# Medical Imaging in Clinical Trials

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*This book is dedicated to my family, who has stood beside me as I have moved us between continents and who has allowed me to pursue my career and ambitions beyond expectations: To my beautiful wife of 25 amazing years – Angie; To my sons, Joe and Elliot, who have kept me young at heart and helped me "update" many life skills; To Katie, my late "adopted daughter," who has brought me fresh perspectives; To Biggles, my faithful golden retriever of 13 years who walked by my side and sat for many hours as I worked on this book, and to Toby my new puppy who wants me to play rather than write.*

*There are many mentors and team members who helped develop the concepts and theories over the years: Without their friendship and intellectual discourse, this book would not have had significant content. A deep and heartfelt "Thank You" to each one.*

*Colin G. Miller*

*There are many people without whom this book would not have been possible. First, I would like to thank the researchers and educators who have mentored me over the years. I would also like to thank those I collaborated with on this book as the final product could have never been reached without our combined efforts. Foremost, I would like to thank my wife, Lisa, and my children, Michael and Emily, for their love and support that made this book possible.*

*Joel Krasnow*

*To Hilda, Martin, Amanda, Rachel, and Alyssa – in order of entrée into my life! You have inspired and taught me, and I hope you will continue to do so. There are big "writing shoes" to fill here; Dad, I hope to make you as proud of me as I am of you.*

*Lawrence H. Schwartz*

# Foreword

Quantitative and functional medical imaging play an increasingly important role in the development of new therapeutics. There is rising demand for quantitative imaging-based biomarkers because they noninvasively detect disease and predict the likelihood of response to therapy and subsequent patient outcomes. Imaging findings, alone and in combination with other markers, are used to make decisions about trial eligibility, to assess response to therapy as either efficacy or safety endpoints, to monitor patients for potential relapse during follow-up periods, or to provide important mechanistic insights. And, as imaging technologies become more widely validated as biomarkers of disease, imaging will play an even larger role in clinical trials. Yet, despite this increased focus on imaging in clinical trials, few clinical trialists possess the detailed knowledge required to optimize imaging contributions. This book provides an essential resource to address that problem.

In the areas of oncology, cardiovascular disease, brain disorders, musculoskeletal disorders (especially arthritis and osteoporosis), and infectious diseases, as well as an array of metabolic, gastroenterological, and inflammatory disorders, imaging plays a vital role in clinical trials to determine the effectiveness of new therapies. The market for imaging analysis in clinical trials in 2009 was approximately $550 M in total annual revenue. Conservative estimates for future annual growth are 5–10 %, although some analysts project more rapid growth. Thus, there is a critical need for imaging expertise to ensure that such an investment returns information that is reliable and meaningful.

Because the use of medical images in clinical trials has accelerated rapidly, government (e.g., NIH) and commercial sponsors are requiring more complex and comprehensive imaging services, which require changes in study design and data interpretation, as well as an expanded knowledge of competing modalities and technologies. Sponsors and investigators are increasingly reliant upon recognized experts to implement complex imaging in clinical trials. Such expertise is essential in study design, for example, in defining inclusion/exclusion criteria and imaging endpoints. These requirements create challenges for researchers who are unfamiliar with complex imaging. Similarly, regulatory agencies such as the US FDA are increasing their expectations and requirements for rigor in the imaging components

of clinical trials. Knowledge of these regulatory guidelines is another necessity for imaging members of clinical trial teams. These issues are extensively addressed in Part I of this book.

Clinical trials of cancer therapies are the largest single area for imaging in drug development and will likely continue to gain share. However, the use of imaging in other therapeutic areas also continues to increase because of the same attributes that are advantageous for imaging's use in cancer. For example, because of the large cost of phase III trials, it is increasingly important to measure tumor response at a relatively early time point so that trials could be terminated or modified if the investigational therapy is not working as expected. Additional considerations that influence the desire to monitor and measure tumor response effectively relate to potential toxicity and cost issues. It is desirable to terminate trials of ineffective, toxic, or expensive therapies as early as possible. Similar considerations apply to other therapeutic areas, especially to brain and heart disorders where biopsy is even less feasible than it is for cancer. Part II of this book provides individual chapters on several of the disease-specific issues that must be considered in therapeutic clinical trials.

There is widespread agreement that extracting objective, quantitative results from imaging studies will reduce the variability inherent in subjective, qualitative interpretations and thereby improve the quality of imaging-related endpoints in clinical trials. Such imaging in clinical trials today necessarily draws on a variety of expertise including, but not limited to, clinical medicine, informatics, computer science, statistics, biology, chemistry, physics, and engineering. Multidisciplinary collaborations are essential. This textbook provides an indispensable resource of fundamental principles and information for the success of these multidisciplinary clinical trial teams.

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# Preface

There are a number of books written about clinical trials [1–5]. They take a biostatistical approach providing generic information about how imaging can be used as clinical endpoints or biomarkers. This book is written specifically to address the questions around the application of medical imaging in the complex and highly regulated environment of clinical trials. It has also been timed to coincide with a new set of guidelines issued by the US Food and Drug Administration (FDA) entitled "Guidance on Standards for Clinical Trial Imaging Endpoints" which we have included verbatim, with permission, as Appendix 1.

Medical imaging has made dramatic advances in the last 30 or 40 years with the advent of higher computing power and new technologies. The magnitude of data that clinical trialists and radiologists have to manage has grown exponentially as have the skills required to accurately evaluate and interpret these images.

