Expert Review of Medical Devices

ISSN: 1743-4440 (Print) 1745-2422 (Online) Journal homepage: informahealthcare.com/journals/ierd20

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To cite this article: Nathan C Hall, Jun Zhang, Stephen P Povoski, Edward W Martin & Michael V Knopp (2009) New developments in imaging and functional biomarker technology for the assessment and management of cancer patients, Expert Review of Medical Devices, 6:4, 347-351, DOI: 10.1586/erd.09.21

To link to this article: https://doi.org/10.1586/erd.09.21

Published online: 09 Jan 2014.

New developments in imaging and functional biomarker technology for the assessment and management of cancer patients

Expert Rev. Med. Devices 6(4), 347–351 (2009)

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"The potential impact that molecular imaging may have on the field of oncology ... ranges from improving preclinical assessment of drug efficacy to determining the effectiveness of therapies at earlier stages during the performance of clinical trials."

Molecular imaging, as it relates to oncology, encompasses a diverse spectrum of both imaging modalities and targeted tracers [1–7]. The impact of molecular imaging on oncology extends from guiding preclinical development of targeted biomarkers and therapeutic agents, to assisting in the diagnosis and staging of malignant diseases, as well as the monitoring of therapeutic response. To date, the use of imaging with and without targeted biomarkers to assess functional measures of disease has yielded promising results [5]. These early results have sparked a broadened interest and rapid growth in molecular imaging technology and the further development of targeted biomarkers [6,7]. The most significant growth has been in the development of combined functional–anatomic imaging modalities (e.g., PET/ computed tomography [CT], single photon emission CT [SPECT]/CT and PET/MRI), as well as in targeted tracer development for use with these modalities [8,9].

One of the most significant limitations impacting the progress of cancer therapy research has historically centered upon having inadequate information regarding tumor response when assessing the effectiveness of drug therapies, both in the preclinical and clinical environment [10–12]. Cancer researchers and clinicians need adequate and accurate information early in the process of drug development. Providing this information has the potential to focus resources in the most promising directions and speed up the process of drug development. Molecular imaging technology has demonstrated great promise for accomplishing this goal.

"...these technologies may decrease the costs associated with the development of new therapeutic agents by allowing for *in vivo*, noninvasive, serial assessment of the biological response..."

The potential impact that molecular imaging may have on the field of oncology, by incorporating targeted biomarkers and functional measures, ranges from improving preclinical assessment of drug efficacy to determining the effectiveness of therapies at earlier stages during the performance of clinical trials [6,7,10–12]. Utilization of these technologies may decrease the costs associated with the development of new therapeutic agents by allowing for *in vivo*, noninvasive, serial assessment of the biological response within an animal model during preclinical evaluation, rather than by traditional *in vitro* cell-culture techniques [13–15]. Herein, we present an overview of the latest developments and progress of imaging-targeted biomarkers and functional measures as they relate to cancer detection and therapy.

EXPERT REVIEWS

  ISSN 1743-4440

Radiopharmaceutical development

Traditionally, preclinical assessment of drug efficacy has largely been performed with *in vitro* cell culture techniques. While these methods are not technically complex, they limit the ability to accurately assess the effects of therapeutic agents in the functional biological setting.

Recent developments in microimaging technology, such as micro-PET/CT/SPECT/MRI systems, have made the assessment of pharmacologic and therapeutic effects of therapeutic agents *in vivo* possible [10,13–15]. These imaging modalities have the ability to provide information on desirable or undesirable biochemical and physiologic pharmacological effects, kinetic information related to drug delivery and drug interaction with the desired target, and information related to absorption, distribution, metabolism and elimination of drug candidates.

Multiple classes of molecular imaging-targeted tracers are being developed, including, but not limited to, agents targeted at protein expression, reporter gene imaging, cell proliferation, blood flow, hypoxia, apoptosis, pharmacokinetics, target inhibition and tumor response to therapy [7,16,17].

One of the key challenges faced in the process of developing these targeted radiopharmaceutical biomarkers is the fact that obtaining US FDA approval for use in humans is a lengthy and difficult process [11,18]. Therefore, many of the promising and proven targeted biomarkers used in preclinical studies are not currently available for use in clinical trials.

