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PET-CT and PET-MRI in Neurology

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Foreword

Neuroimaging can be separated into two broad categories: (i) structural or anatomical imaging and (ii) functional or molecular imaging. Interestingly, one could claim that functional imaging preceded structural imaging by referring to the studies of the Italian neuroscientist Angelo Mosso, who invented the "human circulation balance" in Turin, during the late 1880s. This device could noninvasively measure the redistribution of blood during emotional and intellectual activity. Early in the twentieth century, Walter Dandy (while at Johns Hopkins in Baltimore) developed ventriculography and pneumoencephalography that allowed neurosurgeons for the first time to visualize structural changes in the ventricular system on x-rays that were caused by brain lesions. In the late 1920s, Egas Moniz, professor of neurology in Lisbon, introduced cerebral angiography, whereby both normal and abnormal blood vessels in and around the brain could be visualized with great accuracy (he received a Nobel Prize in 1949). More detailed anatomic images of the brain became available through computerized axial tomography (CAT or CT), which was introduced and refined in the 1960s and 1970s by Oldendorf, Hounfield, and Cormack. This effort translated a research instrument into a safer noninvasive clinical tomograph for imaging the skull and brain and other organs. CT is still extensively used today, which is reflected by the commonplace availability of CT scanners in most hospitals.

Imaging the brain with radiopharmaceuticals was developed in parallel to CT during the 1960s by Lassen, Ingvar, and Skinhoj in Scandinavia. Studies involving Xenon-133 inhalation to image cerebral blood flow used multiple external radiation detectors, plus mathematical algorithms to reconstruct two-dimensional radioactivity images (the forerunner of single-photon emission computed tomography (SPECT)). These blood flow images represented the first modern "functional neuroimaging," reflecting changes in cerebral blood flow from brain activation associated with speaking, reading, visual, or auditory perception and voluntary movement.

Positron emission tomography (PET) was initially developed by Gordon Brownell and William Sweet in the 1950s at the Massachusetts General Hospital, in Boston. A major expansion occurred in St. Louis, where the first positron imaging device was constructed by Ter-Pogossian, Hoffman, and Phleps. The first human PET scanner was developed in 1973 with a hexagonal array of detectors. The inclusion of short-lived oxygen-15-labeled water for PET imaging of cerebral blood flow (allowing multiple studies to be performed on the same subject), along with the ability to generate statistical

parametric maps (SPM) of cerebral activation, was an active area of research in the 1980s and 1990s. This was a major advance in neuroimaging and the assessment of cognitive function of the human brain, namely, the ability to image neural activity in specific brain structures while performing specific tasks, in both normal subjects and in individuals with specific neurological diseases. Currently, such studies are primarily performed using the MRI BOLD technique.

Concurrent with improvements in tomographic imaging technology, there was a parallel expansion in radiochemistry and radiopharmaceutical development for both SPECT and PET in the 1980s and 1990s, which continues to this day. Initially there was a focus on cerebral glucose utilization and neuroreceptor imaging (as PET imaging was limited by head-only tomographs at that time). With the advent of whole-body scanners, FDG PET imaging was rapidly adopted by oncologists to stage the extent and progression of disease and to monitor disease response to therapy. With the current focus on molecular-targeted medicine and individualized patient care, there is an expanding clinical demand to develop new target-specific radiopharmaceuticals for both diagnosis and therapy (theranostics), particularly in oncology where targeted radiopharmaceuticals are being used to assess the response to therapy.

Clinical magnetic resonance imaging (MRI)/magnetic resonance spectroscopy (MRS) was applied shortly after PET and provides both structural and functional images. The absence of radiation exposure and necessity of having a cyclotron and radiochemistry facility nearby, coupled with high-resolution images, were significant advantages and led to the rapid adoption of this imaging technology. Functional MRI/MRS (including BOLD, perfusion/diffusion, arterial spin labeling MRI, etc.) is increasingly being used and has led to MRI/MRS becoming the dominant neuroimaging modality over the past 15 years. This is reflected by the 25,000-plus clinical and research MRI scanners that exist worldwide.