The development of new therapeutics as well as devices within the framework of the FDA and other international regulatory authorities has become more challenging. Yet, there is a drive to get new medications to suffering patients to relieve disease and prolong life. Clinical trial methodology has, by the very nature of the statistical evaluation required, been a very quantitative science with the so-called hard endpoints (e.g., death, myocardial infarct, fracture). Radiology has historically been an interpretative discipline with images being read qualitatively. This has led to the challenge we face today of bridging the "divide" between a quantitative and qualitative or descriptive science.

The quantitative application of medical imaging in clinical trials has really only been in existence for about 20–25 years. Dual-energy X-ray Absorptiometry (DXA) was probably the first modality where this process was fully described and thus could be utilized by pharma in selected clinical trials [6, 7]. As the need for quantification has evolved, the development of the semiquantitative or pseudo-quantification endpoints has grown, especially in the therapeutic area of oncology. Table 1 shows a complete listing of many of these criteria with references, which will surely change over time.

The goal of this book is to present key concepts of medical imaging in clinical trials by assembling the thoughts, concepts, and understanding of key thought

**Table 1** Listing of semiquantitative or pseudo-quantification endpoints/criteria of medical imaging in clinical trials

| Response criterion | Pathology | Year | Link to paper |
|---|---|---|---|
| Choi criteria | GIST | 2008 | http://www.ncbi.nlm.nih.gov/pubmed/18434631<br>Choi H. Response evaluation of gastrointestinal stromal tumors. Oncologist. 2008;13(Suppl 2):4–7. doi:10.1634/theoncologist.13-S2-4. |
| Choi criteria | GIST | 2007 | http://www.ncbi.nlm.nih.gov/pubmed/17470865<br>Choi H, Charnsangavej C, Faria SC, Macapinlac HA, Burgess MA, Patel SR, Chen LL, Podoloff DA, Benjamin RS. Correlation of computed tomography and positron emission tomography in patients with metastatic gastrointestinal stromal tumor treated at a single institution with imatinib mesylate: proposal of new computed tomography response criteria. J Clin Oncol. 2007;25(13):1753–9. |
| RECIST | Malignant mesothelioma | 2004 | http://www.ncbi.nlm.nih.gov/pubmed/14760119<br>Byrne MJ, Nowak AK. Modified RECIST criteria for assessment of response in malignant pleural mesothelioma. Ann Oncol. 2004;15(2):257–60. |
| RECIST | Pediatrics | 2003 | http://www.ncbi.nlm.nih.gov/pubmed/12857700<br>McHugh K, Kao S. Response evaluation criteria in solid tumours (RECIST): problems and need for modifications in paediatric oncology? Br J Radiol. 2003;76(907):433–6. |
| Macdonald and Rano criteria | Supratentorial malignant glioma | 1990 | http://www.ncbi.nlm.nih.gov/pubmed/2358840<br>Macdonald DR, Cascino TL, Schold Jr SC, Cairncross JG. Response criteria for phase II studies of supratentorial malignant glioma. J Clin Oncol. 1990;8(7):1277–80. |
| Macdonald and Rano criteria | High-grade gliomas | 2010 | http://jco.ascopubs.org/content/28/11/1963<br>Wen PY, Macdonald DR, Reardon DA, Cloughesy TF, Sorensen AG, Galanis E, DeGroot J, Wick W, Gilbert MR, Lassman AB, Tsien C, Mikkelsen T, Wong ET, Chamberlain MC, Stupp R, Lamborn KR, Vogelbaum MA, van den Bent MJ, Chang SM. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. J Clin Oncol. 2010;28(11):1963–72. |

| | | | |
|---|---|---|---|
| CRPC, PCWG2 | Castration-resistant prostate cancer | 2011 | http://jco.ascopubs.org/content/29/27/3695<br>Scher HI, Morris MJ, Basch E, Heller G. End points and outcomes in castration-resistant prostate cancer: from clinical trials to clinical practice. J Clin Oncol. 2011;29(27): 3695–704. |
| Immune-related response criteria Wolchok criteria | Melanoma | 2009 | http://clincancerres.aacrjournals.org/content/15/23/7412.full.pdf<br>Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res. 2009;15:7412–20. |
| Image-guided tumor ablation | Solid tumors | 2009 | http://www.ncbi.nlm.nih.gov/pubmed/19560026<br>Goldberg SN, Grassi CJ, Cardella JF, Charboneau JW, Dodd 3rd GD, Dupuy DE, Gervais DA, Gillams AR, Kane RA, Lee Jr FT, Livraghi T, McGahan J, Phillips DA, Rhim H, Silverman SG, Solbiati L, Vogl TJ, Wood BJ, Vedantham S, Sacks D; Society of Interventional Radiology Technology Assessment Committee and the International Working Group on Image-guided Tumor Ablation. Image-guided tumor ablation: standardization of terminology and reporting criteria. J Vasc Interv Radiol. 2009;20(7 Suppl):S377–90. |
| RECIST 1.1 | Malignant lymph nodes | 2009 | http://www.ncbi.nlm.nih.gov/pubmed/19091550<br>Schwartz LH, Bogaerts J, Ford R, Shankar L, Therasse P, Gwyther S, Eisenhauer EA. Evaluation of lymph nodes with RECIST 1.1. Eur J Cancer. 2009;45(2):261–7. |
| RECIST 1.1 | Solid tumors | 2009 | http://www.ncbi.nlm.nih.gov/pubmed/19097774<br>Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228–47. |
| Cheson | Malignant lymphoma | 2007 | http://jco.ascopubs.org/content/25/5/579.full.pdf<br>Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, Coiffier B, Fisher RI, Hagenbeek A, Zucca E, Rosen ST, Stroobants S, Lister TA, Hoppe R T, Dreyling M, Tobinai K, Vose JM, Connors JM, Federico M, Diehl V. Revised response criteria for malignant lymphoma. J Clin Oncol.2007;25:579–86. |

