical Laboratory Scientists gives to the doctor influences the medical treatment a patient will receive. Medical Laboratory Scientists operate complex electronic equipment, computers, and precision instruments costing millions of dollars.

A Medical Laboratory Scientist analyzes human fluid samples using techniques available to the clinical laboratory, such as manual white blood cell differentials, bone marrow counts, analysis via microscopy, and advanced analytical equipment. Medical Laboratory Scientists assist doctors and nurses in choosing the correct lab tests and ensure proper collection methods. Medical Laboratory Scientists then receive the patient specimens, analyze the specimens, interpret and report results. A Pathologist may confirm a diagnostic result, but often the Medical Laboratory Scientist is responsible for interpreting and communicating critical patient results to the physician.

Medical Laboratory Scientists must recognize anomalies in their test results and know how to correct problems with the instrumentation. They monitor, screen, and troubleshoot analyzers featuring the latest technology available on the market. The MLS performs equipment validations, calibrations, quality controls, "STAT" or run-by-run assessment, statistical control of observed data, and recording normal operations. To maintain the integrity of the laboratory process, the medical laboratory scientist recognizes factors that could introduce error and rejects contaminated or sub-standard specimens.

Common tests performed by Medical Laboratory Scientists are complete blood count (CBC), comprehensive metabolic panel (CMP), electrolyte panel, liver function tests (LFT), renal function tests (RFT), thyroid function test (TFT), urinalysis, coagulation profile, lipid profile, blood type, semen analysis (for fertility and post-vasectomy studies), serological studies and routine cultures. In some facilities that have few phlebotomists, or none at all, (such as in rural areas) Medical Laboratory Scientists may perform phlebotomy on patients, as this skill is part of the clinical training.

Role in the healthcare process

A Medical Laboratory Scientist's role is to provide accurate laboratory results in a timely manner. Safeguards, such as experimental controls, calibration of laboratory instruments, delta checks (monitoring of significant changes within a normal series of results, formerly known as the "previous patients check"), and periodic surveys from the College of American Pathologists (CAP), ensure accuracy. Laboratory results aid clinical practitioners in confirming or ruling out diagnoses, monitoring chronic disease changes, and analyzing the effects of medical therapies.

Job title

The informal abbreviations of job titles may be a source of confusion. Medical Laboratory Scientist (ASCP) and Medical Technologists (AMT) or (AAB) are often called "med techs" (based on the era in which they were known as "medical technologists"), but this shorthand term is shared by other healthcare employees,

including pharmacy techs, x-ray techs and, formerly, respiratory techs, (now called respiratory therapists) and medical laboratory technicians (MLTs).

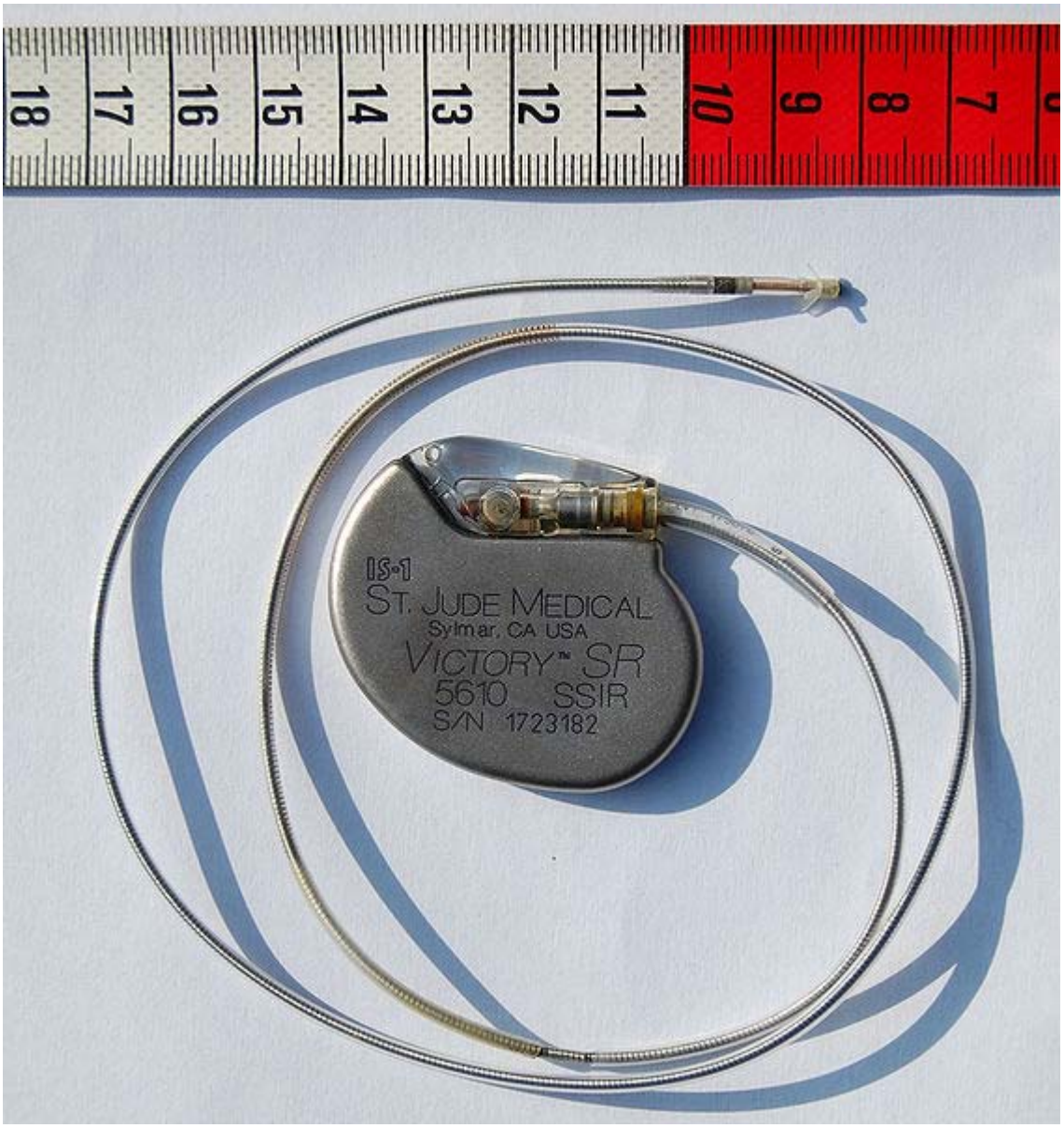
There is a formal distinction between an MLT and an MT/CLS that is not always understood by others. Both may be certified or registered by one or more nationally-recognized professional organizations, but technicians have a two-year associates degree, and may have less classroom training than other professionals. MTs and CLSs have a bachelors degree and usually do more difficult, complex analyses than technicians are trained to do. Scientists and technologists generally earn a higher income than technicians do and have more opportunities for advancement.

Much of the confusion could also be from the fact that the NCA and the ASCP certification agency, had two different titles (clinical laboratory scientist and medical technologist respectively) but with the two of them merging together into a "newer" ASCP and that organization choosing the name "Medical Laboratory Scientist", it can be said that finally the field has a "unified" title between the two organizations, however, the AMT still continues to use the title Medical Technologist.

Chapter 18

Artificial Pacemaker

A pacemaker, scale in centimeters



An artificial pacemaker with electrode for transvenous insertion (from St. Jude Medical). The body of the device is about 4 centimeters long, the electrode measures between 50 and 60 centimeters (20 to 24 inches).

A **pacemaker** (or **artificial pacemaker**, so as not to be confused with the heart's natural pacemaker) is a medical device which uses electrical impulses, delivered by electrodes contacting the heart muscles, to regulate the beating of the heart. The primary purpose of a pacemaker is to maintain an adequate heart rate, either because the heart's native pacemaker is not fast enough, or there is a block in the heart's electrical conduction system. Modern pacemakers are externally programmable and allow the cardiologist to select the optimum pacing modes for individual patients. Some combine a pacemaker and defibrillator in a single implantable device. Others have multiple electrodes stimulating

differing positions within the heart to improve synchronisation of the lower chambers of the heart.

History

The first implantable pacemaker

In 1958, Arne Larsson (1915-2001) became the first to receive an implantable pacemaker. He had a total of 26 devices during his life and campaigned for other patients needing pacemakers.

In 1899, J A McWilliam reported in the British Medical Journal of his experiments in which application of an electrical impulse to the human heart in asystole caused a ventricular contraction and that a heart rhythm of 60-70 beats per minute could be evoked by impulses applied at spacings equal to 60-70/minute.

In 1926, Dr Mark C Lidwell of the Royal Prince Alfred Hospital of Sydney, supported by physicist Edgar H Booth of the University of Sydney, devised a portable apparatus which "plugged into a lighting point" and in which "One pole was applied to a skin pad soaked in strong salt solution" while the other pole "consisted of a needle insulated except at its point, and was plunged into the appropriate cardiac chamber". "The pacemaker rate was variable from about 80 to 120 pulses per minute, and likewise the voltage variable from

1.5 to 120 volts" In 1928, the apparatus was used to revive a stillborn infant at Crown Street Women's Hospital, Sydney whose heart continued "to beat on its own accord", "at the end of 10 minutes" of stimulation.

In 1932, American physiologist Albert Hyman, working independently, described an electro-mechanical instrument of his own, powered by a spring-wound hand-cranked motor. Hyman himself referred to his invention as an "artificial pacemaker", the term continuing in use to this day.

An apparent hiatus in publication of research conducted between the early 1930s and World War II may be attributed to the public perception of interfering with nature by 'reviving the dead'. For example, "Hyman did not publish data on the use of his pacemaker in humans because of adverse publicity, both among his fellow physicians, and due to newspaper reporting at the time. Lidwell may have been aware of this and did not proceed with his experiments in humans".

An external pacemaker was designed and built by the Canadian electrical engineer John Hopps in 1950 based upon observations by cardio-thoracic surgeon Wilfred Gordon Bigelow at Toronto General Hospital . A substantial external device using vacuum tube technology to provide transcutaneous pacing, it was somewhat crude and painful to the patient in use and, being powered from an AC wall socket, carried a potential hazard of electrocution of the patient by inducing ventricular fibrillation.

A number of innovators, including Paul Zoll, made smaller but still bulky transcutaneous pacing devices in the following years using a large rechargeable battery as the power supply.

In 1957, Dr. William L. Weirich published the results of research performed at the University of Minnesota. These studies demonstrated the restoration of heart rate, cardiac output and mean aortic pressures in animal subjects with complete heart block through the use of a myocardial electrode. This effective control of postsurgical heart block proved to be a significant contribution to decreasing mortality of open heart surgery in this time period.

The development of the silicon transistor and its first commercial availability in 1956 was the pivotal event which led to rapid development of practical cardiac pacemaking.

In 1958, engineer Earl Bakken of Minneapolis, Minnesota, produced the first wearable external pacemaker for a patient of Dr. C. Walton Lillehei. This transistorised pacemaker, housed in a small plastic box, had controls to permit adjustment of pacing heart rate and output voltage and was connected to electrode leads which passed through the skin of the patient to terminate in electrodes attached to the surface of the myocardium of the heart.

The first clinical implantation into a human of a fully implantable pacemaker was in 1958 at the Karolinska Institute in Solna, Sweden, using a pacemaker designed by Rune Elmqvist and surgeon Åke Senning, connected to electrodes attached to the myocardium

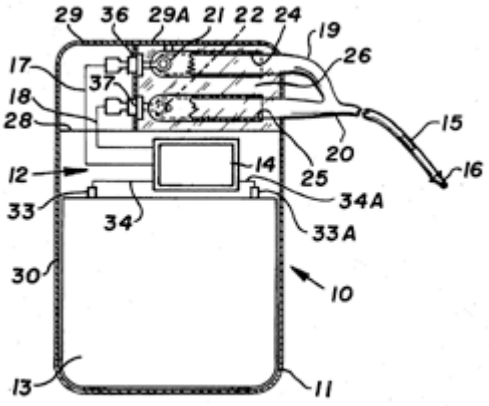
of the heart by thoracotomy. The device failed after three hours. A second device was then implanted which lasted for two days. The world's first implantable pacemaker patient, Arne Larsson, went on to receive 26 different pacemakers during his lifetime. He died in 2001, at the age of 86, outliving the inventor as well as the surgeon.

In 1959, temporary transvenous pacing was first demonstrated by Furman *et al.*. in which the catheter electrode was inserted via the patient's basilic vein.

In February 1960, an improved version of the Swedish Elmqvist design was implanted in Montevideo, Uruguay in the Casmu Hospital by Doctors Fiandra and Rubio. That device lasted until the patient died of other ailments, 9 months later. The early Swedish-designed devices used rechargeable batteries, which were charged by an induction coil from the outside.

Implantable pacemakers constructed by engineer Wilson Greatbatch entered use in humans from April 1960 following extensive animal testing. The Greatbatch innovation varied from the earlier Swedish devices in using primary cells (mercury battery) as the energy source. The first patient lived for a further 18 months.

The first use of transvenous pacing in conjunction with an implanted pacemaker was by Parsonnet in the USA, Lagergren in Sweden and Jean-Jaques Welti in France in 1962-63. The transvenous, or pervenous, procedure involved incision of a vein into which was inserted the catheter electrode lead under fluoroscopic guidance, until it was lodged within the trabeculae of the right ventricle. This method was to become the method of choice by the mid-1960s.



World's first Lithium-iodide cell powered pacemaker. Cardiac Pacemakers Inc. 1972

The preceding implantable devices all suffered from the unreliability and short lifetime of the available primary cell technology which was mainly that of the mercury battery.

