Innovation in Cancer Imaging

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Abstract

Cancer is rapidly becoming the worldwide leading cause of premature death. Iconographic techniques have traditionally provided information on tumor anatomy. The recent introduction of functional and molecular imaging techniques allows probing tumor physiology and biology in addition to mere anatomical description. In addition to the research implications, these novel imaging techniques offer early response assessment and target visualization which, in the era of personalized medicine, may offer significant advances in cancer therapy. Here, we provide an overview of the most important developments in cancer imaging, with a focus on the clinical applications.

Key Words

Oncology · Imaging · PET · DCE-MRI

Introduction

Cancer is a leading cause of death worldwide, accounting for well over 7 million deaths in 2008 [1]. Since most solid cancers are not readily amenable for palpation and inspection, accurate imaging has traditionally been one of the cornerstones of cancer therapy. Indeed, imaging allows for correct anatomical delineation and staging of the malignant process, which have a direct impact on the therapeutic strategy as well as the patient’s prognosis. Until the beginning of the 21st century, medical iconography was primarily focused on anatomical imaging, with computed tomography (CT) and magnetic resonance imaging (MRI) being the most important imaging technologies. These structural imaging modalities can offer images with exquisite spatial resolution within seconds or minutes, but they share the limitation of not being able to detect lesions until the structural changes in the tissue (e.g. tumor growth) are large enough to be detected by these imaging technologies [2].

Recent advances in molecular and functional imaging have had a significant impact on modern oncology practice. First, nuclear techniques such as positron emission tomography (PET) and single-photon emission CT (SPECT) offer the potential of detecting cellular or molecular changes which precede structural abnormalities. Obviously, these techniques, when combined with novel molecular tracers, also hold considerable promise in early drug development. Secondly, functional and molecular imaging allow for rapid assessment of therapy response, which allows disease biology to gauge well before any change in tumor dimension occurs as measured by the traditional RECIST criteria [3]. The use of imaging as a biomarker of response allows tailoring the therapeutic strategy and limiting the cost and side effects of ineffective regimens.
Here, we review the currently available functional and molecular imaging modalities and briefly highlight some promising preclinical developments.

**Diffusion Imaging**

By incorporating diffusion-sensitizing gradients in a $T_2$-weighted spin echo sequence, diffusion-weighted MRI enables quantifying the microscopic mobility of water in biological tissues [4, 5]. Images are acquired at multiple diffusion sensitivities, allowing the calculation of the apparent diffusion coefficient (ADC, in $\mu m^2/s$) in each image element. In general, the cellular proliferation associated with cancer growth results in restricted water mobility (low ADC), while apoptosis and necrosis caused by anticancer therapy results in increased water mobility and thus in increased ADC values [6]. Historically, the application of diffusion-weighted MRI in gastrointestinal cancer has been limited due to physiological organ motility. Several authors have examined its use in rectal cancer, esophageal cancer, and gastrointestinal stromal tumors (table 1). Although the reported findings are not entirely consistent, taken together these studies suggest that pretreatment ADC values and the extent of ADC changes during therapy may serve as imaging biomarkers of response.

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Therapy</th>
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<th>Findings</th>
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<tbody>
<tr>
<td>Rectal cancer</td>
<td>chemotherapy, CRT</td>
<td>14</td>
<td>negative correlation between pretreatment ADC and tumor size change after chemotherapy ($r = -0.67, p = 0.01$) and CRT ($r = -0.83, p = 0.001$)</td>
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<tr>
<td>Rectal cancer</td>
<td>CRT</td>
<td>34</td>
<td>pretreatment ADC significantly lower in pathologic responders ($p &lt; 0.001$, ANOVA)</td>
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<td>Rectal cancer</td>
<td>CRT</td>
<td>9</td>
<td>significant decrease of ADC in the 2nd ($p = 0.028$), 3rd ($p = 0.012$), and 4th ($p = 0.008$) weeks of treatment</td>
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<tr>
<td>Rectal cancer</td>
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<td>76</td>
<td>percentage change between pre- and posttreatment ADC significantly higher in complete pathological responders ($p &lt; 0.0001$). Post-CRT but not pre-CRT ADC were significantly different between complete and noncomplete responders</td>
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<tr>
<td>Rectal cancer</td>
<td>CRT</td>
<td>50</td>
<td>post-CRT but not pre-CRT accurate in predicting complete response</td>
</tr>
<tr>
<td>Rectal cancer</td>
<td>CRT</td>
<td>37</td>
<td>early increase of ADC and low pre-CRT ADC correlate with good response to CRT</td>
</tr>
<tr>
<td>GIST [89]</td>
<td>imatinib</td>
<td>32</td>
<td>low pretherapy ADC and ADC increase at 1 week after therapy is associated with good response to imatinib</td>
</tr>
<tr>
<td>Esophageal cancer</td>
<td>CRT</td>
<td>80</td>
<td>high pre-CRT ADC values predicted response; better survival in high ADC patients</td>
</tr>
<tr>
<td>Esophageal cancer</td>
<td>–</td>
<td>123</td>
<td>negative correlation between ADC and tumor diameter/clinical stage</td>
</tr>
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CRT = Chemoradiation.