(continued)

**Table 1** (continued)

| Response criterion | Pathology | Year | Link to paper |
|---|---|---|---|
| Hallek criteria | Chronic lymphocytic leukemia | 2008 | http://bloodjournal.hematologylibrary.org/content/111/12/5446.full.pdf<br>Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Döhner H, Hillmen P, Keating MJ, Montserrat E, Rai KR, Kipps TJ. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Group 1996 guidelines lymphocytic leukemia updating the National Cancer Institute Working Group 1996 guidelines. Blood. 2008;111(12):5446–56. |
| Multiple myeloma | Myeloma | 2006 | http://www.nature.com/leu/journal/v20/n9/pdf/2404284a.pdf<br>Durie BGM, Harousseau J-L, Miguel JS, Blade'J, Barlogie B, Anderson K, Gertz M, Dimopoulos M, Westin J, Sonneveld P, Ludwig H, Gahrton G, Beksac M, Crowley J, Belch A, Boccadaro M, Turesson I, Joshua D, Vesole D, Kyle R, Alexanian R, Tricot G, Attal M, Merlini G, Powles R, Richardson P, Shimizu K, Tosi P, Morgan G, Rajkumar SV, on behalf of the International Myeloma Working Group. International uniform response criteria for multiple myeloma. Leukemia. 2006;20:1467–73. |
| PERCIST | Solid tumors | 2009 | http://jnm.snmjournals.org/content/50/Suppl_1/122S.full.pdf<br>Wahl RL, Jacene H, Kasamon Y, Lodge MA. From RECIST to PERCIST: evolving considerations for PET response criteria in solid tumor. J Nucl Med. 2009;50:122S–50S. |
| Sarcoma | Sarcoma | 2008 | http://theoncologist.alphamedpress.org/content/13/suppl_2/32.full.pdf<br>Schuetze SM, Baker LH, Benjamin RS, Canetta R. Selection of response criteria for clinical trials of sarcoma treatment. Oncologist. 2008;13(Suppl 2):32–40. |
| Metastatic urogenital cancer | Solid tumors | 2010 | http://content.karger.com/ProdukteDB/produkte.asp?Aktion=ShowPDF&ArtikelNr=000318985&Ausgabe=254445&ProduktNr=224282&filename=000318985.pdf<br>Heidenreich A, Albers P, Classen J, Graefen M, Gschwend J, Kotzerke J, Krege S, Lehmann J, Rohde D, Schmidberger H, Uder M, Zeeb H. Imaging studies in metastatic urogenital cancer patients undergoing systemic therapy: recommendations of a multidisciplinary consensus meeting of the Association of Urological Oncology of the German Cancer Society. Urol Int. 2010;85:1–10. |

| | | | |
|---|---|---|---|
| Hepatocellular carcinoma | Solid tumors | 2010 | http://www.ncbi.nlm.nih.gov/pubmed/20175033<br>Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis. 2010;30(1):52–60. |
| Hepatocellular carcinoma | Solid tumors | 2010 | http://annonc.oxfordjournals.org/content/21/suppl_5/v59.full.pdf<br>Jelic S, Sotiropoulos GC, On behalf of the ESMO Guidelines Working Group. Hepatocellular carcinoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Annals of Oncol. 2010;21 (Suppl 5): v59–64. |
| Cheson | Malignant lymphoma | 2007 | http://jco.ascopubs.org/content/25/5/579.full.pdf<br>Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, Coiffier B, Fisher RI, Hagenbeek A, Zucca E, Rosen ST, Stroobants S, Lister TA, Hoppe RT, Dreyling M, Tobinai K, Vose JM, Connors JM, Federico M, Diehl V. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007;25:579–86. |
| Cheson | Lymphoma | 2007 | http://bloodjournal.hematologylibrary.org/content/110/10/3507.full.pdf<br>Seam P, Juweid ME, Cheson BD. The role of FDG-PET scans in patients with lymphoma. Blood. 2007;110:3507–16. |
| PERCIST | Lymphoma | 2007 | http://jco.ascopubs.org/content/25/5/571.full.pdf<br>Juweid ME, Stroobants S, Hoekstra OS, Mottaghy FM, Dietlein M, Guermazi A, Wiseman GA, Kostakoglu L, Scheidhauer K, Buck A, Naumann R, Spaepen K, Hicks RJ, Weber WA, Reske SN, Schwaiger M, Schwartz LH, Zijlstra JM, Siegel BA, Cheson BD. Use of positron emission tomography for response assessment of lymphoma: consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma. J Clin Oncol. 2007;25:571–8. |

leaders in this discipline. While the key concepts in this text will not change, we recognize that many of the details will. Therefore, we designed the book to be read as needed and not necessarily from beginning to end. This book is broken into two main parts. Part I includes chapters on the design and concept of blinded reads as well as the details of how to write an imaging charter. Each chapter can be read in isolation; on the other hand, for example, Chap. 1, a basic chapter on medical imaging, may be skipped by the experienced radiologists. Part II includes chapters on each of the main therapeutic areas where imaging is employed in clinical trials. This portion of the book has been developed to provide greater detail of the biologic and clinical specifics in each therapeutic area. Part III leads us to the future of imaging in clinical trials, with a pharmaceutical industry perspective regarding imaging techniques. Finally, we end with three appendices to bring some of the key information together in one location. These are Appendix 1, the FDA Guidance for Industry on Standards for Clinical Trial Imaging Endpoints; Appendix 2, a glossary taken from www.ClinicalTrials.gov and a Lexicon developed specifically for Medical Imaging in Clinical Trials in conjunction with the FDA, DIA, and PhRMA; and Appendix 3, Information from the Quantitative Imaging Biomarker Association (QIBA) web site, a group which is looking at the evaluation of new quantitative biomarkers initially for clinical trials but also for clinical use.