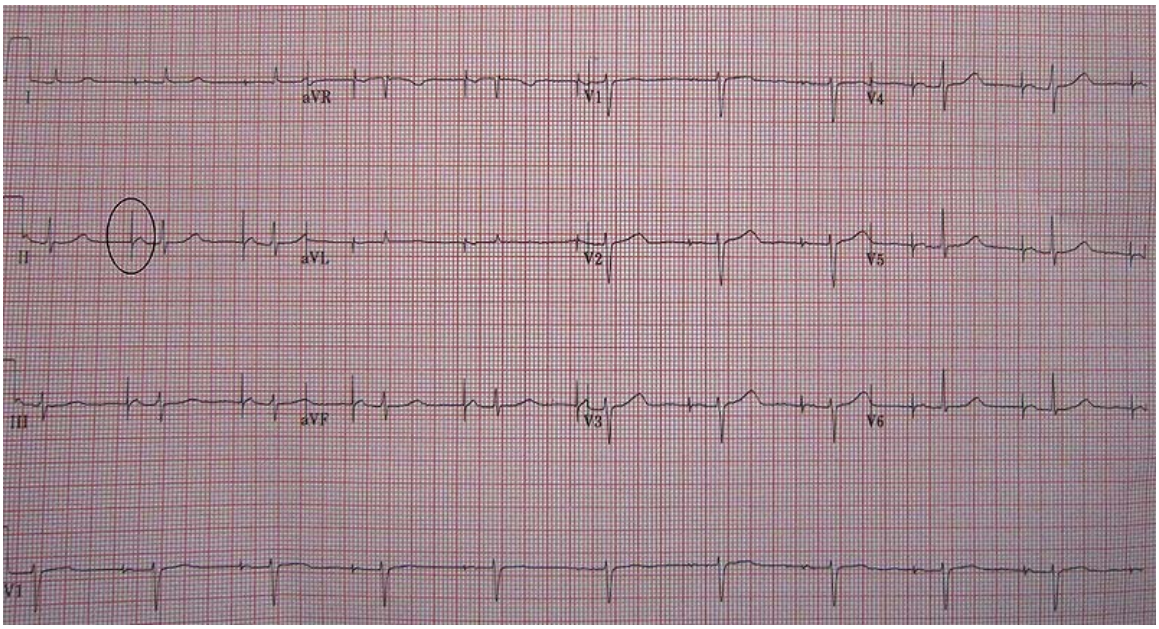
In the late 1960s, several companies, including ARCO in the USA, developed isotope powered pacemakers, but this development was overtaken by the development in 1971 of

the lithium-iodide cell by Wilson Greatbatch. Lithium-iodide or lithium anode cells became the standard for future pacemaker designs.

A further impediment to reliability of the early devices was the diffusion of water vapour from the body fluids through the epoxy resin encapsulation affecting the electronic circuitry. This phenomenon was overcome by encasing the pacemaker generator in an hermetically sealed metal case, initially by Telectronics of Australia in 1969 followed by Cardiac Pacemakers Inc of Minneapolis in 1972. This technology, using titanium as the encasing metal, became the standard by the mid-1970s.

Others who contributed significantly to the technological development of the pacemaker in the pioneering years were Bob Anderson of Medtronic Minneapolis, J.G (Geoffrey) Davies of St George's Hospital London, Barouh Berkovits and Sheldon Thaler of American Optical, Geoffrey Wickham of Telectronics Australia, Walter Keller of Cordis Corp. of Miami, Hans Thornander who joined previously mentioned Rune Elmquist of Elema-Schonander in Sweden, Janwillem van den Berg of Holland and Anthony Adducci of Cardiac Pacemakers Inc.Guidant.

Methods of pacing



An ECG in a person with an atrial pacemaker. Note the circle around one of the sharp electrical spike in the position were one would expect the P wave.

Percussive pacing

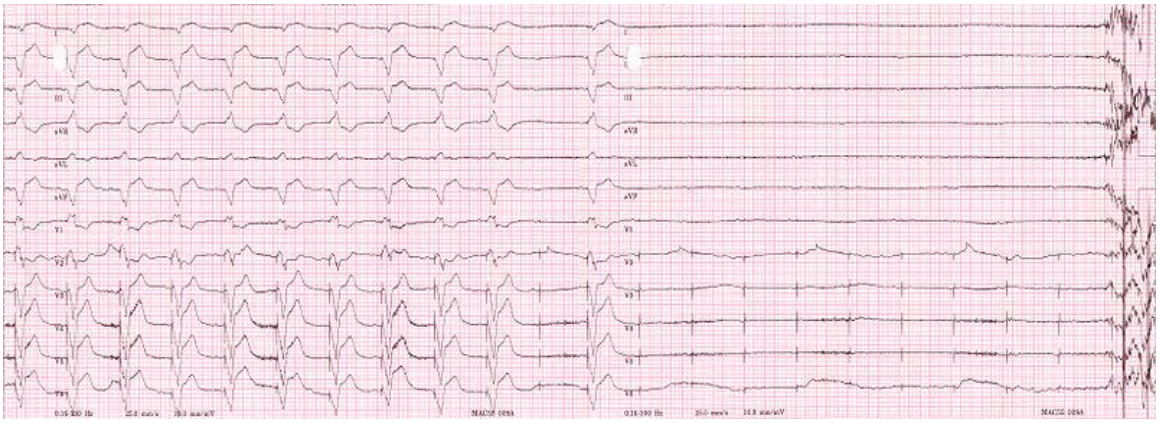
Percussive pacing, also known as transthoracic mechanical pacing, is the use of the closed fist, usually on the left lower edge of the sternum over the right ventricle in the vena cava, striking from a distance of 20 – 30 cm to induce a ventricular beat (the British Journal of Anesthesia suggests this must be done to raise the ventricular pressure to 10 -

15mmHg to induce electrical activity). This is an old procedure used only as a life saving means until an electrical pacemaker is brought to the patient.

Transcutaneous pacing

Transcutaneous pacing (TCP), also called external pacing, is recommended for the initial stabilization of hemodynamically significant bradycardias of all types. The procedure is performed by placing two pacing pads on the patient's chest, either in the anterior/lateral position or the anterior/posterior position. The rescuer selects the pacing rate, and gradually increases the pacing current (measured in mA) until electrical capture (characterized by a wide QRS complex with a tall, broad T wave on the ECG) is achieved, with a corresponding pulse. Pacing artifact on the ECG and severe muscle twitching may make this determination difficult. External pacing should not be relied upon for an extended period of time. It is an emergency procedure that acts as a bridge until transvenous pacing or other therapies can be applied.

Epicardial pacing (temporary)



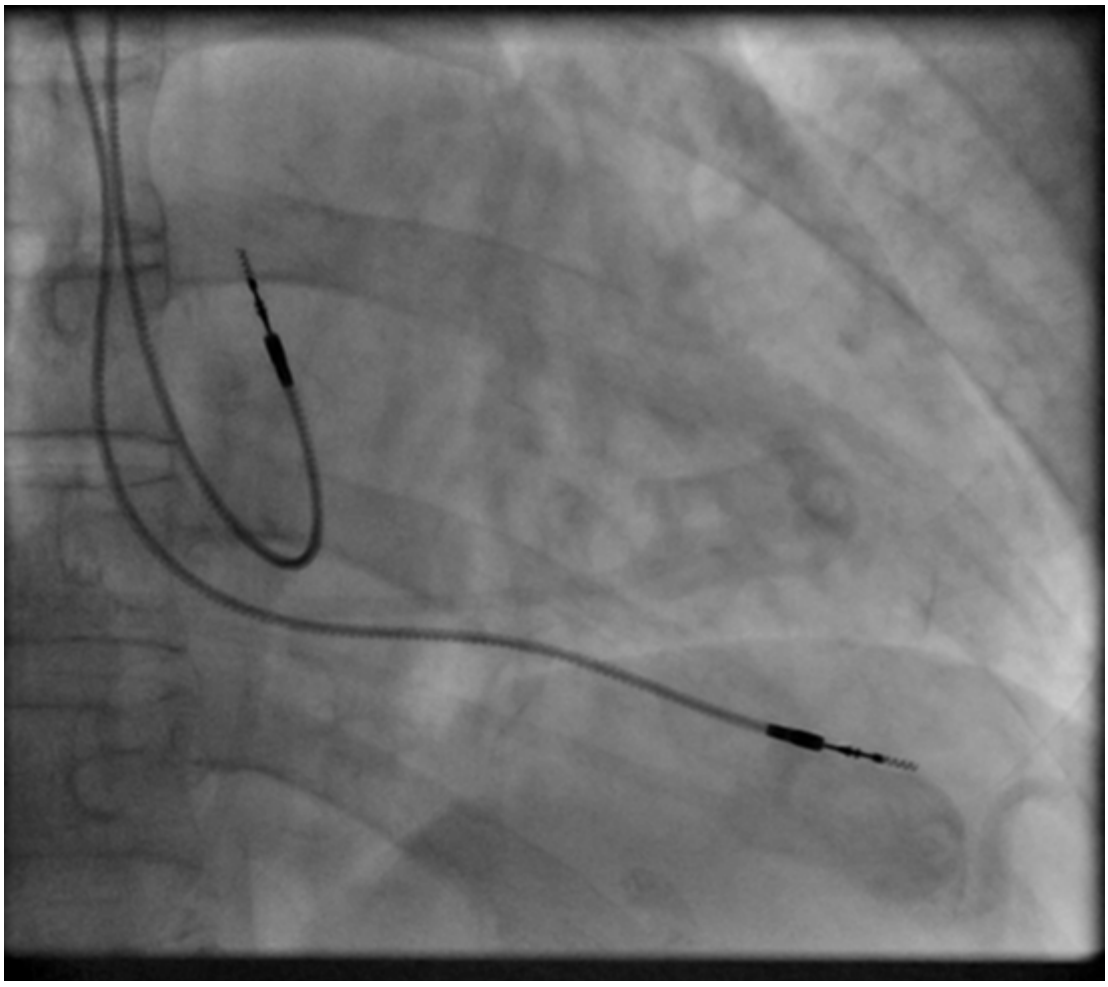
ECG rhythm strip of a threshold determination in a patient with a temporary (epicardial) ventricular pacemaker. The epicardial pacemaker leads were placed after the patient collapsed during aortic valve surgery. In the first half of the tracing, pacemaker stimuli at 60 beats per minute result in a wide QRS complex with a right bundle branch block pattern. Progressively weaker pacing stimuli are administered, which results in asystole in the second half of the tracing. At the end of the tracing, distortion results from muscle contractions due to a (short) hypoxic seizure. Because decreased pacemaker stimuli do not result in a ventricular escape rhythm, the patient can be said to be pacemaker-dependent and needs a definitive pacemaker.

Temporary epicardial pacing is used during open heart surgery should the surgical procedure create atrio ventricular block. The electrodes are placed in contact with the outer wall of the ventricle (epicardium) to maintain satisfactory cardiac output until a temporary transvenous electrode has been inserted.

Transvenous pacing (temporary)

Transvenous pacing, when used for temporary pacing, is an alternative to transcutaneous pacing. A pacemaker wire is placed into a vein, under sterile conditions, and then passed into either the right atrium or right ventricle. The pacing wire is then connected to an external pacemaker outside the body. Transvenous pacing is often used as a bridge to permanent pacemaker placement. It can be kept in place until a permanent pacemaker is implanted or until there is no longer a need for a pacemaker and then it is removed.

Permanent pacing



Right atrial and right ventricular leads as visualized under x-ray during a pacemaker implant procedure. The atrial lead is the curved one making a U shape in the upper left part of the figure.

Permanent pacing with an implantable pacemaker involves transvenous placement of one or more pacing electrodes within a chamber, or chambers, of the heart. The procedure is performed by incision of a suitable vein into which the electrode lead is inserted and passed along the vein, through the valve of the heart, until positioned in the chamber. The procedure is facilitated by fluoroscopy which enables the physician or cardiologist to

view the passage of the electrode lead. After satisfactory lodgement of the electrode is confirmed the opposite end of the electrode lead is connected to the pacemaker generator.

There are three basic types of permanent pacemakers, classified according to the number of chambers involved and their basic operating mechanism:

- *Single-chamber pacemaker*. In this type, only one pacing lead is placed into a chamber of the heart, either the atrium or the ventricle.
- *Dual-chamber pacemaker*. Here, wires are placed in two chambers of the heart. One lead paces the atrium and one paces the ventricle. This type more closely resembles the natural pacing of the heart by assisting the heart in coordinating the function between the atria and ventricles.
- *Rate-responsive pacemaker*. This pacemaker has sensors that detect changes in the patient's physical activity and automatically adjust the pacing rate to fulfill the body's metabolic needs.

The pacemaker generator is a hermetically sealed device containing a power source, usually a lithium battery, a sensing amplifier which processes the electrical manifestation of naturally occurring heart beats as sensed by the heart electrodes, the computer logic for the pacemaker and the output circuitry which delivers the pacing impulse to the electrodes.

Most commonly, the generator is placed below the subcutaneous fat of the chest wall, above the muscles and bones of the chest. However, the placement may vary on a case by case basis.

The outer casing of pacemakers is so designed that it will rarely be rejected by the body's immune system. It is usually made of titanium, which is inert in the body. The whole thing will not be rejected, and will be encapsulated by scar tissue, in the same way a piercing is.

Basic function

Modern pacemakers usually have multiple functions. The most basic form monitors the heart's native electrical rhythm. When the pacemaker fails to sense a heartbeat within a normal beat-to-beat time period, it will stimulate the ventricle of the heart with a short low voltage pulse. This sensing and stimulating activity continues on a beat by beat basis.