Hyperpolarized MRI/MRS is a new imaging technology that provides a marked increase MRS signal from hyperpolarized molecules. It is currently a research tool that can be used to monitor metabolism, such as the conversion of pyruvate-to-lactate in tumors. This enhanced MRS molecular imaging strategy has evolved over the past decade, but remains technologically challenging. It requires the use of stable (nonradioactive) isotopes (e.g., 13C) for incorporation into specific molecules for hyperpolarization by a special hyperpolarization unit that has to be located close to the scanner, since hyperpolarized molecules decay rapidly (minutes).

In this prelude, I have briefly traced the rapidly evolving history of selected imaging modalities that have contributed to both structural and functional "neuroimaging." The benefits of the shift to hybrid PET/CT and PET/MR imaging are now widely recognized, and this shift is reflected in the title of this monograph and the individual contributions to this monograph.

New York, USA Ronald G. Blasberg, MD

Preface

The past decade has been characterized by fast technological growth. This led to the discovery of increasingly sophisticated diagnostic technologies in molecular imaging. Among these, positron emission tomography (PET) has been the imaging technique with the greatest clinical impact in oncology as well as in neurology and cardiology. Technological innovation has subsequently led to the introduction of hybrid modalities, such as PET/CT and more recently PET/MR.

New technologies are generally expensive, and some of the most frequently asked questions are relative to the cost effectiveness and the advantages of the new technology as compared to those previous. Generally, only several years after the introduction of a technology is there enough data to understand what the clinical impact and advantage of the new technology is.

Unfortunately, it is not always possible to wait too long before deciding whether to invest or not in a new technology. Therefore, a difficult problem to overcome is how to plan the acquisition of new technology in the presence of partial and little consolidated data. Without a planning strategy for healthcare development, there is the risk of acquiring potentially useless technology or by contrast wasting too much time before introducing a new useful technology in to clinical practice. In this book we have tried to apply the SWOT analysis to the evaluation of the strengths, weaknesses, opportunities, and threats of hybrid technologies.

SWOT analysis is a decision supporting tool designed for incorporating internal (strengths and weaknesses) and external (opportunities and threats) factors into organizational or technological change planning.

This analytical approach was previously used mainly in policy research to systematically analyze organizations' environments and only recently has been introduced in healthcare systems. When properly used, SWOT analysis may provide decision-makers a strong and structured basis for strategy development. SWOT analysis is performed through the collection of key informant perspectives, which are considered an essential part in achieving the identified objectives.

In this attempt, we have involved many researchers, clinicians, manufacturers, and decision-makers, a large group of experts, distributed around the world involved with different purposes in hybrid technologies. We are grateful to all of them for the essential contribution given to the achievement of this complex endeavor. We wish also to express our gratitude to the manufacturers who gave their contribution to the survey giving us the opportunity to

understand their point of view (Pier Paolo Buó, GE healthcare Srl; Sandro Paini, Philips Spa; Alessandra Tocchio, Siemens Healthcare Srl). Finally, we are grateful to decision-makers for time devoted to the survey, including their opinion of the analysis that gave us the opportunity to complete our data with the point of view of a relevant stakeholder. Finally, we wish to express our gratitude to Dr. Gianfranco Conzi for his significant contribution to the technological renovation project successfully carried out in our hospital.

La Spezia, Italy Andrea Ciarmiello

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Part I

Basics

Physics of Hybrid Imaging

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Girolamo Garreffa, Gisela Hagberg, and Luca Indovina

1.1 Introduction

The main purpose of multimodality imaging is to provide an advanced diagnostic tool by combining measurements of anatomy and physiology obtained with different techniques – in particular PET-TC and PET/MRI. Multimodality imaging can refer to two main fronts each characterized by the space-time context of data acquisition. Either such morphofunctional, multimodal images are generated by fusing images acquired with each technique separately and at different times or they may arise from truly contextual or simultaneous acquisitions. In this latter case, we are speaking of a hybrid system. There are many potential advantages of hybrid imaging, since ideally both anatomical and functional information can be obtained at the same time without any time delays between modalities and without any need for coregistration of the image information. Beyond this attractive prospect, there are some pivotal synergistic effects that come with the integration of multiple modalities, mainly relating to correcting PET data to yield truly quantitative information while maximizing the signal-to-noise ratio. In this chapter we shall briefly recall some basic physics concepts of each single and combined imaging technique: PET, CT, and MRI.