This book has been written to be useful to the imager as well as the clinical trialist without any imaging experience. The editors hope that this book will be a useful contribution to the field of medical imaging in clinical trials and consolidate many different concepts into one location.

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# Part I
# Overview and Trial Management

# Chapter 1
# Medical Imaging Modalities

**Harris A. Ahmad, Hui Jing Yu, and Colin G. Miller**

**Abstract** Medical imaging is now utilized extensively in clinical trials for eligibility, efficacy, and safety evaluations. The uses of imaging span from a qualitative assessment of disease findings to quantitative assessments, each resting on diagnosis of the condition or change in the severity of the condition. This introductory chapter is designed for the novice with a limited or no background in radiological techniques and aims to briefly review the different imaging techniques, technology, terminology, and optimal imaging uses.

**Keywords** Radiology • Planar imaging • Tomographic imaging • Nuclear medicine • Ultrasound techniques

## Introduction

Medical imaging is now utilized extensively in clinical trials for eligibility, efficacy, and safety evaluations. The uses of imaging span from a qualitative assessment of disease findings to quantitative assessments, each resting on diagnosis of the condition or change in the severity of the condition. Several imaging modalities have emerged as the mainstay techniques for evaluating such evaluations in clinical trials across several therapeutic areas. The later chapters in this book will go into these therapeutic specific details.

This introductory chapter is designed for the novice with a limited background in medical imaging and aims to briefly review the techniques, technology, and

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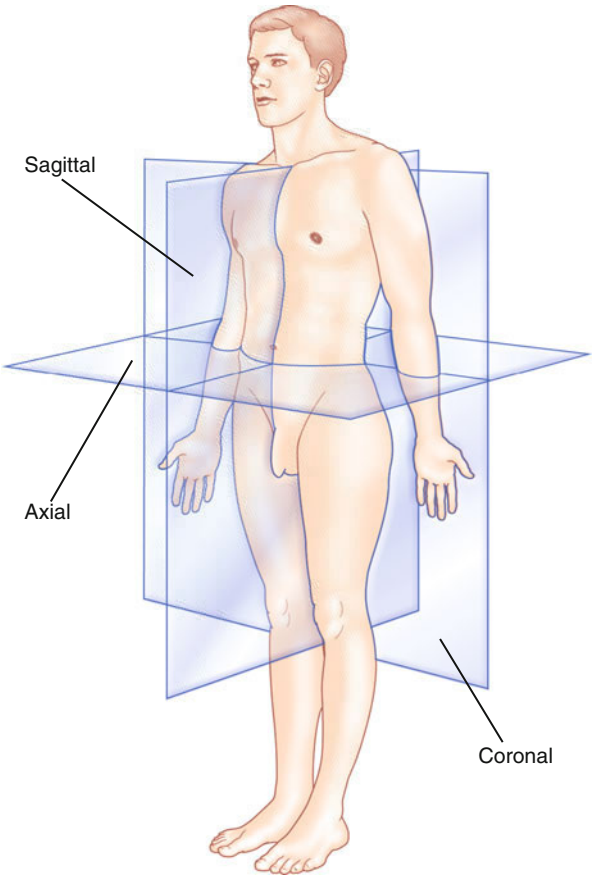


**Fig. 1.1** Three orthogonal directions of the medical imaging of the human body

terminology. It is not designed as an in-depth evaluation of any specific technique nor is it designed to provide the reader anything more than the basic set of pros and cons of each technique and its general applicability.

## Image Orientation

Before discussing the different imaging modalities, it is vital to understand the different orientations of which there are mainly three: axial, coronal, and sagittal. These are demonstrated in Figs. 1.1 and 1.2.

In medical imaging, the axial plane refers to the X–Z plane which divides the human body into superior and inferior positions, i.e., the head from the feet. In other words, each image in axial orientation is similar to a horizontal slice (Fig. 1.3).

The coronal is the X–Y plane which remains perpendicular to the ground and divides the human body into dorsal and ventral regions or front and back slices. This

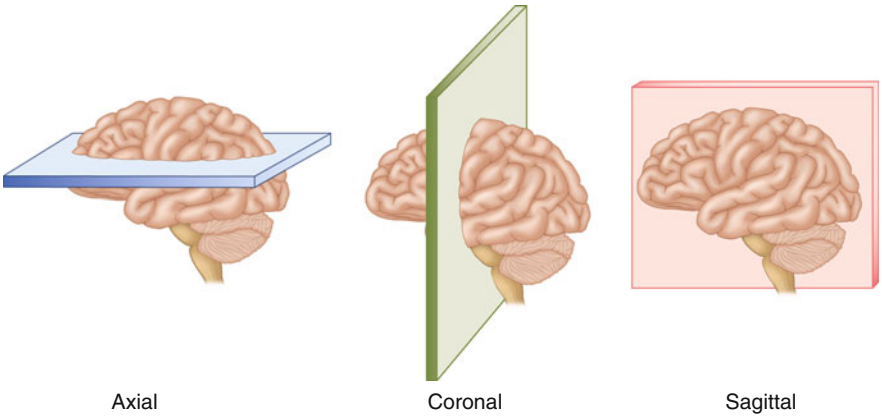


**Fig. 1.2** The three orientations for imaging (Modified with permission from http://users.fmrib.ox.ac.uk/~stuart/thesis/chapter_3/section3_2.html)