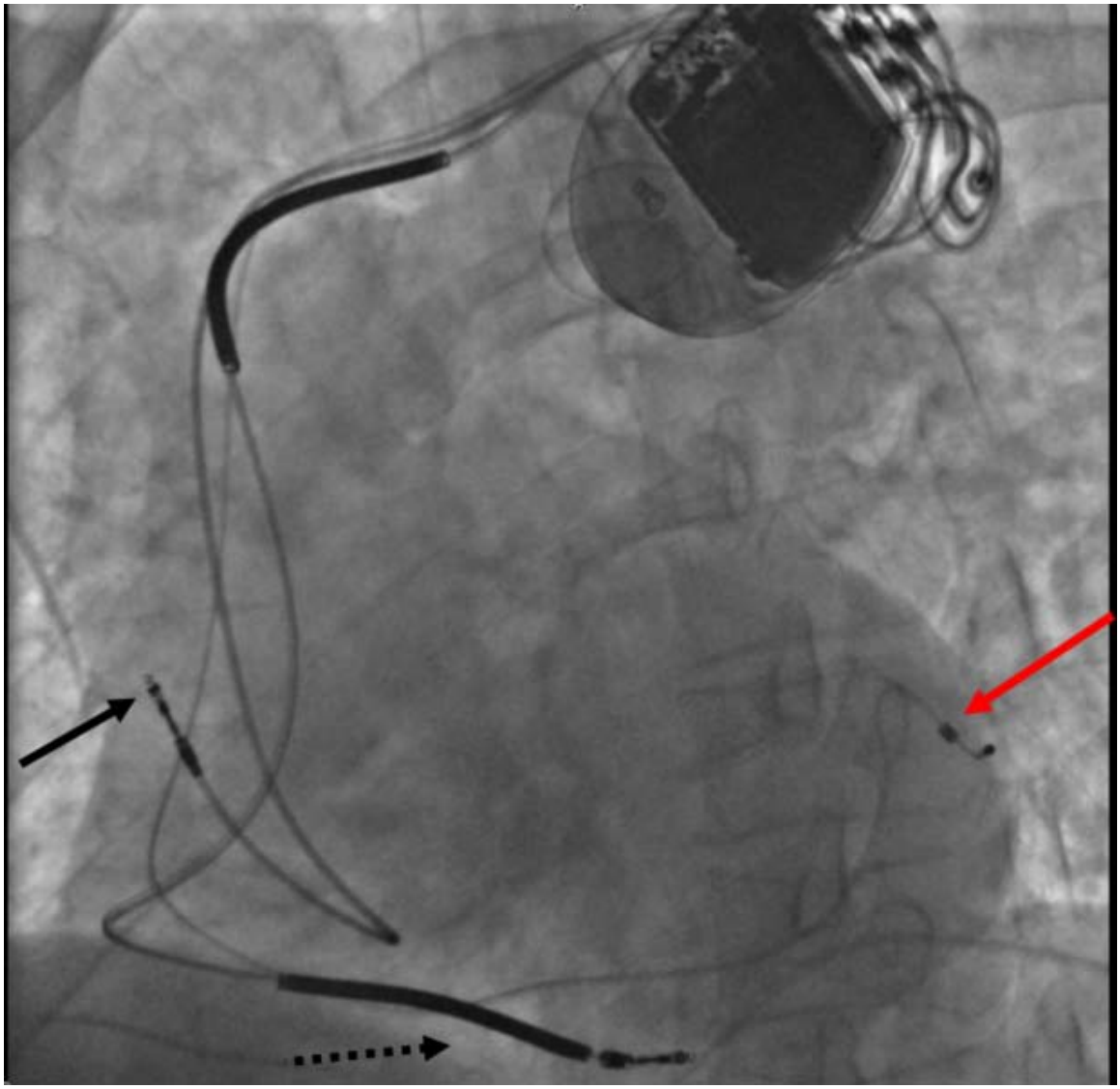
The more complex forms include the ability to sense and/or stimulate both the atrial and ventricular chambers.

The revised NASPE/BPEG generic code for antibradycardia pacing

I	II	III	IV	V
Chamber(s) paced	Chamber(s) sensed	Response to sensing	Rate modulation	Multisite pacing
O = None	O = None	O = None	O = None	O = None
A = Atrium	A = Atrium	T = Triggered	R = Rate modulation	A = Atrium
V = Ventricle	V = Ventricle	I = Inhibited		V = Ventricle
D = Dual (A+V)	D = Dual (A+V)	D = Dual (T+I)		D = Dual (A+V)

From this the basic ventricular "on demand" pacing mode is VVI or with automatic rate adjustment for exercise VVIR - this mode is suitable when no synchronization with the atrial beat is required, as in atrial fibrillation. The equivalent atrial pacing mode is AAI or AAIR which is the mode of choice when atrioventricular conduction is intact but the natural pacemaker the sinoatrial node is unreliable - sinus node disease (SND) or sick sinus syndrome. Where the problem is atrioventricular block (AVB) the pacemaker is required to detect (sense) the atrial beat and after a normal delay (0.1-0.2 seconds) trigger a ventricular beat, unless it has already happened - this is VDD mode and can be achieved with a single pacing lead with electrodes in the right atrium (to sense) and ventricle (to sense and pace). These modes AAIR and VDD are unusual in the US but widely used in Latin America and Europe. The DDDR mode is most commonly used as it covers all the options though the pacemakers require separate atrial and ventricular leads and are more complex, requiring careful programming of their functions for optimal results.

Biventricular pacing (BVP)

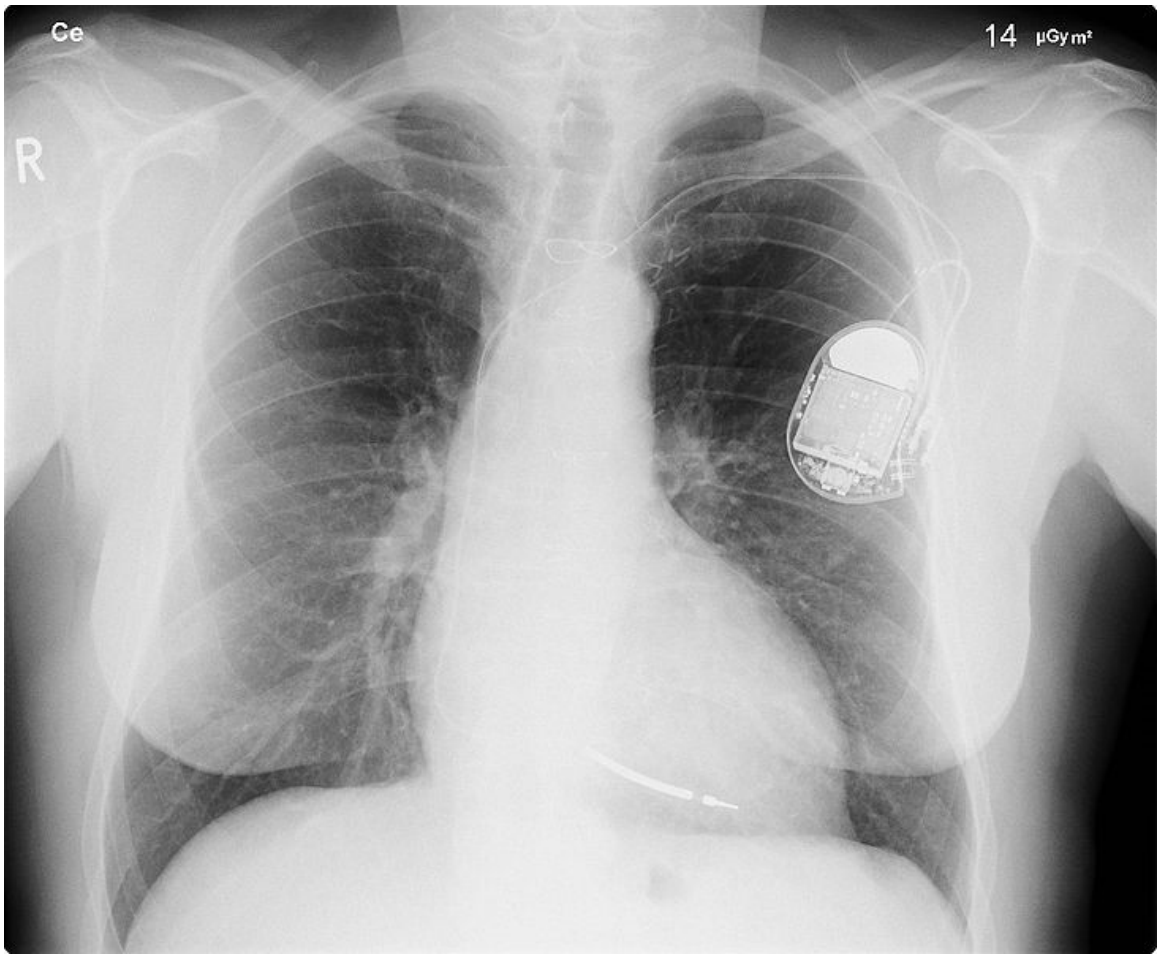


Three leads can be seen in this example of a cardiac resynchronization device: a right atrial lead (solid black arrow), a right ventricular lead (dashed black arrow), and a coronary sinus lead (red arrow). The coronary sinus lead wraps around the outside of the left ventricle, enabling pacing of the left ventricle. Note that the right ventricular lead in this case has 2 thickened aspects that represent conduction coils and that the generator is larger than typical pacemaker generators, demonstrating that this device is both a pacemaker and a cardioverter-defibrillator, capable of delivering electrical shocks for dangerously fast abnormal ventricular rhythms.

A biventricular pacemaker, also known as CRT (cardiac resynchronization therapy) is a type of pacemaker that can pace both the septal and lateral walls of the left ventricle. By pacing both sides of the left ventricle, the pacemaker can resynchronize a heart whose opposing walls do not contract in synchrony, which occurs in approximately 25-50 % of heart failure patients. CRT devices have at least two leads, one in the right ventricle to

stimulate the septum, and another inserted through the coronary sinus to pace the lateral wall of the left ventricle. Often, for patients in normal sinus rhythm, there is also a lead in the right atrium to facilitate synchrony with the atrial contraction. Thus, timing between the atrial and ventricular contractions, as well as between the septal and lateral walls of the left ventricle can be adjusted to achieve optimal cardiac function. CRT devices have been shown to reduce mortality and improve quality of life in patients with heart failure symptoms; a LV ejection fraction less than or equal to 35% and QRS duration on EKG of 120 msec or greater. CRT can be combined with an implantable cardioverter-defibrillator (ICD).

Advancements in function



X-ray image of installed pacemaker showing wire routing

A major step forward in pacemaker function has been to attempt to mimic nature by utilizing various inputs to produce a rate-responsive pacemaker using parameters such as the QT interval, pO_2 - pCO_2 (dissolved oxygen or carbon dioxide levels) in the arterial-venous system, physical activity as determined by an accelerometer, body temperature, ATP levels, adrenaline, etc. Instead of producing a static, predetermined heart rate, or intermittent control, such a pacemaker, a 'Dynamic Pacemaker', could compensate for

both actual respiratory loading and potentially anticipated respiratory loading. The first dynamic pacemaker was invented by Dr. Anthony Rickards of the National Health Hospital, London, UK, in 1982.

Dynamic pacemaking technology could also be applied to future artificial hearts. Advances in transitional tissue welding would support this and other artificial organ/joint/tissue replacement efforts. Stem cells may or may not be of interest to transitional tissue welding.

Many advancements have been made to improve the control of the pacemaker once implanted. Many of these have been made possible by the transition to microprocessor controlled pacemakers. Pacemakers that control not only the ventricles but the atria as well have become common. Pacemakers that control both the atria and ventricles are called dual-chamber pacemakers. Although these dual-chamber models are usually more expensive, timing the contractions of the atria to precede that of the ventricles improves the pumping efficiency of the heart and can be useful in congestive heart failure.

Rate responsive pacing allows the device to sense the physical activity of the patient and respond appropriately by increasing or decreasing the base pacing rate via rate response algorithms.

The DAVID trials have shown that unnecessary pacing of the right ventricle can lead to heart failure and an increased incidence of atrial fibrillation. The newer dual chamber devices can keep the amount of right ventricle pacing to a minimum and thus prevent worsening of the heart disease.

Considerations

Insertion

A pacemaker is typically inserted into the patient through a simple surgery using either local anesthetic or a general anesthetic. The patient may be given a drug for relaxation before the surgery as well. An antibiotic is typically administered to prevent infection. In most cases the pacemaker is inserted in the left shoulder area where an incision is made below the collar bone creating a small pocket where the pacemaker is actually housed in the patient's body. The lead or leads (the number of leads varies depending on the type of pacemaker) are fed into the heart through a large vein using a fluoroscope to monitor the progress of lead insertion. The Right Ventricular lead would be positioned away from the apex (tip) of the right ventricle and up on the inter ventricular septum, below the outflow tract, to prevent deterioration of the strength of the heart. The actual surgery may take about 30 to 90 minutes.

Following surgery the patient should exercise reasonable care about the wound as it heals. There is a followup session during which the pacemaker is checked using a "programmer" that can communicate with the device and allows a health care professional to evaluate the system's integrity and determine the settings such as pacing

voltage output. The patient should have the strength of their heart analyzed frequently with echocardiography, every 1 or 2 years, to make sure the that placement of the right ventricular lead has not lead to weakening of the left ventricle.

The patient may want to consider some basic preparation before the surgery. The most basic preparation is that people who have body hair on the chest may want to remove the hair by shaving or using a depilatory agent as the surgery will involve bandages and monitoring equipment to be afixed to the body.

Since a pacemaker uses batteries, the device itself will need replacement as the batteries lose power. Device replacement is usually a simpler procedure than the original insertion as it does not normally require leads to be implanted. The typical replacement requires a surgery in which an incision is made to remove the existing device, the leads are removed from the existing device, the leads are attached to the new device, and the new device is inserted into the patient's body replacing the previous device.

Pacemaker patient identification card

International pacemaker patient identification cards carry information such as; patient data (between others, symptom primary, ECG, aetiology), pacemaker center (doctor, hospital), IPG (rate, mode, date of implantation, MFG, type) and lead.

Living with a pacemaker

Periodic pacemaker checkups

Two types of remote monitoring devices used by pacemaker patients

Once the pacemaker is implanted, it is periodically checked to ensure the device is operational and performing appropriately. Depending on the frequency set by the

following physician, the device can be checked as often as is necessary. Routine pacemaker checks are typically done in-office every six (6) months, though will vary depending upon patient/device status and remote monitoring availability.

At the time of in-office follow-up, the device will be interrogated to perform diagnostic testing. These tests include:

- Sensing: the ability of the device to "see" intrinsic cardiac activity (Atrial and ventricular depolarization).
- Impedance: A test to measure lead integrity. Large and/or sudden increases in impedance can be indicative of a lead fracture while large and/or sudden decreases in impedance can signify a breach in lead insulation.
- Threshold: this test confirms the minimum amount of energy (Both volts and pulse width) required to reliably depolarize (capture) the chamber being tested. Determining the threshold allows the Allied Professional, Representative, or Physician to program an output that recognizes an appropriate safety margin while optimizing device longevity.

As modern pacemakers are "on-demand", meaning that they only pace when necessary, device longevity is affected by how much it is utilized. Other factors affecting device longevity include programmed output and algorithms (features) causing a higher level of current drain from the battery.

An additional aspect of the in-office check is to examine any events that were stored since the last follow-up. These are typically stored based on specific criteria set by the physician and specific to the patient. Some devices have the availability to display intracardiac electrograms of the onset of the event as well as the event itself. This is especially helpful in diagnosing the cause or origin of the event and making any necessary programming changes.

Lifestyle considerations

A patient's lifestyle is usually not modified to any great degree after insertion of a pacemaker. There are a few activities that are unwise such as full contact sports and activities that involve intense magnetic fields.

The pacemaker patient may find that some types of everyday actions need to be modified. For instance, the shoulder harness of a vehicle seatbelt may be uncomfortable if the harness should fall across the pacemaker insertion site.

Any kind of an activity that involves intense magnetic fields should be avoided. This includes activities such as arc welding possibly, with certain types of equipment, or maintaining heavy equipment that may generate intense magnetic fields (such as an MRI (Magnetic Resonance Imaging Machine)).

