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Molecular imaging for cancer diagnosis and surgery ☆

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ABSTRACT

Novel molecular imaging techniques have the potential to significantly enhance the diagnostic and therapeutic approaches for cancer treatment. For solid tumors in particular, novel molecular enhancers for imaging modalities such as US, CT, MRI and PET may facilitate earlier and more accurate diagnosis and staging which are prerequisites for successful surgical therapy. Enzymatically activatable "smart" molecular MRI probes seem particularly promising because of their potential to image tumors before and after surgical removal without re-administration of the probe to evaluate completeness of surgical resection. Furthermore, the use of "smart" MR probes as part of screening programs may enable detection of small tumors throughout the body in at-risk patient populations. Dual labeling of molecular MR probes with fluorescent dyes can add real time intraoperative guidance facilitating complete tumor resection and preservation of important structures. A truly theranostic approach with the further addition of therapeutic agents to the molecular probe for adjuvant therapy is conceivable for the future.

Contents

1. Introduction

In public discussion, improved drug treatment is often perceived as the main driver in the fight against cancer. However, in the case of solid tumors, early detection has to be considered equally, if not more important for successful treatment because it enables a surgical, curative approach. Surgery is usually limited to tumors detected at an early stage and outcomes decrease significantly once primary surgery is not a treatment option any more. For example, according to 2010 National Cancer Database (NCDB) data, 60% of stage I non-small cell lung cancer (NSCLC) patients had cancer removal surgery as their primary treatment, compared to just 6% diagnosed at stage III [1]. The 5-year survival rate for NSCLC patients whose cancer was surgically resected is 60–80% for stage I and 40–50% for stage II [2]. Concurrently, non-resectable stage III NSCLC treated with chemotherapy is associated with 2-year survival rates of less than 20% [3], emphasizing the importance of early detection and subsequent surgical removal.

Over the past decades, substantial efforts have been made to detect malignancies at an earlier state. Much of the progress made in cancer diagnostics and staging can be attributed to technical advances in ultrasonography (US), computed tomography (CT) and magnetic resonance

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imaging (MRI) which are essential for providing anatomic details for solid cancers [4]. Molecular imaging techniques may very well have the potential to improve every aspect of cancer care by opening up entirely new possibilities for the early detection and the effective treatment of cancer, both of which are essential to successfully fight the disease. Commonly and somewhat unspectacularly, molecular imaging is defined as non-invasive imaging of cellular and sub-cellular events [5]. More specifically, oncologic molecular imaging is based on highlighting distinctive molecular characteristics of malignant cells. Over the past years the genetically determined production of biomolecules by cancer cells has been extensively studied and characterized and individual expression profiles have been defined for certain types of cancer [6,7]. Molecular imaging probes target and highlight these specific characteristics which can be exhibited either directly in, or on, individual malignant cells or in the surrounding extracellular matrix and cells in the vicinity, such as T cells, macrophages, dendritic cells, fibroblasts or endothelial cells [4].

Currently molecular imaging strategies for all major whole body imaging modalities for cancer diagnosis and staging as well as molecular imaging probes for optical imaging in cancer surgery are being developed [8,9] (Table 1). These strategies give US, CT and MR an entirely new dimension by expanding morphological imaging to a cellular, functional level. Selective depiction of cellular properties and their microenvironments characteristic for the malignant state will enable earlier detection, assessment of aggressiveness and lead to a more personalized treatment approach.

Today, many clinicians still primarily associate molecular imaging with positron emission tomography (PET). Indeed, PET imaging with ^{18}F-fluorodeoxyglucose (^{18}F-FDG) depicts the metabolic discrepancies between malignant and healthy cells, making PET the first "true" and most widespread molecular imaging modality. However, its high cost, use of ionizing radiation, and relatively low spatial resolution somewhat restrict its potential. Therefore, molecular imaging with higher resolution modalities, especially MR, is gaining increasing attention. Aside from the whole body imaging applications, molecular imaging probes have also been adapted for optical imaging and can provide intraoperative guidance for cancer surgery. Ideally, molecular imaging probes will allow for earlier diagnostic imaging of solid cancers as well as facilitating better surgical treatment in the future, leading to an overall improved outcome. This review aims to outline relevant molecular imaging applications currently available or in development for the diagnosis, staging (CT, PET, US and MRI) and surgical treatment of cancers.