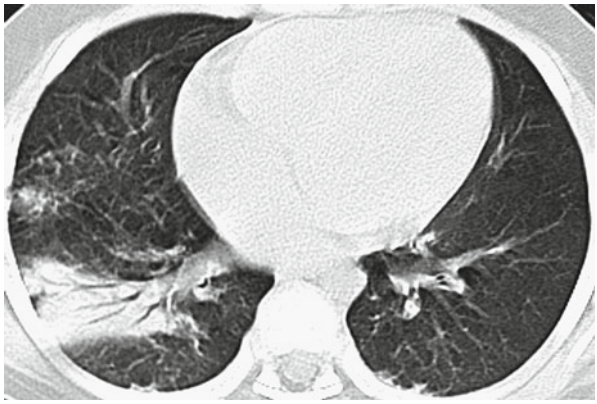

**Fig. 1.3** Computed tomography (CT) of the chest in axial view (Used with kind permission of Springer Science+Business Media from Levine et al. [17])

can also be termed the anterior-posterior or posterior-anterior view in modalities such as X-ray. The more colloquial term is a frontal view.

The sagittal plane, or lateral view, is the Y–Z plane and can be commonly referred to as the side view. It is also perpendicular to the ground and distinguishes the left and right side of the body. The midsagittal plane passes right through the center of the body to create equal halves with this side view. In radiographs, the sagittal view could be termed the lateral view because it is the side angle view of the patient's anatomy. Figure 1.4a–d demonstrates a lateral view of a chest radiograph.

Finally, there is the oblique plane where the beam or radiation passes diagonally through the body and divides it into two diagonal halves or in other words images at a slight angle to that of the traditional view. For example, an oblique coronal would be a front view sliced at a slight angle.

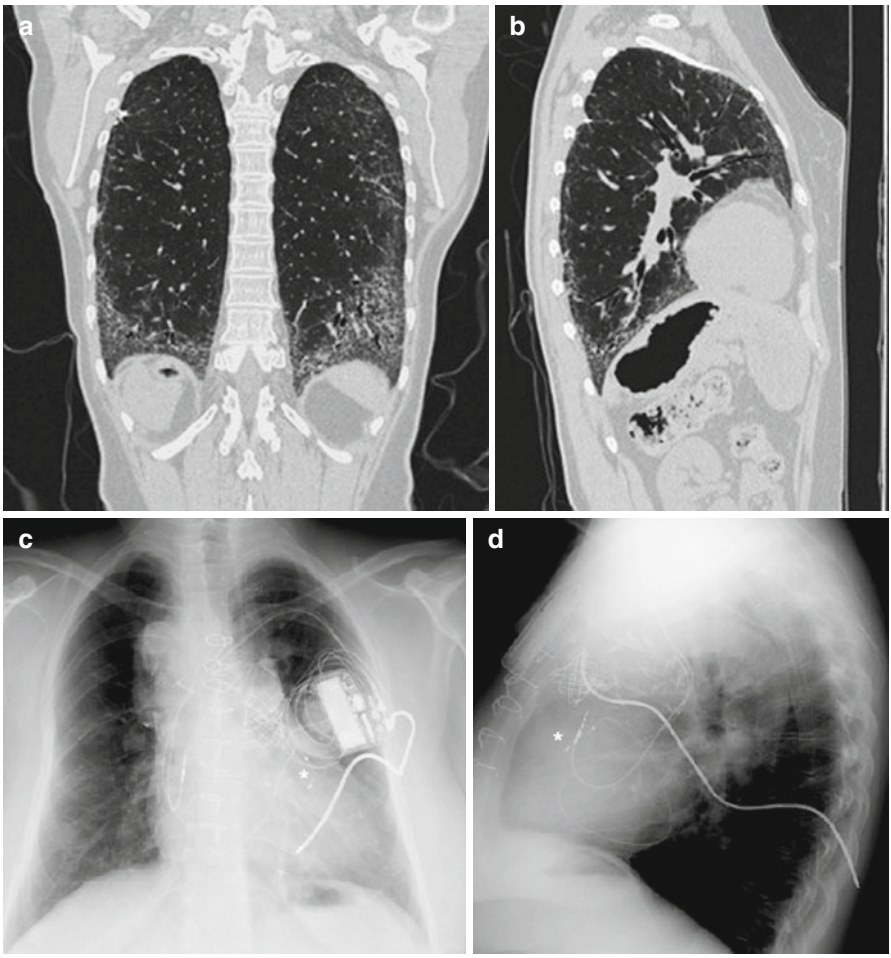


**Fig. 1.4** Chest CT in coronal (**a**) and sagittal (**b**) view. Chest radiograph in a posterior-anterior (**c**) and lateral view with heart indicated by * (**d**) (c, d: Used with permission of Springer Science + Business Media from Gupta et al. [18])

## Planar Imaging: X-Ray Techniques

### *Radiography/X-Ray*

The earliest form of medical imaging was the radiograph or X-ray. This was originally discovered in 1895 by Wilhelm Conrad Roentgen and rapidly became the mainstay of imaging assessment of clinical diseases where applicable for almost a century [1, 2]. Even with all the new complex imaging techniques available, radiography is still an invaluable tool, particularly for the imaging of the skeleton. Further,