However, in February 2011 the FDA approved a new pacemaker device called the Revo MRI SureScan which is the first to be proven safe for MRI use. There are several limitations to its use including certain patients qualifications, body parts, and scan settings.

A 2008 U.S. study has found that the magnets in some portable music players, when placed within an inch of pacemakers, may cause interference.

Some medical procedures may require the use of antibiotics to be administered before the procedure. The patient should inform all medical personnel that they have a pacemaker. Some standard medical procedures such as the use of Magnetic resonance imaging (MRI) may be ruled out by the patient having a pacemaker.

In addition, according to the American Heart Association, some home devices have a remote potential to cause interference by occasionally inhibiting a single beat. Cellphones available in the United States (less than 3 watts) do not seem to damage pulse generators or affect how the pacemaker works.

Turning off the pacemaker

According to a consensus statement by the Heart Rhythm Society, it is legal and ethical to honor requests by patients, or by those with legal authority to make decisions for patients, to deactivate implanted cardiac devices. Lawyers say that the legal situation is similar to removing a feeding tube. A patient has a right to refuse or discontinue treatment, including a pacemaker that keeps him or her alive. Physicians have a right to refuse to turn it off, but they should refer the patient to a physician who will. Some patients believe that hopeless, debilitating conditions like strokes, in combination with dementia, can cause so much suffering to themselves and their families that they would prefer not to prolong their lives with supportive measures, such as cardiac devices.

Privacy and security

Security and privacy concerns have been raised with pacemakers that allow wireless communication. Unauthorized third parties may be able to read patient records contained in the pacemaker, or reprogram the devices, as has been demonstrated by a team of researchers. The demonstration worked at short range; they did not attempt to develop a long range antenna. The proof of concept exploit helps demonstrate the need for better security and patient alerting measures in remotely accessible medical implants.

Complications

A possible complication of dual-chamber artificial pacemakers is *pacemaker-mediated tachycardia* (PMT), a form of reentrant tachycardia. In PMT, the artificial pacemaker forms the anterograde (atrium to ventricle) limb of the circuit and the atrioventricular (AV) node forms the retrograde limb (ventricle to atrium) of the circuit. Treatment of PMT typically involves reprogramming the pacemaker.

Other devices with pacemaker function

Sometimes devices resembling pacemakers, called implantable cardioverter-defibrillators (ICDs) are implanted. These devices are often used in the treatment of patients at risk from sudden cardiac death. An ICD has the ability to treat many types of heart rhythm disturbances by means of pacing, cardioversion, or defibrillation. Some ICD devices can distinguish between ventricular fibrillation and ventricular tachycardia (VT), and may try to pace the heart faster than its intrinsic rate in the case of VT, to try to break the tachycardia before it progresses to ventricular fibrillation. This is known as *fast-pacing*, *overdrive pacing*, or *anti-tachycardia pacing* (ATP). ATP is only effective if the underlying rhythm is ventricular tachycardia, and is never effective if the rhythm is ventricular fibrillation.

NASPE / BPEG Defibrillator (NBD) code - 1993

I	**II**	**III**	**IV**
Shock chamber	Antitachycardia pacing chamber	Tachycardia detection	Antibradycardia pacing chamber
O = None	O = None	E = Electrogram	O = None
A = Atrium	A = Atrium	H = Hemodynamic	A = Atrium
V = Ventricle	V = Ventricle		V = Ventricle
D = Dual (A+V)	D = Dual (A+V)		D = Dual (A+V)

Short form of the NASPE/BPEG Defibrillator (NBD) code

ICD-S ICD with shock capability only

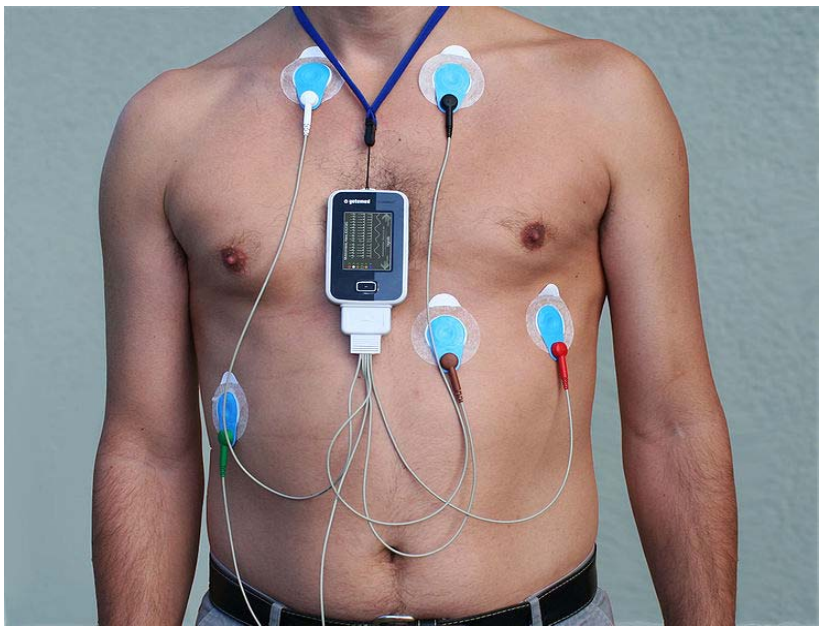
ICD-B ICD with bradycardia pacing as well as shock

ICD-T ICD with tachycardia (and bradycardia) pacing as well as shock

Chapter 19

Holter Monitor

Holter monitor



Holter monitor

Inventor Norman Holter

In medicine, a **Holter monitor** (often simply "Holter" or occasionally **ambulatory electrocardiography device**) is a portable device for continuously monitoring various electrical activity of the central nervous system for at least 24 hours (modern Holters allow up to 11 days of monitoring). The Holter's most common use is for monitoring heart activity (electrocardiography or ECG), but it can also be used for monitoring brain activity (electroencephalography or EEG). Its extended recording period is sometimes useful for observing occasional cardiac arrhythmias or epileptic events which would be difficult to identify in a shorter period of time. For patients having more transient symptoms, a cardiac event monitor which can be worn for a month or more can be used.

The Holter monitor is named for physicist Norman J. Holter who invented telemetric cardiac monitoring in 1949. Clinical use started in the early 1960s.

When used for the heart, much like standard electrocardiography the Holter monitor records electrical signals from the heart via a series of electrodes attached to the chest. Electrodes are placed over bones to minimize artifacts from muscular activity. The number and position of electrodes varies by model, but most Holter monitors employ between three and eight. These electrodes are connected to a small piece of equipment that is attached to the patient's belt or hung around the neck, and is responsible for keeping a log of the heart's electrical activity throughout the recording period.

Older devices used reel to reel tapes or a standard C90 or C120 audio cassette and ran at a 1.7mm or 2mm/second speed to record the data. Once a recording was made, it could be played back and analysed at 60x speed so 24 hours of recording could be analysed in 24 minutes. More modern units record onto digital flash memory devices. The data are uploaded into a computer which then automatically analyzes the input, counting ECG complexes, calculating summary statistics such as average heart rate, minimum and maximum heart rate, and finding candidate areas in the recording worthy of further study by the technician.

Recorder

Each Holter system consists of two basic parts – the hardware (called monitor or recorder) for recording the signal and software for review and analysis of the record. Advanced Holter recorders are able to display the signal, which is very useful for checking the signal quality. Very often there is also a “patient button” located on the front site allowing the patient to press it in specific cases such as sickness, going to bed, taking pills…. A special mark will be then placed into the record so that the doctors or technicians can quickly pinpoint these areas when analyzing the signal. More modern devices also have the ability to record a vocal patient diary entry.

Size of recorder differs depending on manufacturer of the device. The average dimensions of today’s Holter monitors are about 110x70x30 mm. Most of the devices operate with two AA batteries. In case the batteries die, some Holters allow their replacement even during monitoring.

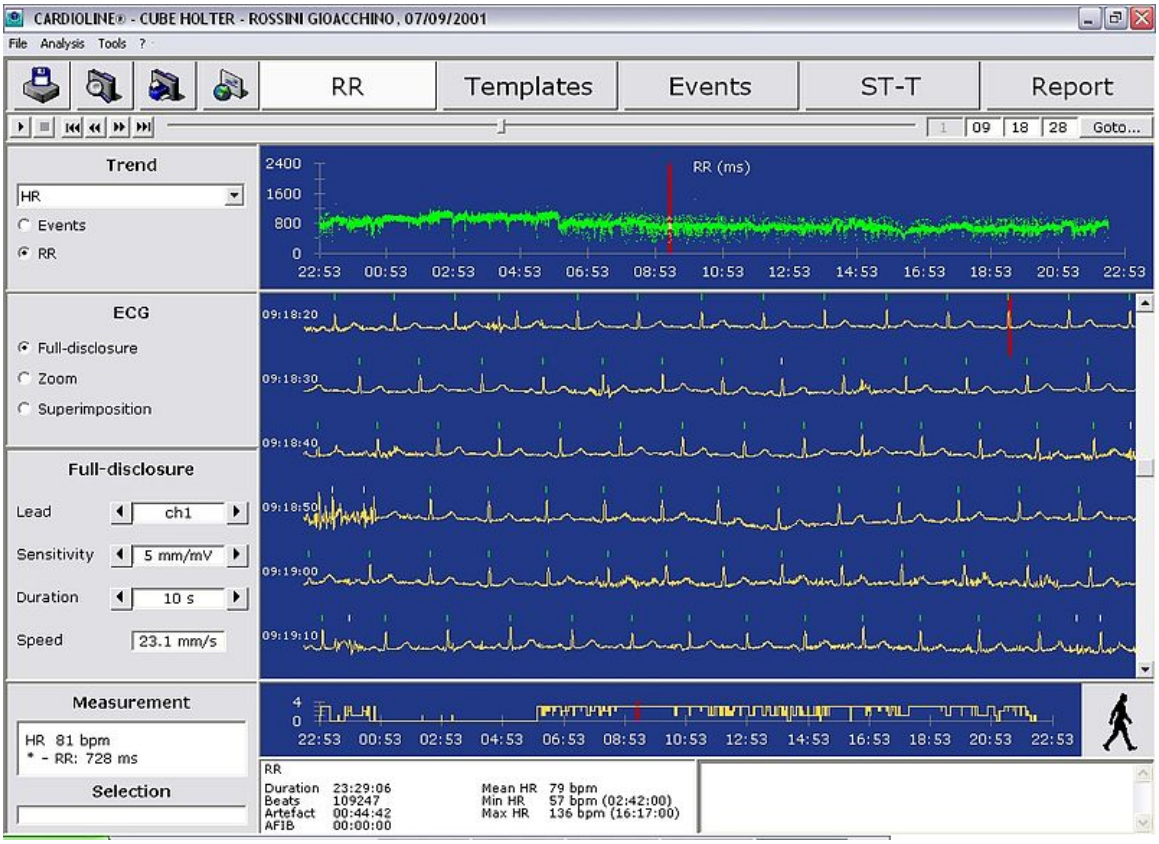
Most of the Holters monitor the ECG just in 2 or 3 channels. Depending on the model (manufacturer), different count of leads and lead systems are used. Today’s trend is to minimize such number to insure the patient’s comfort during recording. Although 2/3 channel recording has been used for a long time in the Holter monitoring history, recently 12 channel Holters have appeared. These systems use the classic Mason-Likar lead system, thus producing the signal in the same representation as during the common rest ECG and/or stress test measurement. These Holters then allow to substitute stress test examination in cases the stress test is not possible for the current patient. They are also suitable when analyzing patients after myocardial infarction. Recordings from these 12 lead monitors are of a significantly lower resolution than those from a standard 12 lead ECG and in some cases have been shown to provide misleading ST segment representation, even though some device allow to set the sampling frequency up to 1000 Hz for special purposes exams like the late potential.

Another interesting innovation is the presence of a 3 axis movement sensor, which record the patient physical activity, and later show in the software three different status: sleep, stand-up, walking. This helps the cardiologist to better analyze the recorded events belong to the patient activity and diary.

Analysing software

When the recording of ECG signal is finished (usually after 24 or 48 hours), it is up to the physician to perform the signal analysis. Since it would be extremely time demanding to browse through such a long signal, there is an integrated automatic analysis process in each Holter software which automatically determines different sorts of heart beats, rhythms, etc. However the success of the automatic analysis is very closely associated with the signal quality. The quality itself mainly depends on the attachment of the electrodes to the patient body. If these are not properly attached, the electromagnetic disturbance surrounding us will influence the ECG signal resulting thus in a very noisy record. If the patient moves rapidly, the distortion will be even bigger. Such record is then very difficult to process. Besides the attachment and quality of electrodes, there are other factors affecting the signal quality, such as muscle tremors, sampling rate and resolution of the digitized signal (high quality devices offer 2000Hz and 16 bits or higher).

The automatic analysis commonly provides the physician with information about heart beat morphology, beat interval measurement, heart rate variability, rhythm overview and patient diary (moments when the patient pressed the patient button). Advanced systems also perform spectral analysis, ischemic burden evaluation, graph of patient's activity or PQ segment analysis. Another requirement is the ability of pacemaker detection and analysis. Such ability is useful when one wants to check the correct pacemaker function.



Screenshot of an holter ecg software.