2. Molecular imaging applications in cancer diagnosis and staging

2.1. New levels of cancer diagnosis and staging

Based on their inherent characteristic of making functional attributes of malignant cells visible, molecular imaging techniques have the potential to enhance cancer diagnosis and staging on multiple levels, most notably tumor detection and characterization. While US, CT and MR imaging technology is continuously advancing, tumor detection today is still largely performed based on anatomical characteristics. Molecular imaging applications can make properties of carcinogenesis visible at much earlier time points because alterations on the cellular level are targeted and can potentially be detected as soon as they occur. For example, abnormalities in malignant cells' glucose metabolism occur at very early time points in carcinogenesis [9,10]. PET imaging with ^{18}F-FDG allows clinicians to detect those changes, although specificity and resolution for this imaging modality are limited. To truly exploit the potential of molecular imaging, e.g. performing regular whole body screening scans for at-risk patients to detect smallest malignant lesions, will depend on the development of more specific molecular imaging probes that target pathologic characteristics, ideally for imaging modalities without radiation exposure for the patient.

Tumor characterization without the need for invasive procedures such as biopsies or even surgery is considered another key feature molecular imaging adds to cancer diagnosis. While differentiation between benign and malignant tumors on conventional CT and MR scans based on morphologic characteristics can be difficult, molecular imaging allows for a much better assessment of aggressiveness because functional properties of malignant cells are visualized [11]. It has also been shown that a PET imaged decline in ^{18}F-FDG uptake after treatment initiation correlates with patient outcome for certain cancers [12,13], allowing for more accurate staging and re-staging, as well as drug response monitoring of patients with molecular imaging technology. Eventually, molecular imaging may also be able to determine the ideal treatment for individual patients. Highly specific visualization of the expression profiles of certain molecular markers, a "molecular phenotype" associated with patient outcomes at the time of cancer diagnosis may provide guidance to a truly personalized treatment approach [9,14,15].

2.2. Molecular targeting approaches

Molecular imaging probes for cancer diagnosis usually comprise a signaling component which is detectable by the respective imaging modality and a targeting element. The latter can be highly specific to detect a certain type of malignancy or be aimed at more general features of malignant physiology.

Imaging probe targets which are not specific for a certain type of malignancy are aimed at functional or phenotypic characteristics exhibited by many cancer variants. The aforementioned PET imaging with ^{18}F-fluorodeoxyglucose (^{18}F-FDG) depicts the metabolic discrepancies between malignant and healthy cells by indicating increased glucose uptake by cancer cells. An example for a more cancer specific approach which however is also not limited to a certain type of malignancy is designing probes which attach to certain integrins which are highly expressed on tumor vascular endothelial cells, while being almost undetectable on normal blood vessels, making them a potential target for imaging during early cancer diagnosis [16–18]. Similarly, probes developed in our collaborative laboratories are targeted at extracellular matrix enzymes, specifically matrix metalloproteinases (MMPs) 2 and 9 which are expressed by a range of tumor cell lines [19–24].

Enzymatically activated molecular imaging probes have additional value because they possibly allow for a more in-depth imaging approach. The amount of contrast enhancement created correlates with tumor cells' development, growth and productivity. Most enzyme targeted probes are engineered to be cleaved by the molecule they target for activation, some others are catalyzed to undergo bond formation which shifts them into a contrast generating state [25].

Activatable molecular imaging probes are also referred to as "smart" probes because they only exhibit a contrast enhancing signal under certain conditions. Besides enzymes, triggers can also be environmental variances, such as certain pH levels. Using pH differences for the detection of malignancies has been pursued for a long time since pH is somewhat lower in tumor cells compared to healthy tissue because of increased glycolytic activity. Several approaches to visualize intracellular pH differences have been reported over the past three decades, including fluorescent pH indicators [26] and MR spectroscopy [27]. Others utilized green fluorescent protein (GFP) mutants' pH-dependent absorbance and fluorescence properties to detect pH changes in cells [28]. This particular technique is useful in animal models but has limited clinical translatability due to the necessity for gene therapy to introduce GFP into human cancers. More recent studies have also investigated gadolinium based pH-sensitive contrast agents for MR imaging [29,30].

Specific molecular imaging probes are constructed to interact with biomolecules characteristic for one specific type or class of malignancy, such as prostate specific antigen (PSA) expressed on prostate cancer cells [31], or carcinoembryonic antigen (CEA) expression on pancreatic cancer cells [32,33]. As antigen–antibody interactions typically have very high specificity [34], they have attracted significant attention for