**Perfusion Imaging**

Since an adequate blood supply is a prerequisite for developing tumors, perfusion imaging may be used to differentiate tumors, assess response to therapy, and aid in prognostication. Dynamic contrast-enhanced (DCE) MRI has been applied to the study of tumor perfusion. DCE-MRI encompasses the dynamic study of tissue enhancement over time after intravascular injection of a paramagnetic contrast agent (CA) [7]. The acquired images provide insight into tumor tissue properties such as blood volume, perfusion, and vascular permeability, all of which have been shown to represent adequate markers of therapy response [8]. The images acquired may be processed to generate semiquantitative (heuristic) parameters such as area under the curve, time to peak enhancement, peak intensity, and CA washout rate. Alternatively, when tissue enhancement is combined with simultaneous measurement of CA concentration in a feeding vessel, pharmacokinetic compartmental modeling becomes possible, which yields parametric maps of parameters such as the endothelial transfer constant $K_{trans}$ [9]. The physiological interpretation of the calculated parameters critically depends on the properties of the CA [10]. When using a small molecule such as gadopentetate dimeglumine, extravasation is ‘perfusion limited’ and mainly re-
flects tissue perfusion, while the use of larger (preclinical) molecules, which do not readily diffuse across the endothelial lining, allows probing vessel permeability (fig. 1). Table 2 lists clinical trials in digestive cancer using DCE-MRI, all of which have shown that a decrease in CA exchange between the vascular and the tumor interstitial compartment represents a valid biomarker of therapy response. Since the imaging endpoints of a DCE study reflect blood supply in the first place, this technique is ideally suited to study the effects of antiangiogenic therapy in early-phase clinical trials [11].

Using similar kinetic modeling methods, dynamic CT may provide insight into tumor perfusion [12]. DCE-CT has been used to monitor the effects of anticancer therapy in lung cancer, rectal cancer, and hepatocellular carcinoma [13, 14]. An attractive perfusion imaging modality is DCE ultrasound using intravenous injection of gas ‘microbubbles’ surrounded by a polymer shell [15, 16]. Obviously, ultrasound-based technology is cheap, portable, and minimally invasive. Contrast-enhanced ultrasound has been used to predict response in liver, renal, and stromal tumors [17, 18]. In addition to the diagnostic information gained by DCE ultrasound, the combination of microbubbles carrying a drug payload and focused ultrasound bursts allow targeted drug delivery under ultrasound guidance [19, 20].

Functional Lymph Node Imaging

Nodal spread is one of the most important prognostic variables in solid cancer, and nodal status may significantly impact the therapeutic strategy as well as the patient’s prognosis. Since morphological criteria have proven insufficiently accurate in the detection of nodal cancer spread, functional imaging techniques that would facilitate nodal staging are under scrutiny.

Ultrasmall Superparamagnetic Iron Oxide

Nodal involvement represents one of the most powerful prognosticators in digestive cancer, and considerable efforts have been invested in techniques allowing accurate detection of lymph node spread. After intravenous injection, ultrasmall superparamagnetic iron oxide (USPIO) will be taken up by nodal tissue, which will darken uniformly and homogeneously on T2- and T2*-weighted MRI. In rectal cancer, several authors have attempted to diagnose mesorectal nodal involvement. Koh et al. [21] compared nodal enhancement patterns after USPIO injection with histological analysis and found that eccentric and uniform high signal intensity were observed in lymph nodes that contained metastases larger than 1 mm in diameter. The same authors found that compared to standard MRI, USPIO-enhanced imaging improved specificity (93 vs. 75%), although sensitivity was similar (65%) when compared to histological analysis [22]. Beets et al. [23] examined the accuracy of USPIO-enhanced MRI in nodal staging of rectal cancer, and found sensitivity, specificity, PPV, and NPV of 97, 94, 66, and 99%, respectively, after node-by-node analysis. Unfortunately, the CA used in these studies (ferumoxtran-10, Sinerem, Combidex) never received FDA approval and production was discontinued several years ago.