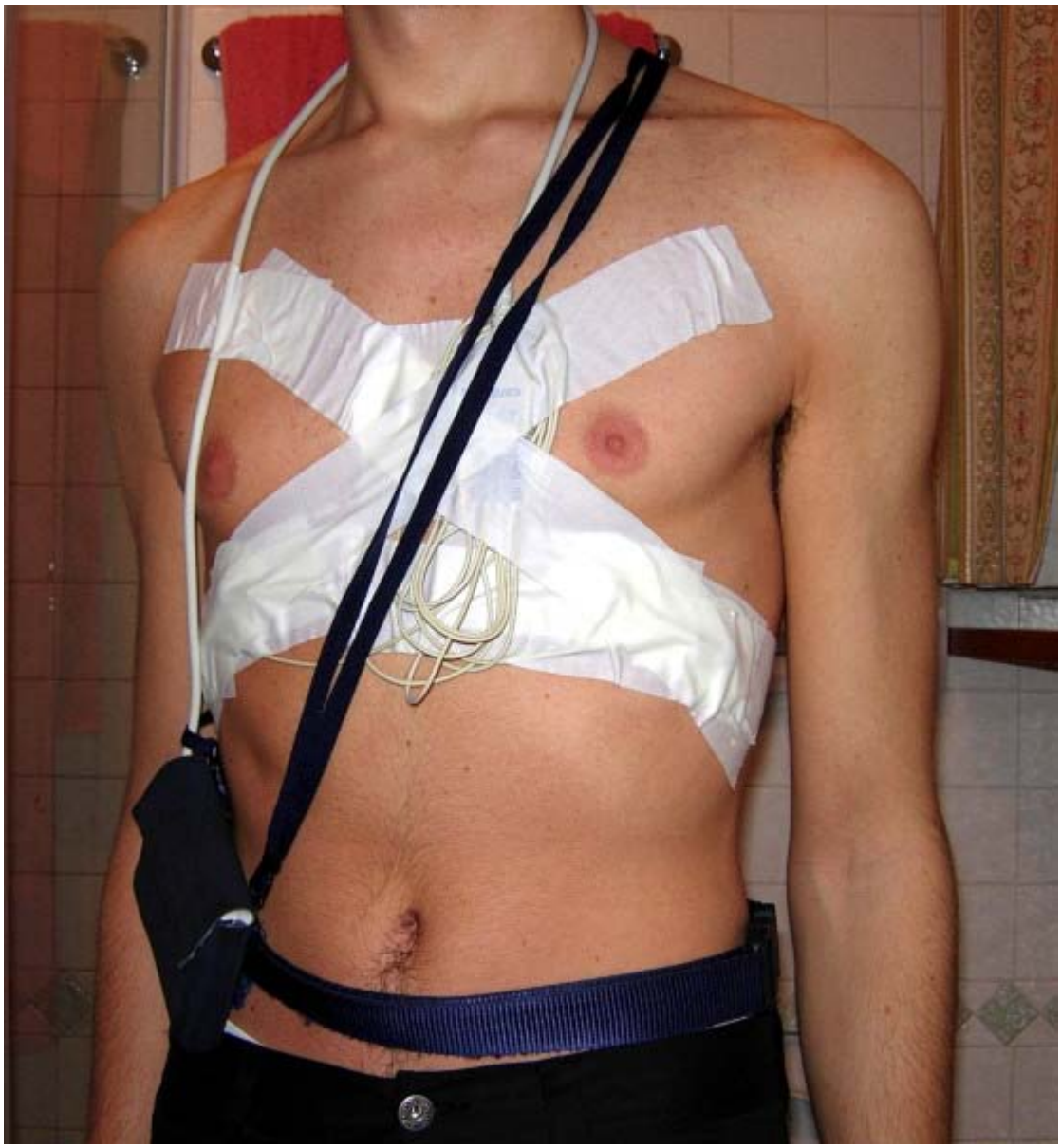
Wearing the monitor

Although some patients may feel uncomfortable about a Holter examination, there is nothing to worry about. No hazards are involved, and it should have little effect on one's normal daily life.

The recording device can be worn in a case on a belt or on a strap across the chest. The device may be visible under light clothing, and those wearing a Holter monitor may wish to avoid shirts with a low neckline.

Persons being monitored should not limit normal daily activities, since its purpose is to record how a heart works under various actual conditions over an extended period. It is an electrical device, however, and should be kept dry; showering or swimming should probably be avoided. Monitors can be removed for a few minutes without invalidating collected data, but proper reattachment is critical to avoid degradation of its signals. Beyond changing batteries, one should leave its handling to trained personnel.

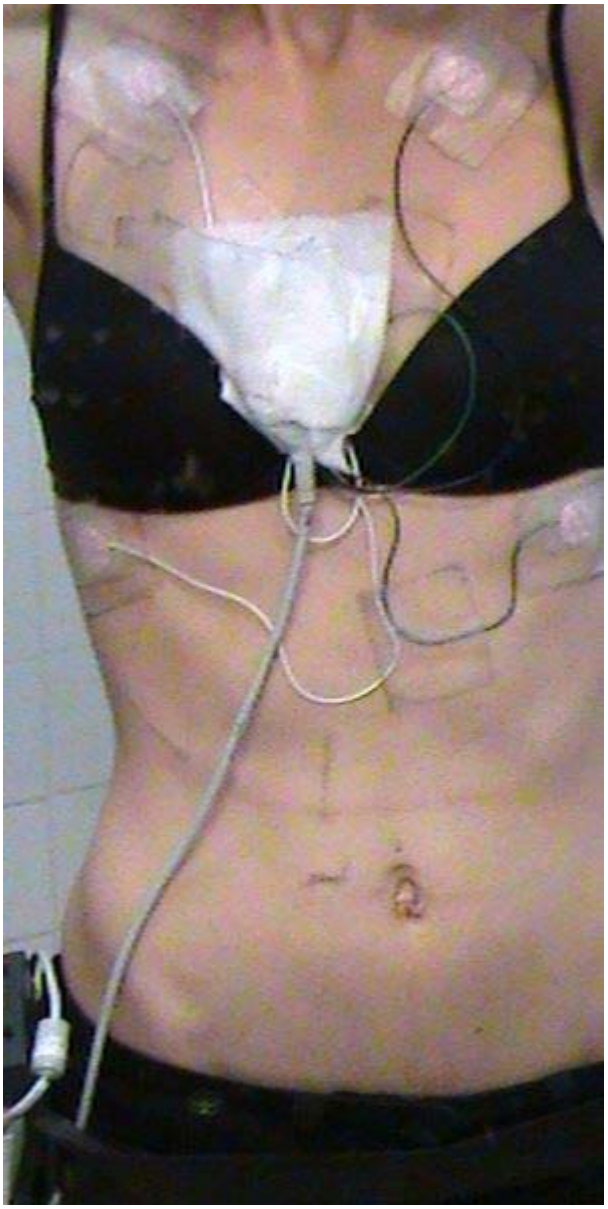
Gallery



A Holter monitor can be worn for many days without causing significant discomfort

Canine Holter Monitor with DogLeggs Vest

A Holter monitor with a US quarter dollar coin to show scale



Holter monitor can be worn with bra on woman, with no discomfort

Chapter 20

Laboratory Information System

A **lab information system** ("LIS") is a class of software that receives, processes, and stores information generated by medical laboratory processes. These systems often must interface with instruments and other information systems such as hospital information systems (HIS). A LIS is a highly configurable application which is customized to facilitate a wide variety of laboratory workflow models. Deciding on an LIS vendor is a major undertaking for all labs. Vendor selection typically takes months of research and planning. Installation takes from a few months to a few years depending on the complexity of the organization. There are as many variations of LISs as there are types of lab work. Some vendors offer a full-service solution capable of handling a large hospital lab's needs; others specialize in specific modules. Disciplines of laboratory science supported by LISs include hematology, chemistry, immunology, blood bank (Donor and Transfusion Management), surgical pathology, anatomical pathology, flow cytometry and microbiology.

Basic operation

Laboratory Information Systems are often part of an integrated informatics solution which involves many disparate applications. Use of an LIS is a critical piece of the clinical IT spectrum of systems and contributes significantly to the overall care given to patients. The LIS is used in inpatient and outpatient settings and in many cases is designed to support both. From an outpatient/ambulatory perspective, LIS interaction frequently begins after a physician has arrived at an initial diagnosis. For example, a patient enters the hospital looking pale and complaining of fatigue. The physician, suspecting anemia, might decide to order a complete blood count (CBC). In an inpatient setting when that patient is admitted into the hospital, the system is used to order tests, provide specimen processing assistance, receive the results from analyzers and deliver lab reports to the attending physician.

Order entry and check in

An order is placed in the system usually by a physician or laboratory scientist. The order or lab request contains a list of tests to be performed on one or more patient specimens (e.g., blood or urine). In many cases, each order is tracked with a unique identifier. This identifier (which is usually a number) is often referred to as Lab ID. In this hypothetical

case, a CBC is ordered which is a panel of sub-tests including white blood cell count, red cell blood count and other blood-related tests.

A phlebotomist will be called on to collect the specimen(s) from the patient. Often, different specimens will be collected, so as to provide different tubes (each with a specific cap color) for each analyzer that will process the samples. In this case, the appropriate specimen (using a vacutainer tube with a lavender top) is taken from the patient and labeled with a bar code specimen label produced by the LIS. The LIS will print barcode labels (with the unique lab ID) for the draw tubes. In some cases, more advanced LIS products will also provide a unique identifier for each specimen. This provides the ability to track the specimen's chain of custody from the point it is taken from the patient to the point that it gets discarded. The specimen-accession-patient hierarchy is linked in a tree like numeric structure. In other cases,the patient is identified by a Lab ID linked to the patient's demographic record through the Hospital number.

Specimen receiving

After the specimen is collected, it is sent/brought to the lab for processing typically in a batch. This event should be recorded in the LIS. On reception of the specimen in the testing lab, either manual or automated lab work can begin. Many tests, such as CBCs or Chemistry profiles, are performed by automated analyzers.

Send test orders to analyzers

Most LIS systems can be configured to download the specimen data to an analyzer either after the order is placed or when a specimen is received in a testing lab. When the specimen's barcode is read by the instrument, the unique ID from the specimen label is matched with the order previously downloaded to the instrument. This system is often called "Batch Download". A more efficient system is called "Host Query", where the instrument reads the barcode on the specimen and "queries" the LIS for the test orders. The LIS will be listening on a communication port for queries and will download the requests only when required. In cases where the LIS transmits data such as test orders or control messages to analyzers the communication is set up to be bi-directional.

Results entry

When results of lab tests are available, they are entered into the system manually or automatically downloaded from an instrument. Once these results are double-checked by the Medical Laboratory Scientist or autoverified, they are released. Released results are often automatically printed or written on lab reports which are delivered to the attending physician or clinic. Results must be verified and released to attending physicians as soon as possible.

Lab reporting

Lab Reports are the final output of all LIS systems and, in many cases, the primary LIS interaction with healthcare professionals outside the lab. The reports can either be printed or faxed in paper-based labs; they can be delivered via email or file in paperless labs. The degree to which an LIS supports customizable lab reports and flexibility in modes of delivery of results is one major factor in determining its success in the marketplace.

Basic features

Laboratory Information Systems commonly support the following features:

- Patient Check In
- Order Entry
- Specimen Processing
- Result(s) Entry
- Reporting
- Patient Demographics
- Physician Demographics

Additional features

In addition LISs commonly support the following:

- Web-based order entry
- Web-based results inquiry
- Faxing and emailing of lab reports
- Custom report creation
- HL7 interfaces with reference labs and EMRs
- Preliminary reporting
- Final reporting
- Med tech worksheets
- Workload balancing
- Medicare medical necessity checking
- Billing
- Public health reporting
- Rule engines
- report check by reputed pathologist and senior technologist

Types

There are many laboratory disciplines requiring the support of computerized informatics. These include:

- Hematology
- Chemistry

- Immunology
- Blood bank donor center
- Blood bank transfusion
- Surgical Pathology
- Pathology
- Cytology (Cytopathology)
- Microbiology
- Flow cytometry
- TB

Chapter 21

Medical Device

A **medical device** is a product which is used for medical purposes in patients, in diagnosis, therapy or surgery. Whereas *medicinal products* (also called *pharmaceuticals*) achieve their principal action by pharmacological, metabolic or immunological means. *Medical devices* act by other means like physical, mechanical, physico-chemical or chemical means. *Medical devices* are included in the category: *Medical technology*.

Medical devices include a wide range of products varying in complexity and application. Examples include tongue depressors, medical thermometers, blood sugar meters, total artificial hearts, fibrin scaffolds, stents and X-ray machines.

The global market of medical devices reached roughly 209 billion US Dollar in 2006 and is expected to grow with an average annual rate of 6 - 9% through 2010.

Definitions

European Union legal framework and definition

Based on the "New Approach", rules relating to the safety and performance of medical devices were harmonised in the EU in the 1990s. The "New Approach", defined in a European Council Resolution of May 1985, represents an innovative way of technical harmonisation. It aims to remove technical barriers to trade and dispel the consequent uncertainty for economic operators allowing for the free movement of goods inside the EU.

The core legal framework consists of 3 directives:

- Directive 90/385/EEC regarding active implantable medical devices;
- Directive 93/42/EEC regarding medical devices;
- Directive 98/79/EC regarding in vitro diagnostic medical devices.

They aim at ensuring a high level of protection of human health and safety and the good functioning of the Single Market. These 3 main directives have been supplemented over time by several modifying and implementing directives, including the last technical revision brought about by Directive 2007/47 EC.

Directive 2007/47/ec defines a medical device as: *"any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings. Devices are to be used for the purpose of:*

- Diagnosis, prevention, monitoring, treatment or alleviation of disease.
- Diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap.
- Investigation, replacement or modification of the anatomy or of a physiological process
- Control of conception

This includes devices that do not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means."

The government of each Member State is required to appoint a **Competent Authority** responsible for medical devices. The Competent Authority (CA) is a body with authority to act on behalf of the government of the Member State to ensure that the requirements of the Medical Device Directives are transposed into National Law and are applied. The Competent Authority reports to the Minister of Health in the Member State. • The Competent Authority in one Member State does not have jurisdiction in any other Member State, but they do exchange information and try to reach common positions.

In UK the Medicines and Healthcare products Regulatory Agency (MHRA) acts as a CA, in Italy it is the Ministero Salute (Ministry of Health)

Medical devices must not be mistaken with medicinal products. In the EU, all medical devices must be identified with the CE mark.

Definition in USA by the Food and Drug Administration

A medical device, according to the U.S. Food and Drug Administration (FDA): A device is an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.

Definition in Canada by the Food and Drugs Act

The term medical devices, as defined in the Food and Drugs Act, covers a wide range of health or medical instruments used in the treatment, mitigation, diagnosis or prevention of a disease or abnormal physical condition. Health Canada reviews medical devices to assess their safety, effectiveness and quality before being authorized for sale in Canada.

Classification

The regulatory authorities recognize different classes of medical devices, based on their design complexity, their use characteristics, and their potential for harm if misused. Each country or region defines these categories in different ways. The authorities also recognize that some devices are provided in combination with drugs, and regulation of these combination products takes this factor into consideration.

Canada

The Medical Devices Bureau of Health Canada has recognized four classes of medical devices based on the level of control necessary to assure the safety and effectiveness of the device. Class I devices present the lowest potential risk and do not require a licence. Class II devices require the manufacturer's declaration of device safety and effectiveness, whereas Class III and IV devices present a greater potential risk and are subject to in-depth scrutiny. . A guidance document for device classification is published by Heath Canada .

