

Chapter 2

The Molecular Imaging Pathway to Biomedical Physics

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2.1 Introduction

According to Policy Statement 1 issued by the International Organization for Medical Physics (IOMP) [1], “Medical physics is a branch of physics that is concerned with the application of physics concepts and techniques to the diagnosis and treatment of human diseases.” Although including the many areas in which medical physicists are not dealing with ionizing radiation (e.g. physiology, neurology, audiology), the well-known domains of medical physicists are radiotherapy, radiological diagnostics, and nuclear medicine. Traditional medical physics as a branch of applied physics has been driven mainly by the physical roots, that is, development of instrumentation and measurement techniques, specifically in the radiological fields concerning quality assurance, optimization of radiation applications, modelling, and simulation. With the rapid progress of biology and its ever-increasing role in all medical sciences, medical physics also is challenged to incorporate more and more biological knowledge, particularly what is designated with the buzz terms *molecular biology* or *molecular medicine*. In fact, nuclear medicine has been per se a “molecular” science since its beginnings, with radioisotopes used to bind to specific biomolecules either as biomarkers or as therapeutic weapons to attack malignant cancer cells, for instance. However, in radiotherapy and radiodiagnostics, the clinical impact of molecular biology is still limited; during the last decade, this has significantly increased. In particular, the potential use of molecular biology for the entire radiation treatment process can hardly be overestimated. Accordingly, also the medical physicist cannot ignore the current trend of integrating more biology knowledge in daily work, particularly when including molecular imaging data in the treatment optimization process. Actually, medical physics is expanding towards biomedical physics, as shown by the increasing number of departments and institutions with “biomedical physics” included in their name. It is molecular imaging that has an impact on radiotherapy and hence challenges the medical physicist to

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appreciate the new face of traditional medical physics, more appropriately termed *biomedical physics*.

As an example of the closer entanglement of medical physics and biology, this chapter illustrates some obvious opportunities and promises of the molecular approach of radiotherapy and its impact on medical physics or, better, biomedical physics.

2.2 Fundamentals of Molecular Imaging

Molecules are the building blocks of all life. Any failures within the molecular and cellular processes may lead to disorders of organs, organ systems, and normal tissue. Still a major life threat, cancer may originate from just a single aberrant molecule of a single cell. Medical interventions at the earliest stage therefore present a challenge: detection of such molecular aberrations. Prevention, diagnosis, and therapy of cancer are hoped to be most effectively performed at the molecular level.

The term *molecular imaging* was coined by Weissleder and Mahmood [2]. Accordingly, molecular imaging aims to investigate the molecular signature of diseases through “in-vivo characterization and measurement of biologic processes at the cellular and molecular level.” Molecular imaging addresses any molecular modification at the genomic, transcriptomic, proteomic, metabolomic levels, ranging from subcellular and cellular structures to the tissue and finally the organ.

Some biological processes accessible via imaging and relevant in cancer diagnosis and therapy are glycolysis, DNA synthesis, amino acid and lipid metabolism, apoptosis, tumour angiogenesis, and hypoxia.

Molecular imaging is based on the selection of an adequate technique combined with a suitable contrast agent. The most appealing imaging techniques are by far positron emission tomography (PET) and magnetic resonance (MR). Remarkable progress has been observed in ultrasound and optical imaging technologies, such as fluorescence absorption, reflectance, and luminescence. The characteristics of some imaging systems with particular relevance for clinical application are summarized in Table 2.1.

To increase efficiency, hybrid imagers have been developed, such as PET combined with computed tomography (CT), which combines high-resolution CT anatomical imaging and high-specificity and -sensitivity PET biological imaging in the same system. In the clinical environment, PET-CT imagers are invaluable in localization, treatment planning, and treatment monitoring for cancer. Further clinical hybrid scanners are single-photon emission computed tomography (SPECT) combined with CT and, most recently, MR-PET systems.