Gadolinium-Based Blood Pool Agents

Using large CAs with a prolonged plasma half-life facilitates measurement of neovascular permeability as well as lymphangiography and nodal staging. Many of these compounds are in preclinical development, but at present only MS-325 (gadofosveset), a gadolinium chelate that is chemically modified causing it to bind strongly but reversibly to plasma albumin, is available for clinical use.
Lambregts et al. [25] reported on the use of gadofosveset-enhanced MRI for nodal staging in rectal cancer. When comparing it to histology as the standard, they found that sensitivity and specificity improved from 76 and 82% to 80 and 97%, respectively, when using gadofosveset ($p < 0.001$). Other macromolecular CAs composed of albumin, polylysine, polysaccharides, poly(ethylene glycol), copolymers of cystamine and cystine with GD-DTPA, and dendritic structures based on polyamidoamine and polylysine (Gadomers) seem very promising, but are presently unavailable for clinical use [26].

### Metabolic Imaging

The cornerstone of imaging tumor metabolism is PET using radiolabeled glucose. The use of glucose-based PET imaging is based on the Warburg effect, i.e. the phenomenon that under aerobic conditions, tumor tissues metabolize approximately tenfold more glucose to lactate in a given time than normal tissues, notwithstanding preserved mitochondrial respiration [27]. With the exception of prostate cancer, the uptake of $^{18}$F-fluorodeoxyglucose (FDG) is increased in most cancer types and correlates with the proliferation and number of malignant cells [28]. Since changes in metabolic activity are an early manifestation of a drug’s anticancer effect, there is considerable interest in the use of FDG-PET to measure tumor response. One of the drawbacks associated with FDG-PET is the variability in methods to measure FDG uptake, which renders comparison between studies difficult. Tracer uptake is usually measured semiquantitatively by calculating the standardized uptake value, defined as the tumor radiotracer concentration (in MBq/ml) $\times$ body weight (in kg) divided by the injected activity (in MBq). Alternatively, kinetic modeling (Patlak plot) may be used to derive the metabolic rate for glucose using measurements of the time course of radioactivity in tissue and in serial arterial blood samples [29].

A recent systematic review of the accuracy of FDG-PET in the prediction of response to neoadjuvant therapy in esophageal cancer showed a pooled sensitivity of 67% and specificity of 68% [30]. There was significant heterogeneity between included studies, which led the author to conclude that the results of FDG-PET should not be used to guide therapy in this patient population. In rectal cancer patients treated with neoadjuvant CRT, several small studies have demonstrated that FDG-PET uptake predicts the pathological response of the tumor [31–33]. On the other hand, FDG-PET was shown to be insufficiently accurate in predicting nodal involvement [34].

### Hypoxia Imaging

Tissue oxygenation has been recognized as a central microenvironmental parameter in solid tumors for at least 100 years [35]. Areas of varying degrees of hypoxia (defined as $O_2$ partial pressure <2.5 mm Hg) are present in most tumors as a consequence of limited oxygen diffusion, increased utilization by vessel-proximal cells, and perfusion deficiencies resulting from a structurally and functionally abnormal microvascular bed. Hypoxia represents an adverse predictive and prognostic factor, and
Proliferation Imaging

Cellular proliferation is one of the hallmarks of cancer. 18F-FLT (3'-fluoro-3' deoxythymidine)-PET is incorporated by proliferating cells in the pyrimidine salvage pathway during the S-phase. The tracer is then phosphorylated by thymidine kinase 1, after which it accumulates in the cells [45]. Several clinical studies have confirmed that uptake was significantly correlated with tumor cell proliferation [46]. Several clinical studies have aimed to use FLT-PET to monitor the response to antiproliferative therapy. In breast cancer, FLT-PET enabled early response prediction, i.e. after one course of chemotherapy [47, 48]. Similarly, FLT avidity changes reflected early therapy response in head and neck cancer patients, whereas discrimination between malignant and reactive lymph nodes turned out to be impossible due to reactive B-lymphocyte proliferation [49, 50]. Wieder et al. [51] used sequential FLT-PET before and after neoadjuvant CRT in rectal cancer patients. Although a significant decrease in standardized uptake value was observed, the degree of change in FLT uptake did not correlate with histological tumor regression. Along the same line, Muijs et al. [52] compared CT and FLT-PET in the primary staging of rectal cancer and found that compared to CT, FLT-PET performed poorly in delineation of the tumor as well as in malignant node detection. A comparison of FDG-PET with FLT-PET in colorectal cancer patients was reported by Yamamoto et al. [53]. They found that FLT uptake was significantly lower than FDG uptake, and that neither imaging modality correlated with the Ki67 proliferation index. More favorable results were noted in gastric cancer patients. Herrmann et al. [97] compared FLT-PET with FDG-PET and found FLT uptake in all 45 patients, whereas 14 gastric tumors were not FDG avid.