Canadian classes of medical devices generally correspond to the European Council Directive 93/42/EEC (MDD) devices as follows: Class IV (Canada) generally corresponds to Class III (ECD), Class III (Canada) generally corresponds to Class IIb (ECD), Class II (Canada) generally corresponds to Class IIa (ECD), and Class I (Canada) generally corresponds to Class I (ECD) . Examples are surgical instruments (Class I); contact lenses, ultrasound scanners (Class II); orthopedic implants, hemodialysis machines (Class III); and cardiac pacemakers (Class IV) .

United States

The Food and Drug Administration has recognized three classes of medical devices based on the level of control necessary to assure the safety and effectiveness of the device. The classification procedures are described in the Code of Federal Regulations, Title 21, part 860 (usually known as 21 CFR 860).

Class I: General controls

Class I devices are subject to the least regulatory control. Class I devices are subject to "General Controls" as are Class II and Class III devices. General controls include provisions that relate to adulteration; misbranding; device registration and listing; premarket notification; banned devices; notification, including repair, replacement, or

refund; records and reports; restricted devices; and good manufacturing practices. Class I devices are not intended for use in supporting or sustaining life or to be of substantial importance in preventing impairment to human health, and they may not present a potential unreasonable risk of illness or injury. Most Class I devices are exempt from the premarket notification and/or good manufacturing practices regulation. Examples of Class I devices include elastic bandages, examination gloves, and hand-held surgical instruments.

Class II: General controls with special controls

Class II devices are those for which general controls alone are insufficient to assure safety and effectiveness, and existing methods are available to provide such assurances. In addition to complying with general controls, Class II devices are also subject to special controls. A few Class II devices are exempt from the premarket notification. Special controls may include special labeling requirements, mandatory performance standards and postmarket surveillance. Devices in Class II are held to a higher level of assurance than Class I devices, and are designed to perform as indicated without causing injury or harm to patient or user. Examples of Class II devices include powered wheelchairs, infusion pumps, and surgical drapes.

Class III: general controls and premarket approval

A Class III device is one for which insufficient information exists to assure safety and effectiveness solely through the general or special controls sufficient for Class I or Class II devices. Such a device needs premarket approval, a scientific review to ensure the device's safety and effectiveness, in addition to the general controls of Class I. Class III devices are usually those that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury. Examples of Class III devices which currently require a premarket notification include implantable pacemaker, pulse generators, HIV diagnostic tests, automated external defibrillators, and endosseous implants.

European Union (EU) and European Free Trade Association (EFTA)

The classification of medical devices in the European Union is outlined in Annex IX of the Council Directive 93/42/EEC. There are basically four classes, ranging from low risk to high risk.

- Class I (including Is & Im)
- Class IIa
- Class IIb
- Class III

The authorization of medical devices is guaranteed by a Declaration of Conformity. This declaration is issued by the manufacturer itself, but for products in Class Is, Im, IIa, IIb or III, it must be verified by a Certificate of Conformity issued by a Notified Body. A

Notified Body is a public or private organisation that has been accredited to validate the compliance of the device to the European Directive. Medical devices that pertain to class I (on condition they do not need to be sterilised or are not used to measure a function) can be put on the market purely by self-certification.

The European classification depends on rules that involve the medical device's duration of body contact, its invasive character, its use of an energy source, its effect on the central circulation or nervous system, its diagnostic impact or its incorporation of a medicinal product.

Certified medical devices should have the CE mark on the packaging, insert leaflets, etc.. These packagings should also show harmonised pictograms and EN standardised logos to indicate essential features such as instructions for use, expiry date, manufacturer, sterile, don't reuse, etc.

Radio-frequency identification

Medical devices incorporating RFID

In 2004, the FDA authorized marketing of two different types of medical devices that incorporate radio-frequency identification, or RFID. The first type is the SurgiChip tag, an external surgical marker that is intended to minimize the likelihood of wrong-site, wrong-procedure and wrong-patient surgeries. The tag consists of a label with passive transponder, along with a printer, an encoder and a RFID reader. The tag is labeled and encoded with the patient's name and the details of the planned surgery, and then placed in the patient's chart. On the day of surgery, the adhesive-backed tag is placed on the patient's body near the surgical site. In the operating room the tag is scanned and the information is verified with the patient's chart. Just before surgery, the tag is removed and placed back in the chart.

The second type of RFID medical device is the implantable radiofrequency transponder system for patient identification and health information. One example of this type of medical device is the VeriChip, which includes a passive implanted transponder, inserter and scanner. The chip stores a unique electronic identification code that can be used to access patient identification and corresponding health information in a database. The chip itself does not store health information or a patient's name.

Practical and information security considerations

Companies developing RFID-containing medical devices must consider product development issues common to other medical devices that come into contact with the body, are implanted in the body, or use computer software. For example, as part of product development, a company must implement controls and conduct testing on issues such as product performance, sterility, adverse tissue reactions, migration of the implanted transponder, electromagnetic interference, and software validation.

Medical devices that use RFID technology to store, access, and/or transfer patient information also raise significant issues regarding information security. The FDA defines "information security" as the process of preventing the modification, misuse or denial of use, or the unauthorized use of that information. At its core, this means ensuring the privacy of patient information.

Four components of information security

The FDA has recommended that a company's specifications for implantable RFID-containing medical devices address the following four components of information security: confidentiality, integrity, availability and accountability (CIAA).

- Confidentiality means data and information are disclosed only to authorized persons, entities and processes at authorized times and in the authorized manner. This ensures that no unauthorized users have access to the information.

- Integrity means data and information are accurate and complete, and the accuracy and completeness are preserved. This ensures that the information is correct and has not been improperly modified.

- Availability means data, information and information systems are accessible and usable on a timely basis in the required manner. This ensures that the information will be available when needed.

- Accountability is the application of identification and authentication to ensure that the prescribed access process is followed by an authorized user.

Although the FDA made these recommendations in the context of implantable RFID-containing medical devices, these principles are relevant to all uses of RFID in connection with pharmaceuticals and medical devices.

List of medical devices

High-risk devices

High-risk devices are life supports, critical monitoring, energy emitting and other devices whose failure or misuse is reasonably likely to seriously injure patient or staff. Examples include:

- Anesthesia units
- Anesthesia ventilators
- Apnea monitors
- Argon enhanced coagulation units
- Aspirators
- Auto transfusion units
- Cardiac defibrillator, external or internal

- Electrosurgical units
- External pacemaker
- Fetal monitors
- Heart-lung machine
- Incubators
- Infusion pump
- Invasive blood pressure units
- Pulse oximeters
- Radiation-therapy machines
- Ventilator
- Stent

An example of the stent used in an EVAR procedure

Medium-risk devices

These are devices including many diagnostic instruments whose misuse, failure or absence (e.g. out of service) with no replacement available would have a significant impact on patient care, but would not be likely to cause direct serious injury. Examples include:

- ECG
- EEG
- Treadmills
- Ultrasound sensors
- Phototherapy units
- Endoscopes
- Human-implantable RFID chips
- Surgical drill and saws
- Laparoscopic insufflators
- Phonocardiographs
- radiant warmers (adult)
- Zoophagous agents (e.g., medicinal leeches; medicinal maggots)
- Lytic bacteriophages

Low-risk devices

Devices in this category are those whose failure or misuse is unlikely to result in serious consequences. Examples include:

- Electronic thermometer,
- Breast pumps
- Surgical microscope
- Ultrasonic nebulizers
- Sphygmomanometers
- Surgical table
- Surgical lights.
- Temperature monitor
- Aspirators
- X-ray diagnostic equipment
- Lensometer
- keratometer

Standardization and regulatory concerns

The ISO standards for medical devices are covered by ICS 11.100.20 and 11.040.01 . The quality and risk management regarding the topic for regulatory purposes is convened by ISO 13485 and ISO 14971. Further standards are IEC 60601-1, for electrical devices (mains-powered as well as battery powered) and IEC 62304 for medical software. The

US FDA also published a series of guidances for industry regarding this topic against 21 CFR Subchapter H—Medical Devices.

Starting in the late 1980s the FDA increased its involvement in reviewing the development of medical device software. The precipitant for change was a radiation therapy device (Therac-25) that overdosed patients because of software coding errors. FDA is now focused on regulatory oversight on medical device software development process and system-level testing.

Packaging standards

Medical device packaging is highly regulated. Often medical devices and products are sterilized in the package. The sterility must be maintained throughout distribution to allow immediate use by physicians. A series of special packaging tests is used to measure the ability of the package to maintain sterility. Relevant standards include: ASTM D1585- Guide for Integrity Testing of Porous Medical Packages, ASTM F2097- Standard Guide for Design and Evaluation of Primary Flexible Packaging for Medical Products, EN 868 Packaging materials and systems for medical devices which are to be sterilized. General requirements and test methods, ISO 11607 Packaging for terminally sterilized medical devices, and others.

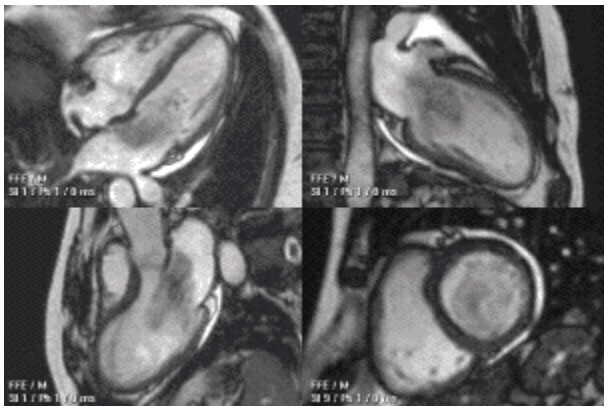
Academic resources

- *Medical & Biological Engineering & Computing*
- *Expert Review of Medical Devices*
- *Journal of Clinical Engineering*

Chapter 22

Cardiovascular Magnetic Resonance Imaging

Cardiovascular magnetic resonance imaging (CMR), sometimes known as **cardiac MRI**, is a medical imaging technology for the non-invasive assessment of the function and structure of the cardiovascular system. It is derived from and based on the same basic principles as magnetic resonance imaging (MRI) but with optimisation for use in the cardiovascular system. These optimisations are principally in the use of ECG gating and rapid imaging techniques or sequences. By combining a variety of such techniques into protocols, key functional and morphological features of the cardiovascular system can be assessed.



History and nomenclature

The phenomenon of nuclear magnetic resonance (NMR) was first described in molecular beams (1938) and bulk matter (1946), work later acknowledged by the award of a joint Nobel prize in 1952. Further investigation laid out the principles of relaxation times leading to nuclear spectroscopy. In 1973, the first simple NMR image was published and the first medical imaging in 1977, entering the clinical arena in the early 1980s. In 1984, NMR medical imaging was renamed MRI. Initial attempts to image the heart were confounded by respiratory and cardiac motion, solved by using cardiac ECG gating, faster scan techniques and breath hold imaging. Increasingly sophisticated techniques were developed including cine imaging and techniques to characterise heart muscle as

normal or abnormal (fat infiltration, oedematous, iron loaded, acutely infarcted or fibrosed).

As MRI became more complex and application to cardiovascular imaging became more sophisticated, the Society for Cardiovascular Magnetic Resonance, SCMR was set up (1996) with an academic journal, (JCMR) in 1999, which is going open source in 2008. In a move analogous to the development of 'echocardiography' from cardiac ultrasound, the term 'Cardiovascular Magnetic Resonance' (CMR) was proposed and has gained acceptance as the name for the field.

Physics

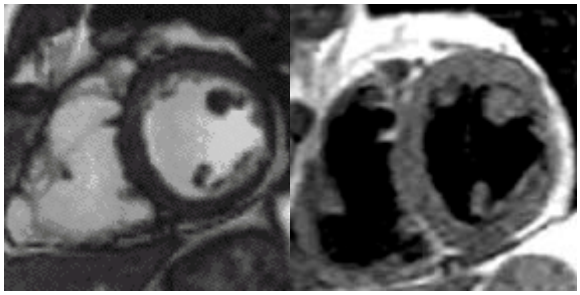
CMR uses the same basic principles as other MRI techniques with the addition of ECG gating. Most CMR uses only ^{1}H nuclei MR, which are abundant in human tissue. By using magnetic fields and radiofrequency (RF) pulses, the patient's own ^{1}H nuclei absorb and then emit energy, which can be measured and translated into images, without using ionising radiation.

Techniques

CMR uses several different techniques within a single scan. The combination of these results in a comprehensive assessment of the heart and cardiovascular system. Examples are below:

Visualising heart muscle scar or fat without using a contrast agent

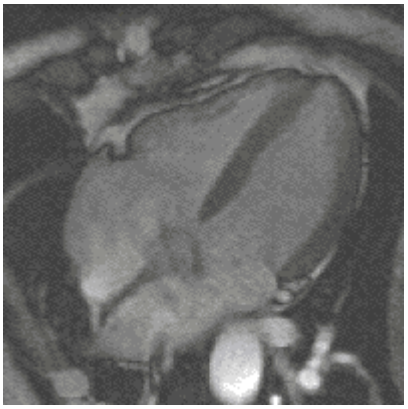
Typically a sequence called spin-echo is used. This causes the blood to appear black. These are high resolution still images which in certain circumstances identify abnormal myocardium through differences in intrinsic contrast.



Heart function using cine imaging

Images of the heart may be acquired in real-time with CMR, but the image quality is limited. Instead most sequences use ECG gating to acquire images at each stage of the cardiac cycle over several heart beats. This technique forms the basis of functional assessment by CMR. Blood typically appears bright in these sequences due to the contrast properties of blood and its rapid flow. The technique can discriminate very well

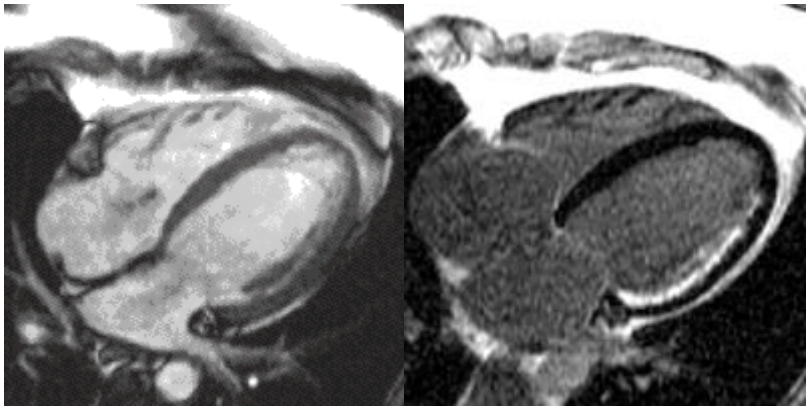
between blood and myocardium. The current technique typically used for this is called balanced steady state free precession (SSFP), implemented as TrueFISP, b-FFE or Fiesta, depending on scanner manufacturer.