The visualization of aberrant molecules or molecules that are an integral part of a certain biological process needs essentially imaging methods with a high degree of specificity and sensitivity. Therefore, it is the target that defines the selection of the contrast agent. Thus, the specificity of molecular imaging is to a great deal dependent on the imaging agents, which in turn depend on the imaging system. Widely

Table 2.1 Characteristics of some molecular imaging systems with direct impact on clinical application

Feature	Ultrasound	CT	MRI	SPECT	PET
Image acquisition method	Reflexion at interfaces	X-ray attenuation	Electromagnetic excitation of nuclei; relaxation	Single-photon emission of radioisotopes	β^+ -Decay of radioisotopes, annihilation radiation
Spatial resolution	1–3 mm	30 μm	<30 μm – 1 mm	0.3–1.5 mm	1–4 mm
Acquisition time	10–30 s	1 s per scan	1–10 min	10–60 min	10–80 min
Sensitivity	Good	Low	Low/medium	High	Very high
Specificity	Low	Low	Medium	High	Very high

CT computed tomography, *MRI* magnetic resonance imaging, *PET* positron emission tomography, *SPECT* single-photon emission computed tomography.

used molecular imaging agents are radiopharmaceuticals, paramagnetic materials, fluorescent/luminescent materials, and microbubbles. Reporter gene imaging, which provides data on the location, duration, and extent of gene expression, is rapidly progressing, particularly in biomedical research. More recent molecular imaging modalities are based on nanoparticle vehicles, smart contrast agents, and target-specific optical or radiolabelled agents.

2.3 Application of Biological Imaging in the Radiotherapy Process

There is clinical evidence that small cancers that have not yet metastasized can be cured by local treatment (i.e., surgery or radiotherapy or combined modalities). In this regard, the potential of molecular imaging is early detection of cancer. A successful cancer treatment requires elimination of all stem cells of a particular tumour whilst minimizing the radiation damage to the surrounding normal tissue. Hence, the strategy of radiation therapy is to modulate the delivered dose distribution correspondingly. Combining anatomical and biological imaging (multimodal imaging) is essential in all four phases of the radiotherapy treatment process: (1) tumour staging, (2) target volume definition, (3) treatment delivery and monitoring, and (4) treatment response. This sequence may be considered as a feedback loop in which tumour staging is the prerequisite for the choice of the most efficient therapy scheme, and the response to the selected treatment allows assessment of the prognosis of the disease. In clinical practice, contouring of target volumes benefits most from combining, for instance, CT and PET data sets. A second area in which only molecular imaging provides the essential information is biological tumour heterogeneity. Modern linear accelerators equipped with multileaf collimators are capable of applying intensity-modulated radiation therapy (IMRT) beams.

Ling [3] pioneered the concept of biological adapted therapy, that is, to modulate the dose distribution in the target corresponding to the profile of varying radiation sensitivity throughout the tumour. The essential steps of this concept, often called *dose painting* or *dose sculpting*, are (1) selecting appropriate biomarkers, (2) imaging the biological tumour subvolumes, (3) transforming the image data sets into a dose prescription, (4) optimizing the dose distribution and finally (5) delivering the modulated dose distribution. Hypoxia is well established, causing resistance in radiation therapy. In many malignancies, hypoxia has been identified as a major negative prognostic factor for tumour progression. Therefore, enhancing the dose locally at hypoxic tumour subvolumes is expected to lead to better treatment results. As surrogate markers for tumour hypoxia, PET imaging ^{18}F -Misonidazole (Miso), ^{18}F -labeled azomycin-arabioside (AZA), and ^{60}Cu -labeled diacetyl-bis (N4-methylthiosemicarbazone) (ATSM) are used, and the first clinical studies have been just initiated. Dose prescription is difficult, but by applying the linear-quadratic model, an assessment can be made. The last step, transforming activity to dose distribution, is typically based on biological models. In general, there is rather poor information about the dynamics of the temporal variation of the tracer distribution. According to our own measurements on patients with head and neck tumours, there are significant changes during the initial phase immediately after injection of the tracer that require at least about 5 min to achieve some balancing. Translation of the concept of biological-driven dose modulation into clinics is not a common standard yet.

Treatment monitoring and response assessment are some of the most promising features of molecular imaging. The benefits for clinical outcome are the adaption of the treatment to the response, to indicate earlier whether a tumour responds to treatment, to monitor receptor expression with specifically labelled receptor ligands, and to monitor tumour response by labelling cell metabolites. Traditionally, standard CT anatomic evaluation of a tumour treatment needs several months to identify morphological changes. In contrast, when measuring the ^{18}F -fluorodeoxyglucose uptake it is possible to detect tumour regression or recurrence in just a few hours.

2.4 Conclusion

Molecular imaging as the hallmark of individualized therapy becomes more and more important in radiotherapy, ranging from early tumour detection via biologically and physically optimized treatment planning, image-guided treatment delivery, and early response assessment of the treatment. Accordingly, this trend challenges the medical physicist to incorporate more biological knowledge into his or her clinical work. Traditional medical physics is slowly mutating towards biomedical physics. Current education and training schemes for medical physicists should be adapted properly to include more biology and imaging technology.

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