Apoptosis Imaging

Induction of apoptosis is assumed to be the most important mechanism by which anticancer drugs exert their effect. One of the discriminating features of the apoptotic cell is the rapid redistribution of phosphatidylserine from the inner to the outer layer of the plasma membrane. Phosphatidylserine-binding agents therefore represent attractive targets for apoptosis imaging. The first radiolabeled tracer with a nanomolar affinity for membrane-bound phosphatidylserine was 99mTc-annexin V, the activity of which is imaged using SPECT. Kartachova et al. [54] used sequential annexin V imaging in lung cancer patients treated with platinum-based chemotherapy, and found a significant correlation between annexin V uptake and treatment response. Similar results were obtained by Rottey et al. [55], who showed that sequential annexin V scintigraphy using a 25% change threshold allowed discrimination of nonresponders with 94% accuracy after 3 days of chemotherapy initiation in solid tumor patients (fig. 2). Compared with SPECT, the use of PET offers the advantages of higher count rate, quantitative imaging, and improved resolution. Efforts have therefore been invested in the synthesis of annexin V-based PET tracers. Examples in preclinical development include labeling of annexin V with gallium-68 or N-succinimidyl 4-[18F]fluorobenzoate, and labeling of the annexin V-128 with N-[4-([4-[18F]fluorobenzylidene)aminooxy]butyl]maleimide ([F-18], FBABM) [56–58]. Other apoptosis tracer targets include synaptotagmin, caspase inhibitors, and hydrophobic cations. Recently, Hoglund et al. [59] reported on a study in healthy volunteers with 18F-labeled 2-[(5-fluoropentyl)-2-methyl malonic acid ([18F]-ML-10), a PET apoptosis tracer. In addition to a favorable pharmacokinetic and safety profile, the authors observed tracer binding to apoptotic cells in testicular tissue, where these occur in normal circumstances.
Another feature of the apoptotic process is the sudden halt in protein synthesis, including that of choline and choline-containing molecules. Decreases in choline synthesis may be detected using $^1$H magnetic resonance spectroscopy. Thus, several authors have demonstrated that reduction of tumor choline content represents a valid biomarker of chemotherapy response in breast cancer patients [60, 61]. In prostate cancer, the maximal choline + creatine to citrate ratio and choline to creatine ratios as measured by magnetic resonance spectroscopy were shown to separate low-grade from higher-grade tumors [62]. An exciting development is the use of hyperpolarization techniques to dramatically (more than 10,000-fold) increase the sensitivity of magnetic resonance spectroscopy tracers based on stable isotopes such as $^{13}$C and $^{15}$N, which hold significant promise in probing the biochemical pathways associated with cancer [63].

**Optical Imaging**

Optical imaging is a rapidly emerging field, with widespread applications ranging from clinical diagnosis to molecular biology. In the clinic, the endoscope has served as an optical imaging tool since the 17th century. Compared to cross-sectional imaging modalities, endoscopy can provide real-time images with high spatial resolution, enabling the detection of very small anatomic changes, and offers immediate intervention, such as biopsy of neoplastic lesions. With the introduction of fluorescent CA, the functions of traditional endoscopy are further extended. Chromoendoscopy involves the application of spraying a fluorescent CA onto the mucosa using a spray catheter passed through a standard endoscope. It has been shown that in large human studies, chromoendoscopy improves earlier diagnosis of adenomas and colorectal cancers [64]. Another study showed that chromoendoscopy permits more accurate diagnosis of the extent and the severity of neoplastic lesions [65]. Despite these positive preliminary results, some studies have shown that the fluorescent CA used during chromoendoscopy (methylene blue) might induce DNA damage, and consequently accelerate carcinogenesis [66]. Such risks need to be carefully balanced against the possible benefits of improved earlier disease detection.