A 4 chamber view of the heart using SSFP cine imaging. Compare the image orientation (4 chamber) with the short axis view of the movie above

Infarct imaging using contrast

Scar is best seen after giving a contrast agent, typically one containing gadolinium bound to DTPA. With a special sequence, Inversion Recovery (IR) normal heart muscle appears dark, whilst areas of infarction appear bright white.

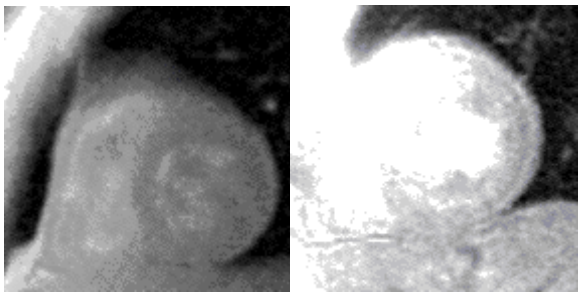


CMR in the 4 chamber view comparing the cine (left) with the late gadolinium image using inversion recovery (right). The subendocardial infarct is clearly seen. Fat around the heart also appears white.

Perfusion

In angina, the heart muscle is starved of oxygen by a coronary artery narrowing, especially during stress. This appears as a transient perfusion defect when a dose of

contrast is given into a vein. Knowing whether a perfusion defect is present and where it is helps guide intervention and treatment for coronary artery narrowings.



CMR perfusion. Contrast appears in the right ventricle then left ventricle before blushing into the muscle, which is normal (left) and abnormal (right, an inferior perfusion defect).

Uses

In the investigation of cardiovascular disease the physician has a wide variety of tools available. The key disadvantages of CMR are limited availability, expense, operator dependence and a lack of outcome data. The key advantages are image quality, non-invasiveness, accuracy, versatility and no ionising radiation.

A good overview of the clinical indications for CMR can be found here and here

Children and congenital heart disease

Congenital heart defects are the most common type of major birth defect. Accurate diagnosis is essential for the development of appropriate treatment plans. CMR can provide comprehensive information about the nature of congenital hearts defects in a safe fashion without using x-rays or entering the body. It is rarely used as the first or sole diagnostic test for congenital heart disease. Rather, it is typically used in concert with other diagnostic techniques. In general, the clinical reasons for a CMR examination fall into one or more of the following categories: 1) when echocardiography (cardiac ultrasound) cannot provide sufficient diagnostic information, 2) as an alternative to diagnostic cardiac catheterization which involve risks including x-ray radiation exposure, 3) to obtain diagnostic information for which CMR offers unique advantages such as blood flow measurement or identification of cardiac masses, and 4) when clinical assessment and other diagnostic tests are inconsistent. Examples of conditions in which CMR is often used include tetralogy of Fallot, transposition of the great arteries, coarctation of the aorta, single ventricle heart disease, abnormalities of the pulmonary veins, atrial septal defect, connective tissue diseases such as Marfan syndrome, vascular rings, abnormal origins of the coronary arteries, and cardiac tumors.

CMR examinations in children typically last 15 to 60 minutes. In order to avoid blurry images the child must remain very still during the examination. In general, most children 7 years of age and older can cooperate sufficiently for a good quality examination.

Providing an age-appropriate explanation of the procedure to the child in advance will increase the likelihood of a successful study. After proper safety screening, parents can be allowed into the MRI scanner room to help their child complete the examination. Some centers will allow children to listen to music or watch movies through a specialized MRI-compatible audiovisual system to reduce anxiety and improve cooperation. If the child cannot cooperate sufficiently, sedation with intravenous medications or general anesthesia may be necessary. In very young babies, it may be possible to perform the examination while they are in a natural sleep.

Different magnet types

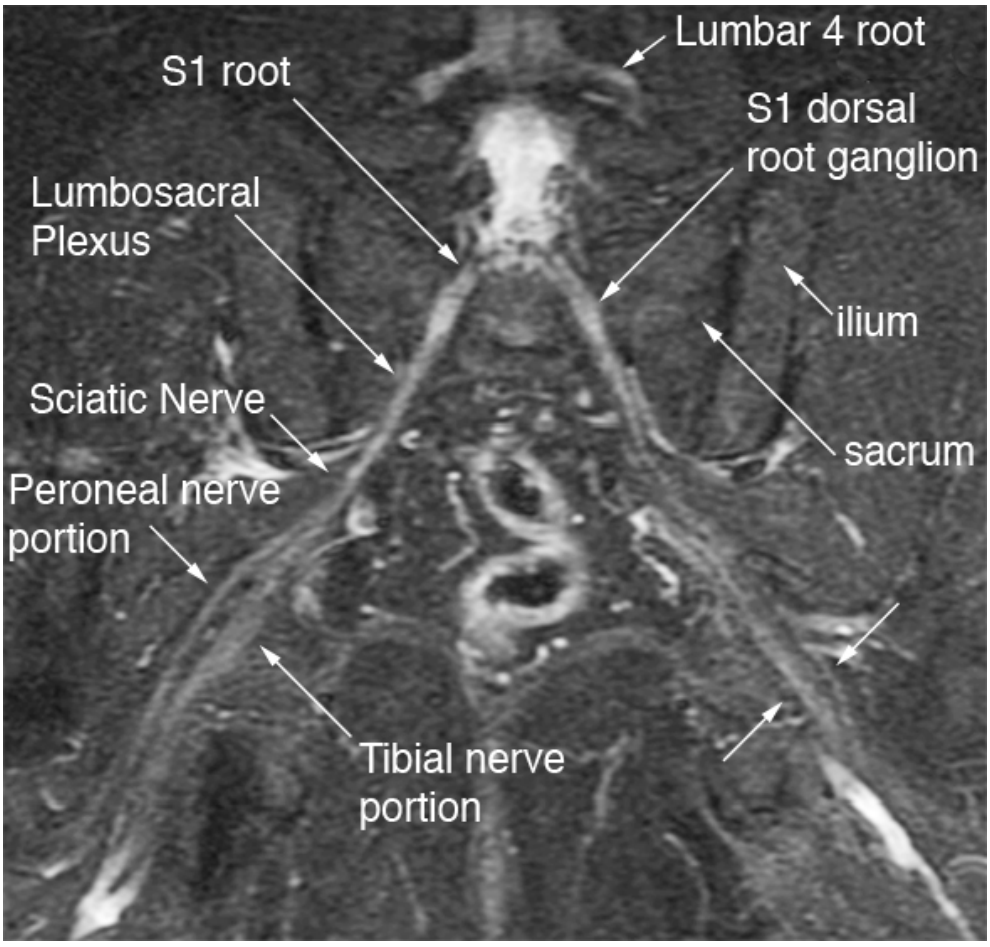
CMR scanners have to be modern. 'Open' magnet are not so good for cardiac as they do not cope with the beating heart very well. There are two magnet strengths mainly in use in CMR - 1.5 Tesla and 3 Tesla. The 3 Tesla has advantages as it potentially doubles the amount of information acquired in the same. It offers particular advantages for perfusion. The downside of 3Tesla is cost and potentially artefact degrading the pictures.

Training

Training is being increasingly protocolised and is now formal with stages of training and accreditation.

Chapter 23

Magnetic Resonance Neurography



Bilateral Split Sciatic Nerve

Magnetic resonance neurography (MRN) is the direct imaging of nerves in the body using special modifications of magnetic resonance imaging. The technique obtains a true detailed image of a nerve in which the resonance signal arises from in the nerve itself rather than from surrounding tissues or from fat in the nerve lining. Because of the intraneural source of the image signal, the image provides a medically useful set of information about the internal state of the nerve such as the presence of irritation, nerve swelling (edema), compression, pinch or injury. Standard MR images can show the

outline of some nerves in portions of their courses but does not show the intrinsic signal from nerve water. MR Neurography is used to evaluate major nerve compressions such as those affecting the sciatic nerve (e.g. piriformis syndrome), the brachial plexus nerves (e.g. thoracic outlet syndrome), the pudendal nerve, or virtually any named nerve in the body. A related technique for imaging neural tracts in the brain and spinal cord is called magnetic resonance tractography or diffusion tensor imaging.

History and physical basis

Magnetic resonance imaging (MRI) is based on differences in the physical properties of protons in water molecules in different tissues in the body. The protons and the water molecules of which they are part have subtly different movement characteristics that relate to their biophysical surroundings. Because of this, MRI is capable of differentiating one tissue from another; this provides "tissue contrast." From the time of the first clinical use of MRI in the mid 1970s until 1992, however, despite the active work of many thousands of researchers, there was no reliable method for visualizing nerve. In some parts of the body, nerves could be observed as areas of absent signal delineated by bright fat, or as bland grey structures that could not be reliably distinguished from other similar-appearing structures in cross sectional images.

In 1992, Aaron Filler and Franklyn Howe, working at St. George's Hospital Medical School in London, succeeded in identifying the unique water properties of nerve water that would make it possible to generate tissue-specific nerve images. The result was an initial "pure" nerve image in which every other tissue was made to disappear leaving behind only the image of the nerves. The initial pure nerve image served as a "Rosetta Stone" leading to discovery of a series of other MRI pulse sequence techniques that would make nerves imageable as well. All of these methods are applicable for any nerve anywhere in the body. Further, because they demonstrate water signal arising in the neural tissue itself, they can also reveal abnormalities that affect only the nerve and that do not affect surrounding tissues. More than three million patients seek medical attention every year for nerve-related disorders such as sciatica, carpal tunnel syndrome or various other nerve injuries, yet before 1992, no radiologists were trained to image nerves, and most physicians believed it simply could not be done usefully

There are two main physical bases for the imaging discovery. Firstly, it was known at the time that water diffused preferentially along the long axis of neural tissue in the brain – a property called "anisotropic diffusion". Diffusion MRI had been developed to take advantage of this phenomenon to show contrast between white matter and grey matter in the brain. However, diffusion MRI proved ineffective for imaging of peripheral nerves for reasons that were not initially clear. Filler and Howe discovered that the problem was that the most of the image signal in nerve came from protons that were not involved in anisotropic diffusion. They developed a collection of methods to suppress the "isotropic signal" and this resulted in allowing the anisotropic signal to be unmasked. This was based on the discovery that Chemical Shift Selection could be used to suppress "short T2 water" in the nerve and that this mostly affected isotropic water.

The endoneurial fluid compartment in nerve can be unmasked by similar techniques resulting in a "T2" based neurography as well as the original diffusion based neurography technique. Endoneurial fluid increases when nerve is compressed, irritated or injured, leading to nerve image hyperintensity in an MR Neurography image. Subsequent research has further demonstrated the biophysical basis for the ability of MR Neurography to show nerve injury and irritation.

Measurements of the T2 relaxation rate of nerve by Filler and Howe revealed that previous reports of a short relaxation time were wrong and that—once signal from lipid protons was suppressed—the primary image signal from nerve had long T2 relaxation rates best imaged with pulse sequence echo times in the range of 50 to 100 milliseconds. In addition, they later showed that T2-neurography differs from most other MR imaging in that the conspicuity or relative prominence of nerve is affected by the angle of voxel orientation during the acquisition of the image. When acquisitions are done with echo times below 40 milliseconds, there can be "magic angle effects" that provide some spurious information, so MR Neurography is always done with echo times greater than 40 milliseconds. The need for long echo times also characterizes the type of inversion recovery fat suppression sequences used for neurography nerve imaging.

Within a few months of the initial findings on diffusion-based peripheral nerve imaging, the diffusion technique for peripheral nerve imaging was adapted to permit for visualization of neural tracts in the spinal cord and brain via Diffusion Tensor Imaging.

Clinical uses

The most significant impact of MR Neurography is on the evaluation of the large proximal nerve elements such as the brachial plexus (the nerves between the cervical spine and the underarm that innervate shoulder, arm and hand), the lumbosacral plexus (nerves between the lumbosacral spine and legs), the sciatic nerve in the pelvis, as well as other nerves such as the pudendal nerve that follow deep or complex courses.

Neurography has also been helpful for improving image diagnosis in spine disorders. It can help identify which spinal nerve is actually irritated as a supplement to routine spinal MRI. Standard spinal MRI only demonstrates the anatomy and numerous disk bulges, bone spurs or stenoses that may or may not actually cause nerve impingement symptoms.

Many nerves, such as the median and ulnar nerve in the arm or the tibial nerve in the tarsal tunnel, are just below the skin surface and can be tested for pathology with electromyography, but this technique has always been difficult to apply for deep proximal nerves. MR Neurography has greatly expanded the efficacy of nerve diagnosis by allowing uniform evaluation of virtually any nerve in the body.

There are numerous reports dealing with specialized uses of MR Neurography for nerve pathology such as cervical radiculopathy, guidance for nerve blocks, demonstration of cysts in nerves, carpal tunnel syndrome, and obstetrical brachial plexus palsy. In addition several formal large scale outcome trials carried out with high quality "Class A"

methodology have been published that have verified the clinical efficacy and validity of MR Neurography.

Reliance on MR Neurography has become widespread in neurology and neurosurgery as the implications of its value in diagnosing various causes of sciatica has become clear. There are 1.5 million lumbar MRI scans performed in the US each year for sciatica, leading to surgery for a herniated disk in about 300,000 patients per year. Of these, about 100,000 surgeries fail. Therefore there is successful treatment for sciatica in just 200,000 and failure of diagnosis or treatment in up to 1.3 million annually in the US alone. The success rate of the paradigm of lumbar MRI and disk resection for treatment of sciatica is therefore about 15%(Filler 2005). Neurography has been applied increasingly to evaluate the distal nerve roots, lumbo-sacral plexus and proximal sciatic nerve in the pelvis and thigh to find other causes of sciatica. It is increasingly important for brachial plexus imaging and for the diagnosis of thoracic outlet syndrome. Active research and development in the clinical use of diagnostic neurography has taken place at Johns Hopkins, the Mayo Clinic, UCLA, UCSF, Harvard, the University of Washington in Seattle, University of London, and Oxford University as well as through the Neurography Institute. Courses have been offered for radiologists on an annual basis at the annual meetings of the Radiological Society of North America (RSNA), and at the International Society for Magnetic Resonance in Medicine and for surgeons at the annual meetings of the American Association of Neurological Surgeons and the Congress of Neurological Surgeons. The use of imaging for diagnosis of nerve disorders represents a change from the way most physicians were trained to practice over the past several decades, but it is increasingly becoming a standard of care when older routine tests fail to identify the diagnosis for nerve related disorders. The New England Journal of Medicine in July 2009 published a report on whole body neurography using a diffusion based neurography technique. This signals appreciation by the editors of the leading medical journal that MR Neurography is now of interest to all physicians. In 2010, RadioGraphics - a publication of the Radiological Society of North America that serves to provide continuing medical education to radiologists - published an article series taking the position that Neurography has an important role in the evaluation of entrapment neuropathies.