Imaging modality development

Over the past decade, significant advancements have been made in PET- and SPECT-instrumentation technology [19–24]. One of the most important advancements is the development of combined imaging devices, such as PET/CT and SPECT/CT [24]. These combined modalities allow for the acquisition of anatomic and functional data sets on the same equipment without moving the patient. Automated hardware–software fusion of these data sets allows for more accurate anatomic correlation of functional/metabolic findings and has significantly improved the specificity and accuracy of PET and SPECT. The developments in instrumentation technology apply to both clinical scanners and preclinical and/or small animal scanners. Combined PET/CT and SPECT/CT clinical scanners are currently widely available [24]. Imaging devices combining all three modalities are also currently available for use in the preclinical setting.

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The development of combined PET/MRI scanners for whole-body applications has great potential for revolutionizing functional imaging [25–33]. MRI offers the benefit of improved soft tissue contrast and does not expose patients to the ionizing radiation of CT. Combined PET/MRI holds great potential for expanding upon functional–functional and functional–anatomic imaging platforms.

The rapid growth of MRI technology, including higher field strengths, functional MRI, magnetic resonance spectroscopy and diffusion-tensor imaging, combined with new developments in functional radiotracer-guided metabolic imaging, provides limitless combinations that could revolutionize the diagnosis, staging, restaging and assessment of the response to therapy in oncology patients [34,35]. Used in conjunction with PET/CT (low dose for attenuation correction) for whole-body surveys, PET/MRI could provide a unique biochemical, physiologic and metabolic picture of the tumor for guiding therapy and assessing therapy response [25]. Software fusion of PET/CT and MRI has demonstrated diagnostic benefit over either modality used alone [26–29]. Hardware-combined PET/MRI prototype scanners appear promising [30]. With the development of whole-body PET/MRI technology, these preliminary advancements can be utilized to advance functional–functional and functional–anatomic imaging platforms [30–33].

Preclinical imaging

Preclinical small-animal imaging devices, such as with micro-PET/CT/SPECT/MRI, have become an integral part of translational research in oncology [14,15,30,33,34,36–39]. Since the trend is towards such translational research relying more and more heavily upon imaging end points, the use of these noninvasive small-animal imaging technologies is key to the further development of targeted tracers and therapeutic agents [11,13–15,36]. The functional imaging capabilities of these noninvasive small-animal imaging devices have been critical to translational drug development [11,14]. In addition to providing the opportunity to quantify functional measures of tumors *in vivo*, such a noninvasive imaging strategy allows for the opportunity to study the effects of drugs in a longitudinal and serial fashion, yet without the necessity of sacrificing animals to assess the therapeutic response [13–15,37–39].

Recent developments in small-animal imaging devices that combine functional–anatomic imaging modalities has dramatically improved the ability of imaging technology to answer key questions regarding new agents and has helped to focus resources on the specific development of agents that appear to hold the most promise for demonstration of a therapeutic response. The most readily available, state-of-the-art small-animal imaging devices provide combined PET, SPECT and CT capabilities [13–15,36–39]. Very recently, combined PET/MRI small-animal scanners have been introduced [30,33].

Clinical trials

There is rapidly increasing interest in incorporating targeted imaging biomarkers into clinical trials. The scope of imaging end points includes size measures (e.g., Response Evaluation Criteria in Solid Tumors) [40,41], metabolic quantification (e.g., using ^{18}F-fluorodeoxyglucose), receptor binding and functional MRI parameters, as well as many others.