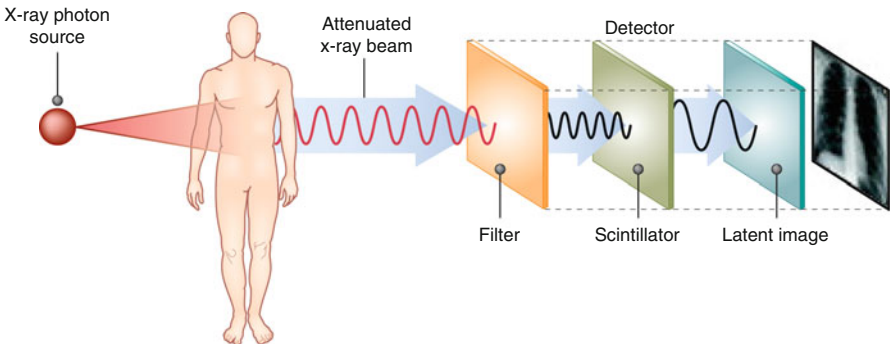


**Fig. 1.5** X-ray from source to image (Modified with kind permission of Springer Science + Business Media from Aberle et al. [19])

it continues to be heavily relied upon by the FDA for ongoing and future trial endpoints as a consistent comparison to historic data, e.g., rheumatoid arthritis (see Chap. 11).

In radiography, the production of an image starts with a high-voltage electric current which creates a stream of electrons which are fired at a metal plate. The resulting interaction is the creation of X-rays which are collimated into a beam. This source produces X-rays which are directed towards the desired object to be imaged such as the patient. Three results of this X-ray beam are possible and as a consequence produce an image. The X-ray could pass through the patient, be absorbed by the patient, and/or be scattered or in other words the beam is attenuated. In the original and basic form, the X-rays are detected on a sheet of film in an X-ray cassette. The film is developed and the resulting image is a negative image of the attenuation [2]. Nowadays, most radiology departments use a digital system using a detector and hence digital X-ray or DXR, as shown in Fig. 1.5.

The X-ray beam is attenuated more of the material through which it is passing. Hence bones, predominantly consisting of calcium, attenuate the beam to a much higher degree than soft tissue [2]. Any X-rays that are attenuated do not obviously expose the film and therefore appears as white or radiopaque. The density of the tissues among the patient can vary and therefore be the determining factor in how much of the X-ray beam is attenuated [1]. Figure 1.6 shows how the density of these tissues and their respective atomic weights can result in either a radiopaque or radiolucent appearance on X-ray. This difference creates the image as those tissues with a high density such as enamel of teeth or bone result in a radiopaque image, while those with a very low density such as air result in a "black" area or radiolucent area of the film. Air is the least dense patient area followed in ascending order by fat, water, bone, and metal [3].

Despite its limitation as a 2D image with only a spectrum of black to white, X-ray remains one of the most useful imaging techniques in clinical practice with the major advantages, disadvantages, and applications listed in Table 1.1. The low

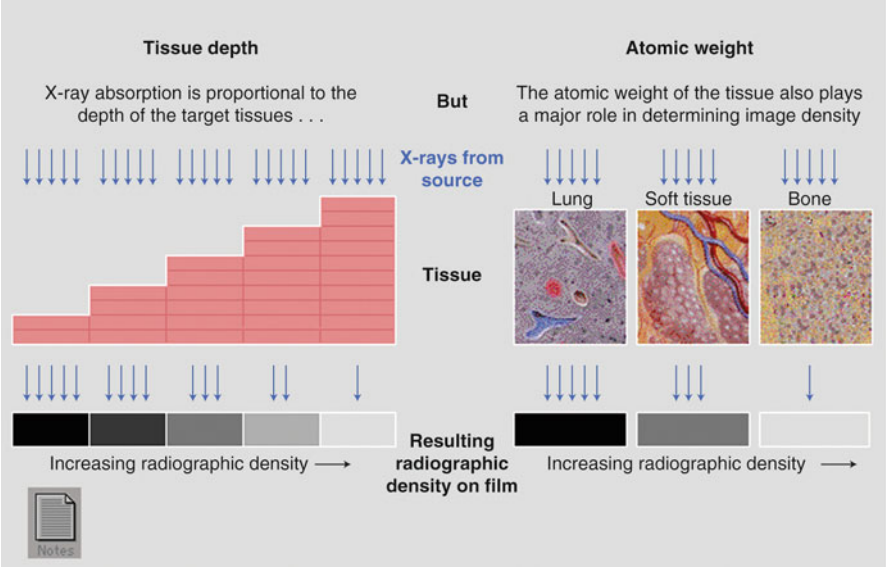


**Fig. 1.6** Relationship of radiographic density as a gray scale verses atomic weight (Modified with permission of Patrick Lynch, Yale University, from http://www.yale.edu/imaging/techniques/radiographic_density/index.html)

**Table 1.1** Radiography: applications, advantages, and disadvantages

| | |
|---|---|
| Applications | Fractures, bone diseases, pneumonia, pulmonary edema, intestinal obstructions, renal or gallbladder stones |
| Advantages | Low cost, widely available, portable, bedside |
| Disadvantages | Radiation, limited color spectrum, 2D information |

cost of equipment and acquisition is very attractive in comparison to more involved methods such as magnetic resonance imaging (MRI), computed tomography (CT), and imaging using radioisotopes. Further, the radiation dose is a quite a small fraction as compared to CT. Another advantage of course is the mobility of the X-ray acquisition at bedside of the patient, in the emergency room, or in a small outpatient practice. In clinical trials, this cost-effective, widely available, and well-practiced technique among radiology technologists contributes to its continued use as an efficacy endpoint in therapeutic areas such as rheumatoid arthritis, osteoporosis, and osteoarthritis. The chest X-ray continues to be of particular use for diagnosis and management of pneumonia, pulmonary edema and detection of calcified masses, while the abdominal X-ray can help detect and manage intestinal obstructions and associated pathology such as gallstones or renal stones. However, in clinical trials for oncology in which a volumetric or cross-sectional diameter assessment of lesions is paramount to determining response to therapy, the modalities such as CT and MRI clearly outperform planar radiography.