1.2 Position Emission Tomography (PET)

Positron emission tomography (PET) is an imaging modality, or radiotracer imaging technique, born in the early 1970s [1, 2] which has unique advantages as an investigative tool for studying biological functions at the molecular level. Tracer-molecules, labeled with radionuclide-emitting positrons (e^+), are injected into the subject under investigation with the aim to track biochemical and physiological processes in vivo. When a positron is emitted by a radionuclide, it will travel a few millimeters before interacting with an electron in the surrounding tissue causing the annihilation process: the two oppositely charged particles will be completely converted

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into two photons emitted into opposite directions with a minimal energy of 511 keV (Fig. 1.1). The role of PET is to measure the exact position of the point of annihilation through detection of the two photons emitted during the annihilation process in coincidence and through detection of the exact time that the two photons travel before reaching a pair of detectors placed opposite to each other in a ring containing several such detector pairs in a PET device. Today, PET is able to detect the position of annihilation events (i.e., the position of radiolabeled molecules in the patient body) through the so-called time-of-flight (TOF) technology (Fig. 1.2). With time-of-flight PET imaging, the relative time difference (Δt) between the detection of the two annihilation photons is used to determine the most likely location (D) of the annihilation event along the line of annihilation or, using technical terminology, along the line of response (LOR) as follows:

$$D = c\Delta t / 2 \tag{1.1}$$

where c is the speed of light, i.e., the speed at which the annihilation photon travels toward the detector.

Radionuclides used in PET (most common are, e.g., ^{11}C, ^{18}F, ^{13}N, ^{15}O, ^{68}Ga) emit positrons because they are in a particular unstable nuclear composition. They emit a positron in order to decay to a stable nuclear state with a characteristic half-life, $T_{1/2}$ (h), which represents the time required to reduce the initial number of positron-emitting nuclei (i.e., the initial activity A_0) by one-half. The decay process is described by an exponential law arising from the circumstance that the number of events (decaying nuclei) per second is always proportional to the number of undecayed nuclei (i.e., $A(t)$) at a given time. Mathematically, this can be expressed as

$$A(t) = A_0 \exp\left(-\lambda t / T_{1/2}\right) \tag{1.2}$$

The half-life $T_{1/2}$ of different positron-emitting radionuclides ranges between 10^{-6}s and 10^{10} years. The activity, A, is measured in units of Becquerel (Bq) where 1 Bq = 1 decay event per s or also in Curie (Ci) where 1 Ci = $3.7 \cdot 10^{10}$ decay events per s, a common value in practice is 1 mCi = 37 MBq.

PET scanners consist of several rings of detector elements available to measure *coincidence events* from the annihilation process of positrons

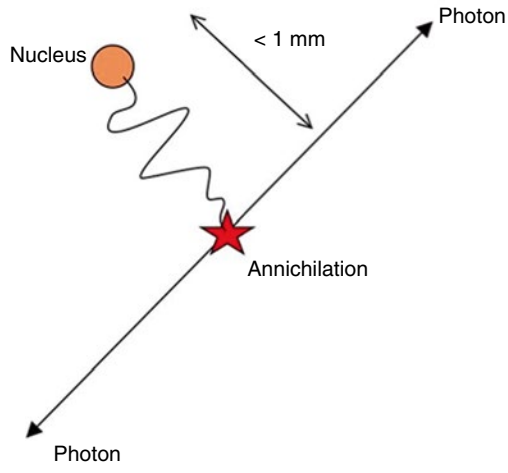

Fig. 1.1 Annihilation of positron and electron with production of two photons: generally after a submillimeter displacement from its origin

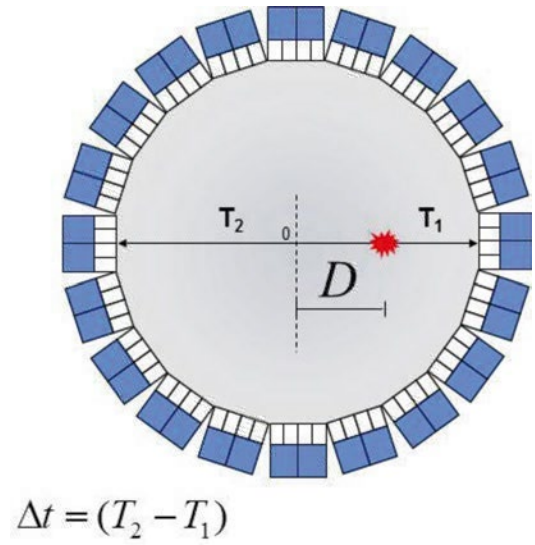

Fig. 1.2 Time-of-flight (*TOF*) technology: Δt is the time difference between the detection of the two annihilation photons used to determine the most likely location (D) of the annihilation event along the line of annihilation or, using technical terminology, along the line of response (*LOR*)

in the scanner. From the beginning of their clinical use, PET scanners were built with a number of detector rings that enabled an axial field of view ranging from 15 to 25 cm. PET images are generated from *true coincidences* measured in the detector elements and refer to a big number of photons. It means that PET images are performed avoiding *scattered and random coincidences*, which are discriminated and considered as background events (Fig. 1.3).