The development and incorporation of core facilities for central evaluation of image data sets for clinical trials has recently evolved in response to the exponential growth and success of functional imaging technology. The National Cancer Institute (NCI) has recognized the importance of incorporating functional imaging end points into clinical trials by organizing and supporting the Image Response Assessment Teams (IRAT) Network [101]. Support for this concept exists at both the inter- and intra-institutional levels. The IRAT awards were designed to facilitate the organization of oncologic image response-assessment teams within comprehensive cancer centers so as to advance the role of imaging in assessment of response to therapy. The overall goal of this initiative was to increase the application of quantitative anatomic, functional and molecular imaging end points in clinical therapeutic trials. An additional resultant goal of this effort was to develop consensus guidelines and methods for quantitative analysis, interpretation and integration of imaging data in response to therapy trials, with dissemination and communication of these methods with IRATs at other institutions. This overall effort was designed to facilitate and encourage collaboration between imaging scientists and clinical oncology investigators and cancer centers to encourage the identification and implementation of new oncologic imaging research opportunities in clinical trials and expand the use of targeted imaging biomarkers in clinical therapeutic trials. In this regard, the specific utilization of ^{18}F-fluorodeoxyglucose PET in clinical trials has proven to have accelerated drug discovery and development [38].

> "The development and incorporation of core facilities for central evaluation of image data sets for clinical trials has recently evolved in response to the exponential growth and success of functional imaging technology."

A national effort has been put forth through cooperation between the FDA, the NCI and the Centers for Medicare and Medicaid Services to develop and evaluate medical imaging based upon the Oncology Biomarker Qualification Initiative (OBQI) [102]. The OBQI effort supports collaborations on oncology-related issues, including the development and qualification of biomarkers and standardization of approaches for evaluating biomarkers, as well as the development of tools for providing effective cancer therapies and assessing therapeutic response in cancer clinical trials for the purpose of accelerating medical drug development.

In addition, there are multiple government-sponsored core imaging laboratories whose goals in this effort are to assist in and promote the use of targeted imaging biomarkers in clinical trials. Two of these are the American College of Radiology Imaging Network [42] and the Cancer and Leukemia Group B Imaging Core Laboratory [103]. The function of both of these groups is to assist in protocol development, equipment validation, site training, data collection, quality control and compliance monitoring, data management and analysis, standard digital imaging and communications in medicine de-identification and central review coordination for multicenter clinical trials. These groups are working to develop, standardize and improve quantification methods in order to improve the ability to monitor response to therapy with functional imaging technologies [42,103].

Future potential challenges & impacts

The future of targeted imaging biomarkers and functional measures in the assessment and management of cancer patients is very promising [1–7]. The rapid growth and development of functional imaging technology, both preclinically and clinically, combined with the development of a wide variety of targeted diagnostic and therapeutic biomarkers, is revolutionizing the development of conventional therapeutic agents and changing how we approach the care and management of cancer patients.

> "The rapid growth and development of functional imaging technology ... combined with the development of a wide variety of targeted diagnostic and therapeutic biomarkers, is revolutionizing the development of conventional therapeutic agents..."

With continued improvement in molecular imaging technology and targeted biomarker development, we will be able to evaluate patients earlier in the disease process, as well as improve our ability to screen patients for cancer. It may even become possible to noninvasively determine gene expression and subtypes of disease without the need for invasive tissue sampling. These advancements will help to facilitate personalized medicine and may significantly improve our ability to detect, diagnose, stage, monitor and guide treatment response, as well as determine prognosis in many diseases [4–7,43–46].

One of the major challenges related to the advancement of the use of targeted imaging biomarkers and functional measures is the cost and time associated with obtaining approval for use in humans [18]. Despite the fact that these targeted biomarkers are typically used in microquantities with little to no physiologic impact, obtaining approval for use of these compounds in humans involves the same regulatory processes, clinical trials and safety and efficacy evaluation as for any other drug. The combined cost and time burden will probably be the limiting factor when it comes to the progress and impact of using targeted imaging biomarkers to improve cancer treatment and outcomes [11,18]. Improving and expediting these regulatory processes would also help to facilitate the translation of preclinical trial findings to clinical trials.

The potential impact of targeted imaging biomarkers and functional measures on the field of oncology is very significant, and we are in a very exciting time as we witness how molecular imaging technology can revolutionize the way in which we manage and treat cancer patients [4–7]. Utilization of these targeted imaging biomarkers and functional measures will continue to

improve our ability to monitor and assess patient response to therapy earlier in their therapeutic time-course and will allow for redirection in their treatment plans if therapy is proving unsuccessful. Furthermore, the future holds great promise for directing treatment in real-time for radiation therapy and surgical management by providing real-time information during these therapeutic interventions [43–46].

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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