## *Dual Energy X-Ray Absorptiometry*

Dual energy X-ray absorptiometry (DXA or DEXA) was first described by Cameron and Sorenson in 1963 [4]. In this first publication they not only described the concept of single photon absorptiometry but also developed the basic underlying equations that are the core of DXA measurements. The basic operational concepts are that an X-ray beam of two discrete energies (or two X-ray beams) is passed over the body or region of interest and the attenuation of the X-ray beam(s) calculated, since the number of X-ray photons being emitted is a known quantity. The next underlying assumption is that the body consists of three compartments: fat tissue, lean tissue, and bone. In the area of soft tissue, there are two components – fat and lean – and so with two compartments of known attenuation coefficients at the two discrete energies, simultaneous equations can be built. With two unknowns (the amount of fat and lean) the equations can be solved, and the quantities of both tissues derived. This provides the information for body composition. A second major assumption is then made that the soft tissue composition juxtaposition to the bone remains consistent where over the bone and called the r or k value depending on manufacturer. This constant is then used to define a second set of simultaneous equations for soft tissue and bone mineral content (BMC). The quantity of bone can then be derived. The key measurement that is required is the bone mineral density (BMD) and the underlying equation is:

$$BMD = BMC / Area$$

The area of bone can be identified by an attenuation threshold methodology and hence the BMD of bone calculated. As can be appreciated by this definition, DXA is a 2D measurement technique and creates a so-called areal density of the bone and body composition. With all the inherent assumptions and calculations, DXA has been shown to be remarkably precise and accurate. Precision for spine and total body BMD and body composition measurements in healthy individuals is around 1 %. The precision measurements around the proximal femur (the other key measurement site for BMD, besides the AP lumbar spine) are 2–3 %. Accuracy has some different issues, since there is debate as to how the accuracy of areal BMD should be defined. There is not the space here to go into this debate but enough to say that there is a calibration offset between the two manufacturers of between 10 % and 15 %, which means this has to be accounted for in clinical trials along with calibration shifts etc. This is well documented in other textbooks [4] and will not be discussed here.

However, DXA is well established as an imaging modality and as a surrogate for fracture, at least in prevention of osteoporosis with the measurement of BMD. It is also a good measure of fat and lean tissue and has been used in many clinical trials to demonstrate the change in body composition. It is therefore extensively used as a modality in trials evaluating therapies in osteoporosis, obesity, diabetes, and sarcopenia. The body composition assessments using DXA are detailed further in Chap. 12. The BMD assessment is covered in more depth in Chap. 11. The two main

manufacturers of DXA equipment are GE Lunar (Madison, Wisconsin, USA) and Hologic Inc. (Bedford, Massachusetts, USA), and, unlike BMD values, they are more closely calibrated for body composition measurements.

## Computed Tomography

In essence, X-ray and computed tomography (CT) are very similar to each other in the physics of the technique. X-ray beams are targeted at the patient and, depending on the physical properties of the patient's differing tissues, they are attenuated; however, unlike "plain film X-ray," CT is a tomographic technique [1]. An early CT scanner consisted of a single X-ray emitter and an in-line detector that could rotate around the object or patient that was placed within the tube that housed the emitter and detector. A single "slice" or image of the body was scanned and the body moved a centimeter or more through the tube and the scan was repeated, thereby building up a series of tomographic images of the object or subject [2].

As technology progressed more detectors were introduced into the system and then more X-ray emitters. As the complexity grew, the acquisition speed increased and the slice thickness decreased. The X-ray tube and the electronic detectors are now present in the gantry or the circular structure. As soon as this information is received by the detectors, they are passed on to the computer for the calculation of attenuation of X-rays as shown in Fig. 1.7a, b. This structure can be rotated in different angles to take images of various portions of the body from various angles thereby producing an image in multiple planes as shown in Fig. 1.1.

In the modern systems it is not unusual to have 64, 128, or even 256 detectors and emitters which allow for very rapid acquisition. Furthermore the system spirals around the patient without the need for discrete steps (hence spiral CT), since the reconstruction algorithms on the image processing side have become more complex and elegant [5].

The differences in the physical properties of the tissue again compromise the characteristic images but now in an axial dimension. With this technique, CT provides a cross-sectional view of the body and can produce views in the 3 dimensions as described previously: axial, coronal, and sagittal. The differences in the densities of tissues are displayed on CT as Hounsfield units (HU) with a range of approximately −1,000 to +1,000. Air has the lowest HU ranging from −1,000 to −200 with metal at +500 to +1,000. The lower the HU, the "blacker" the color is on the CT image. Therefore, from black to white the sequential order are air, fat, water, soft tissue, blood, bone, and metal (which are the same for plane film X-rays). This distinct difference on a black and white color spectrum on CT is very advantageous for distinguishing key anatomy and pathology.