Indocyanine green has been heavily tested for adverse reactions and is a fluorescent CA that rapidly binds to blood proteins after intravenous injection [67]. It can be used to provide information of the vasculature of the digestive tract that cannot be obtained by conventional endoscopy [68]. Kimura et al. [69] evaluated the effectiveness of fluorescent endoscopy for the preoperative evaluation of tumor invasion in patients with superficial gastric tumors, and concluded that submucosal invasion has a higher correlation with fluorescence than macroscopic morphology of tumors and histopathologic tumor differentiation. Indocyanine green has also been used for the detection of metastases to a sentinel lymph node in melanoma, gastric cancer, and lung cancer patients [70–72].

Recently, more sophisticated optical probes have been developed that target or interact with biological processes on a molecular level after being exogenously delivered. Most of these probes are completing preclinical validation in mouse models and the design of such probes involves the attachment of a fluorophore to a targeting moiety, such as a peptide, an antibody or a fragment of an antibody, small molecules, and nanoparticles [73–75]. Another class of optical agents changes their fluorescent properties after target interaction, rather than targeting surface receptors and proteins. These smart probes are initially optically silent and become fluorescent as a result of enzymatic cleavage of fluorophores from a delivery backbone in the presence of protease [76]. This technique has been proven to be very successful in combination with endoscopic applications [77].

**Fig. 2.** Example of sequential $^{99}$mTc-hydrazinonicotinamide-annexin V imaging for predicting response to chemotherapy. A significant increase in tracer uptake is noted over time in a primary breast tumor (arrows). Reproduced with permission from Rottey et al. [55].
Multimodality Imaging

In previous paragraphs, various structural, functional, and molecular imaging technologies were introduced. Table 3 lists some performance parameters of different imaging modalities available. Since the properties of anatomical (CT, MRI) and functional (PET, SPECT) imaging modalities are rather complementary, integrating the information obtained from these modalities into one platform takes ‘the best of both worlds’. Multimodality platforms – such as PET/CT, SPECT/CT, PET/MRI, and SPECT/MRI – with each modality having its unique strengths and limitations play an increasingly important role in the diagnosis and staging of human disease [78]. The major technological advances in PET instrumentation before the advent of CT, excellently documented by Muehllehner and Karp [79], culminated in the introduction of a hybrid PET/CT system in 1998 [80]. This was undeniably a very important step to use PET as a viable clinical tool, with PET/CT being the most widely used multimodality platform today. Among multimodality platforms, PET/MRI may ultimately provide the greatest yield of scientific information, combining the impressive technological developments of PET with the excellent anatomic resolution and soft-tissue contrast provided by MRI [81]. An important advantage of PET/MRI over the other multimodality platforms is that PET and MRI data can be acquired simultaneously, rather than sequentially. A clinical PET/MRI device that allows the simultaneous acquisition of whole-body PET and MRI images became commercially available in 2011 (Biograph™ mMR, Siemens).

Preclinically, there is a trend to combine optical imaging and radionuclide (PET/SPECT) imaging. Besides the large difference in the energy of the emitted photons (1–2 eV vs. $10^5$ eV), optical and radionuclide imaging are quite similar. Both are based on the detection of photons emitted from a source inside the body, and both use highly sensitive photon detectors positioned outside the body to detect the signals. In addition, for both the measured signal is directly proportional to the biological process under examination. Due to these similarities, and because optical imaging suffers from poor tissue penetration, it is natural to consider the development of combined optical/radionuclide imaging devices and dual-modality probes that can be used in a similar fashion to produce optical signals when used in small animals, or yield PET/SPECT signals to facilitate the translation to the clinic. In the clinic, these dual-modality probes can provide, next to radionuclide images, additional information when combined with surgical techniques, where the excited tissue can be visualized optically [82].

Conclusion

Cancer imaging has evolved from a mere morphological investigation to a physiology-based in-depth analysis of tumor biology. In the era of personalized medicine, functional and molecular imaging will allow us to tailor treatment according to predictive and prognostic imaging-based biomarkers. Standardization and clinical validation of novel imaging modalities should be a priority in clinical cancer therapy and incorporated in interventional cancer trials.

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Disclosure Statement

None of the authors have any conflict of interest to declare.
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