MR Neurography does not pose any diagnostic disadvantage relative to standard MR because Neurography studies typically include high resolution standard MRI image series for anatomical reference along with the neurographic sequences. However, the patient will generally have a longer time in the scanner compared to a routine MRI scan. MR Neurography is very demanding of the imaging system so it can only be performed in 1.5 tesla cylindrical type scanners and can't really be done effectively in lower power "open" MR scanners - this can pose significant challenges for claustrophobic patients. Although it has been in use for fifteen years and is the subject of more than 150 research publications, some insurance companies still classify this test as experimental and decline reimbursement. There is no documented standard by which insurance companies are required to advance a technique from "experimental" to "indicated" so patients may need to file appeals with their insurance company to try to recoup out of pocket costs.

Chapter 24

Medical Radiography

Radiography is the use of ionizing electromagnetic radiation such as X-rays to view objects. Although not technically radiographic techniques, imaging modalities such as PET and MRI are sometimes grouped in radiography because the radiology department of hospitals handle all forms of imaging. Treatment using radiation is known as radiotherapy.

History

Radiography started in 1895 with the discovery of X-rays (later also called Röntgen rays after the man who first described their properties in rigorous detail), a type of electromagnetic radiation. Soon these found various applications, from helping to find shoes that fit, to the more lasting medical uses. X-rays were put to diagnostic use very early, before the dangers of ionising radiation were discovered. Initially, many groups of staff conducted radiography in hospitals, including physicists, photographers, doctors, nurses, and engineers. The medical speciality of radiology grew up around the new technology, and this lasted many years. When new diagnostic tests involving X-rays were developed, it was natural for the radiographers to be trained and adopt this new technology. This happened first with fluoroscopy, computed tomography (1960s), and mammography. Ultrasound (1970s) and magnetic resonance imaging (1980s) was added to the list of skills used by radiographers because they are also medical imaging, but these disciplines do not use ionising radiation or X-rays. Although a nonspecialist dictionary might define radiography quite narrowly as "taking X-ray images", this has only been part of the work of an "X-ray department", radiographers, and radiologists for a very long time. X-rays are also exploited by industrial radiographers in the field of nondestructive testing, where the newer technology of ultrasound is also used.

Diagnostic radiography

Diagnostic radiography involves the use of both ionising radiation and non-ionising radiation to create images for medical diagnoses. The predominant test is still the X-ray (the word X-ray is often used for both the test and the actual film or digital image). X-rays are the second most commonly used medical tests, after laboratory tests. This application is known as diagnostic radiography. Since the body is made up of various substances with differing densities, X-rays can be used to reveal the internal structure of the body on film by highlighting these differences using attenuation, or the *absorption* of

X-ray photons by the denser substances (like calcium-rich bones). Medical diagnostic radiography is undertaken by a specially trained professional called a diagnostic radiographer in the UK, or a radiologic technologist in the USA.

There are several sub-specialities:

Projection radiography

The creation of images by exposing an object to X-rays or other high-energy forms of electromagnetic radiation and capturing the resulting remnant beam (or "shadow") as a latent image is known as "projection radiography." The "shadow" may be converted to light using a fluorescent screen, which is then captured on photographic film, it may be captured by a phosphor screen to be "read" later by a laser (CR), or it may directly activate a matrix of solid-state detectors (DR—similar to a very large version of a CCD in a digital camera). Bone and some organs (such as lungs) especially lend themselves to projection radiography. It is a relatively low-cost investigation with a high diagnostic yield.

Projection radiography uses X-rays in different amounts and strengths depending on what body part is being imaged:

- Hard tissues such as bone require a relatively high energy photon source, and typically a tungsten anode is used with a high voltage (50-150 kVp) on a 3-phase or high-frequency machine to generate braking radiation. Bony tissue and metals are denser than the surrounding tissue, and thus by absorbing more of the X-ray photons they prevent the film from getting exposed as much. Wherever dense tissue absorbs or stops the X-rays, the resulting X-ray film is unexposed, and appears translucent blue, whereas the black parts of the film represent lower-density tissues such as fat, skin, and internal organs, which could not stop the X-rays. This is usually used to see bony fractures, foreign objects (such as ingested coins), and used for finding bony pathology such as osteoarthritis, infection (osteomyelitis), cancer (osteosarcoma), as well as growth studies (leg length, achondroplasia, scoliosis, etc.).

- Soft tissues are seen with the same machine as for hard tissues, but a "softer" or less-penetrating X-ray beam is used. Tissues commonly imaged include the lungs and heart shadow in a chest X-ray, the air pattern of the bowel in abdominal X-rays, the soft tissues of the neck, the orbits by a skull X-ray before an MRI to check for radiopaque foreign bodies (especially metal), and of course the soft tissue shadows in X-rays of bony injuries are looked at by the radiologist for signs of hidden trauma (for example, the famous "fat pad" sign on a fractured elbow).

- Dental radiography uses a small radiation dose with high penetration to view teeth, which are relatively dense. A dentist may examine a painful tooth and gum using X-ray equipment. The machines used are typically single-phase pulsating

DC, the oldest and simplest sort. Dental technicians or the dentist may run these machines—radiologic technologists are not required by law to be present.

- Mammography is an X-ray examination of breasts and other soft tissues. This has been used mostly on women to screen for breast cancer, but is also used to view male breasts, and used in conjunction with a radiologist or a surgeon to localise suspicious tissues before a biopsy or a lumpectomy. Breast implants designed to enlarge the breasts reduce the viewing ability of mammography, and require more time for imaging as more views need to be taken. This is because the material used in the implant is very dense compared to breast tissue, and looks white (clear) on the film. The radiation used for mammography tends to be softer (has a lower photon energy) than that used for the harder tissues. Often a tube with a molybdenum anode is used with about 30 000 volts (30 kV), giving a range of X-ray energies of about 15-30 keV. Many of these photons are "characteristic radiation" of a specific energy determined by the atomic structure of the target material (Mo-K radiation).

Other modalities are used in radiography when traditional projection X-ray cannot image what doctors want to see. Below are other modalities included within radiography; they are only summaries and more specific information can be viewed by going to their individual pages:

Fluoroscopy (angiography, gastro-intestinal fluroscopy)

Fluoroscopy is a term invented by Thomas Edison during his early X-ray studies. The name refers to the fluorescence he saw while looking at a glowing plate bombarded with X-rays.

This is a technique that provides moving projection radiographs of lower quality. Fluoroscopy is mainly performed to view movement (of tissue or a contrast agent), or to guide a medical intervention, such as angioplasty, pacemaker insertion, or joint repair/replacement. The latter are often carried out in the operating theatre, using a portable fluoroscopy machine called a C-arm. It can move around the surgery table and make digital images for the surgeon.

Angiography is the use of fluoroscopy to view the cardiovascular system. An iodine-based contrast is injected into the bloodstream and watched as it travels around. Since liquid blood and the vessels are not very dense, a contrast with high density (like the large iodine atoms) is used to view the vessels under X-ray. Angiography is used to find aneurysms, leaks, blockages (thromboses), new vessel growth, and placement of catheters and stents. Balloon angioplasty is often done with angiography.

Fluoroscopy can be used to examine the digestive system using a substance which is opaque to X-rays, (usually barium sulfate or gastrografin), which is introduced into the digestive system either by swallowing or as an enema. This is normally as part of a *double contrast technique,* using positive and negative contrast. Barium sulfate coats the

walls of the digestive tract (positive contrast), which allows the shape of the digestive tract to be outlined as white or clear on an X-ray. Air may then be introduced (negative contrast), which looks black on the film. The barium meal is an example of a contrast agent swallowed to examine the upper digestive tract. Note that while soluble barium compounds are very toxic, the insoluble barium sulfate is non-toxic because its low solubility prevents the body from absorbing it.

- A number of substances have been used as positive contrast agents: silver, bismuth, caesium, thorium, tin, zirconium, tantalum, tungsten and lanthanide compounds have been used as contrast agents. The use of thoria (thorium dioxide) as an agent was rapidly stopped as thorium causes liver cancer.

Most modern injected radiographic positive contrast media are iodine-based. Patients who suffer from allergy to shellfish may be allergic to iodine, and should consult their physician regarding pre-medication to lessen risk of allergic reaction. Iodinated contrast comes in two forms: ionic and non-ionic compounds. Non-ionic contrast is significantly more expensive than ionic (approximately three to five times the cost), however, non-ionic contrast tends to be safer for the patient, causing fewer allergic reactions and uncomfortable side effects such as hot sensations or flushing. Most imaging centers now use non-ionic contrast exclusively, finding that the benefits to patients outweigh the expense.

- Negative radiographic contrast agents are air and carbon dioxide (CO_2). The latter is easily absorbed by the body and causes less spasm. It can also be injected into the blood, where air absolutely cannot.

Dual energy X-ray absorptiometry

DEXA, or bone densitometry, is used primarily for osteoporosis tests. It is not projection radiography, as the X-rays are emitted in 2 narrow beams that are scanned across the patient, 90 degrees from each other. Usually the hip (head of the femur), lower back (lumbar spine) or heel (calcaneum) are imaged, and the bone density (amount of calcium) is determined and given a number (a T-score). It is not used for bone imaging, as the image quality is not good enough to make an accurate diagnostic image for fractures, inflammation etc. It can also be used to measure total body fat, though this isn't common. The radiation dose received from DEXA scans is very low, much lower than projection radiography examinations.

Computed tomography

Computed tomography or CT scan (previously known as CAT scan, the "A" standing for "axial") uses a high amount of ionizing radiation (in the form of X-rays) in conjunction with a computer to create images of both soft and hard tissues. These images look as though the patient was sliced like bread (thus, "tomography"-- "tomo" means "slice"). The machine looks similar to an MRI machine to many patients, but is not related. The exams are generally short, most lasting only as long as a breath-hold. Contrast agents are

often used, depending on the tissues needing to be seen. Radiographers perform these examinations, sometimes in conjunction with a radiologist (for instance, when a radiologist performs a CT-guided biopsy).

Technical considerations

X-ray photons are formed in events involving electrons and are the mainly form of ionizing electromagnetic radiation used in medical radiography. This radiation is much more energetic than the more familiar types such as radio waves and visible light. Proper production and detection of photons are important in the creation of good radiograms.

Photon production

X-ray radiation for medical imaging is typically produced by X-ray tubes, which operate through bombarding the anode with high energy electrons emitted from a hot cathode. Image sharpness, contrast, and patient dosage are important considerations in medical radiography and these requirements determined the desired energies of the tube, the type of material used on the anode, and the method in which the power is generated to drive the tube. Although the technical definition of x-rays range from 1-700 keV, medical x-rays typically use 5-150 keV x-rays. The photons emitted come in discrete bands of energy corresponding to the material of the anode, and the undesired bands are removed. Choice of the anode and its emitted radiation energies depends on the application and the tissues being imaged, for instance molybdenum is often used in mammography because of its 20 keV x-rays. Too high radiation energies will result in poor pictures since the radiation cannot be readily attenuated, however too low energies will increase the radiation dosage of the patient without improvements in image quality.

Sharpness of a radiographic image is strongly determined by the size of the x-ray source. This is determined by the area of the electron beam hitting the anode. A large photon source results in more blurring in the final image and is worsened by an increase in image formation distance. This blurring can be measured as a contribution to the modulation transfer function of the imaging system.

Power generation

The power used by the x-ray tube is generated by a specialized generator, which supplies the voltage and current required to drive the tube. The generator needs to supply high voltages with small exposure times. An exposure thus can be described by two factors:

1. The *peak voltage* of the cathode to anode
2. The *milliamprere seconds* exposure time

These variables can be controlled by the operator but are more typically assigned automatically by the x-ray machinery through sampling the emitted radiation. Power generators convert standard 120 or 220 volt AC to higher DC voltages and typically

employ rectified and filtered multiphase transformers which maintain a constant voltage and can be turn rapidly on and off for millisecond exposures.

Photon detection

Photons images that have been shadowed from an imaging subject must be detected at high fidelity and resolution to allow for diagnosis. There are three main types of image detection methods used namely: film/screens, image intensifiers, and digital detectors, with the latter fast becoming the standard for x-ray image detection. The ability of an x-ray detector to produce high-quality images is determined largely by the modulation transfer function (MTF) and detective quantum efficiency (DQE) of the system.

Film/Screens

X-ray film is almost always used in conjunction with x-ray sensitive screen because high resolution film is quite poor at detecting x-rays. These screens contain rare earth minerals and phosphor materials thatconvert x-ray radiation to visible light or lows EM energies to which the film is sensitive. Screen generally have to have good contrast, dynamic range, and resolution, with the former two factors being competing properties. The resolution of the screen also affects the sensitivity of the detectors since more sensitive screens are generally thicken, which causes the more blurring because of spreading light.

The film speed also play a factor in image quality. Higher speeds are more sensitive to photons but are generally lower in resolution and more susceptible to noise. Lower speed films produce images of good resolution and dynamic range but requires more photons for exposure and increases the radiation dosage of the subject.

Image intensifiers and array detectors

Image intensifiers are analog devices that readily convert the acquired x-ray image into one visible on a video screen. This device is made of a vacuum tube with a wide input surface coated on the inside with caesium iodide (CsI). When hit by x-rays material phosphors which causes the photocathode adjacent to it to emit electrons. These electron are then focus using electron lenses inside the intensifier to an output screen coated with phosphorescent materials. The image from the output can then be recorded via a camera and displayed.

Digital devices known an array detectors are becoming more common in fluoroscopy. These devices are made of discrete pixelated detectors known as TFTs which can either work *indirectly* by using photo detectors that detect light emitted from a scintillator material such as CsI, or *directly* by capturing the electrons produced when the x-rays hit the detector. Direct detector do not tend to experience the blurring or spreading effect caused by phosphorescent scintillators of or film screens since the detectors are activated directly by x-ray photons.

Obsolete terminology

The term *skiagrapher* was used until about 1918 to mean *radiographer*. It was derived from Ancient Greek words for 'shadow' and 'writer'.