A contrast agent can be given on CT to obtain further distinction of certain anatomical structures and pathology. A contrast agent is often an injected or ingested liquid that has a distinct density as compared to physiologic tissues [3]. This allows

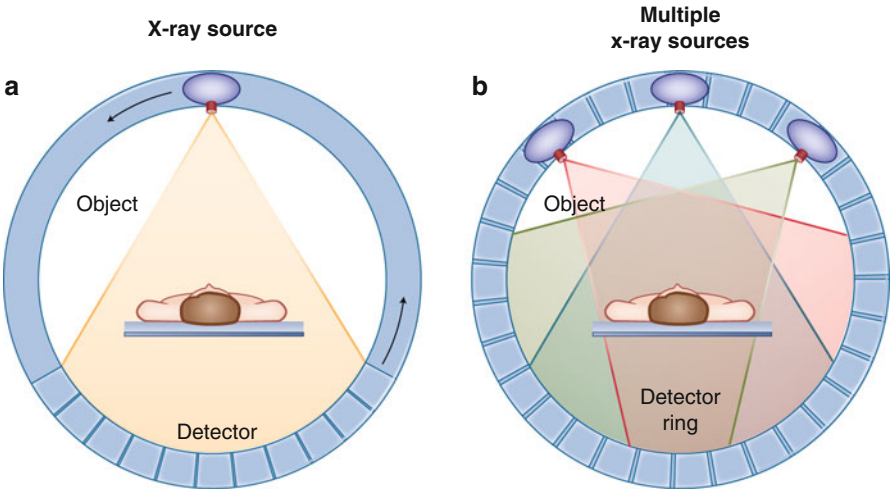


**Fig. 1.7** (**a**, **b**) Multiple X-ray sources (**b**) arranged in a configuration to produce a CT scan (Modified with permission from Zhang et al. [20])

**Table 1.2** Computed tomography: applications, advantages, and disadvantages

| | |
|---|---|
| Applications | Lesion assessment, trauma evaluation, evaluation of nearly all organ systems (gastrointestinal, neurologic, bone, vascular etc.) |
| Advantages | Cross-sectional view, tissue contrast, rapid acquisition |
| Disadvantages | Radiation, contrast allergy, cost |

for differentiation or "highlighting" of internal organs and structures for evaluation. For example, the function of an injected vascular contrast material is to raise the density of vascular structures and organs and delineate any pathology such as a mass in the bowel wall or aneurysm of the vascular wall. Bowel anatomy and associated pathology can also be distinguished through oral ingestion of the material before the scan. Proper timing and dosage is key to an accurate scan [5].

Numerous applications and advantages of CT as listed in Table 1.2 have made the modality one of the most clinically robust imaging techniques. A cross-sectional view as described previously with the delineation of different tissues with and/or without contrast has proven to be major advantages at all stages of clinical care. Examples include assessment of lesion size in oncology studies, cardiac disease detection and management, gastrointestinal disease diagnosis and management, and other numerous applications such as traumatic injury evaluation.

However, the disadvantage of radiation dosage and possible carcinogenic effects of the dosage have resulted in some concerns of overuse of the imaging modality. Further, contrast medium risk particularly in those patients with renal failure or allergic responses to the agent is also of concern. CT carries with it some of the less attractive features for the patient such as being in a closed machine and the adverse reactions to contrast administration such as nausea, vomiting, pain at the injection

site, as well as further compromise of renal function. These allergies and renal contraindications can be life threatening, and therefore, assessment of each patient's clinical status through proper history and lab work is often required delaying an otherwise urgent scan. Lastly, there is a high cost of acquisition and maintenance of a CT scanner in comparison to radiography.

## Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is used to image nuclei of atoms (e.g., $^{1}H$, $^{13}C$, $^{14}N$, $^{23}Na$, $^{31}P$) inside the body based on the principles of nuclear magnetic resonance (NMR). The NMR phenomenon was first reported in 1946, and the use of NMR was then established as a technique for in vivo imaging in the early 1970s, known as MRI today. Since then, several Nobel Prizes have been rewarded to the field of NMR, demonstrating the importance of such technology.

The majority of clinical MRI focuses on imaging hydrogen nuclei ($^{1}H$) which are abundant in the human body and have a relatively large magnetic moment. In the absence of an external magnetic field, the hydrogen nuclei in the body are randomly oriented, and the net macroscopic magnetic moment is zero. In the presence of an external magnetic field (i.e., a patient placed in a MR scanner, Fig. 1.8), water becomes polarized such that hydrogen nuclei are oriented in the direction of the applied magnetic field.

To obtain a MR signal, a radio frequency or RF pulse is applied. Protons absorb energy from RF excitation that brings them out of equilibrium. When the RF pulse is turned off, the system of protons relaxes back to its equilibrium while dissipating the absorbed energy to their surroundings (Fig. 1.9a, b). The spins return to their equilibrium usually by two spin relaxation mechanisms known as T1 or longitudinal relaxation and T2 or transverse relaxation (Fig. 1.10a, b). T1 relaxation is caused by the protons giving up their energy to the surrounding environment. The T1 relaxation time describes the time constant for restoring the net magnetization to 63 % of its original strength in the direction parallel to the applied field (i.e., longitudinal magnetization). T2 relaxation is caused by protons exchanging energy with their neighbors, resulting in the loss of magnetization perpendicular to the external field (i.e., transverse magnetization). The T2 relaxation time represents the time it takes for the transverse magnetization to decay to 63 % of its original strength. Since the physical properties of the tissue affect the T1 and T2 relaxation times, tissue contrast can be generated [6, 7].

Tissues differ in relaxation constants and thus measuring the MR signal during the relaxation period provides image contrast which translates into grayscale visualization, unlike CT, grayscale intensity reflects tissue density. Table 1.3 shows the list of water relaxation time (in ms) at 1.5 T [8].

By changing the imaging parameters, the images can be "weighted" to reflect one type of relaxation more than another. Within the MRI pulse sequence, the echo