In the early years of PET systems, in an attempt to eliminate scatter and random coincidences, annular septa (~1 mm tick and radial width of 7–10 cm) made of tungsten or lead were inserted between rings. Only direct coincidence events between detector pairs placed in the same detector ring were recorded (2D data acquisition mode) reducing scatter coincidences to less than 10–15 %. In 2D mode (i.e., 2D PET), direct plane events or cross plane events are detected in order to maximize the number of events available to generate PET images. Considering the overall sensitivity, defined as the total true activity detected in the scanner in term of true coincidences with respect to the total activity present inside the scanner, the overall sensitivity in 2D mode is not bigger than 2 % or 3 % [3]. In more recent PET systems, to increase this value, septa are retractable or are not available at all (3D mode). All coincidence events from all possible combinations of detector pairs, regardless of position, are counted (Fig. 1.4). The 3D mode (i.e., 3D PET) increases the number of scattered coincidences to 30–40 % but also increases the overall sensitivity by a factor of almost 4–8.

Concluding this brief introduction to PET systems, it is important to highlight that PET imaging can be used for quantitative imaging. It means that physicians know that PET images are able to provide information regarding the specific activity (kBq/ml) contained in a specific volume of interest (VOI). To obtain quantitative data by PET, the number of true coincidence events has to be corrected for attenuation. Indeed, the 511 keV annihilation photons are attenuated, and this attenuation may differ between photons depending on the density and the composition of the tissue traversed before reaching the detector. In stand-alone PET imaging, a good scattering and attenuation correction can be achieved based on additional transmission scans, acquired by the use of rotating radiation rods as gamma ray sources (typically consisting of ^{68}Ga/^{68}Ge). The source is rotated around the scanner bore to uniformly expose all detector pairs to radiation, prior to image reconstruction and generation of correction maps [4]. However, for traditional transmission scans acquired by 3D PET, the increased amount of scattered radiation reduces the available signal-to-noise ratio to such a point that it is hardly possible to obtain an accurate attenuation correction using this approach.

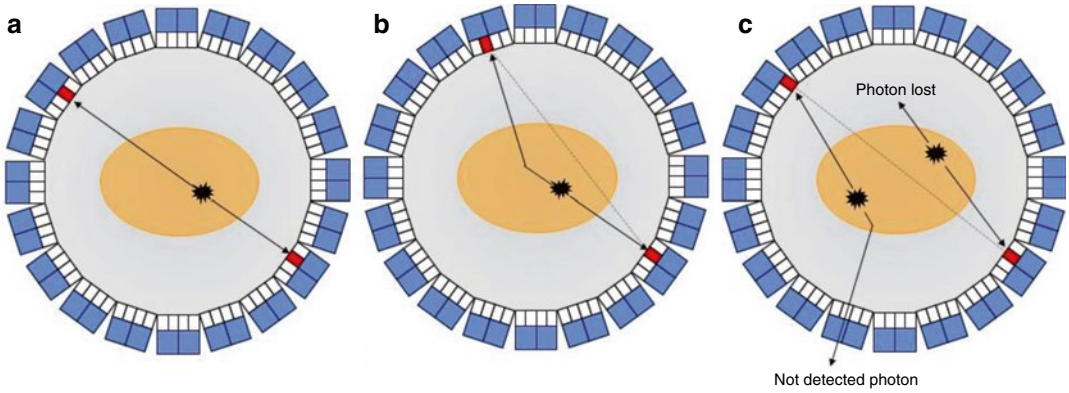

Fig. 1.3 Coincident events: true coincidence (**a**), scattered coincidence (**b**), and random coincidence (**c**) are plotted. Only true coincidences are able to give the exact annihilation position and they are used to generate PET images