Quantitative imaging as cancer biomarker

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ABSTRACT

The ability to assay tumor biologic features and the impact of drugs on tumor biology is fundamental to drug development. Advances in our ability to measure genomics, gene expression, protein expression, and cellular biology have led to a host of new targets for anticancer drug therapy. In translating new drugs into clinical trials and clinical practice, these same assays serve to identify patients most likely to benefit from specific anticancer treatments. As cancer therapy becomes more individualized and targeted, there is an increasing need to characterize tumors and identify therapeutic targets to select therapy most likely to be successful in treating the individual patient's cancer. Thus far assays to identify cancer therapeutic targets or anticancer drug pharmacodynamics have been based upon in vitro assay of tissue or blood samples. Advances in molecular imaging, particularly PET, have led to the ability to perform quantitative non-invasive molecular assays. Imaging has traditionally relied on structural and anatomic features to detect cancer and determine its extent. More recently, imaging has expanded to include the ability to image regional biochemistry and molecular biology, often termed molecular imaging. Molecular imaging can be considered an in vivo assay technique, capable of measuring regional tumor biology without perturbing it. This makes molecular imaging a unique tool for cancer drug development, complementary to traditional assay methods, and a potentially powerful method for guiding targeted therapy in clinical trials and clinical practice. The ability to quantify, in absolute measures, regional in vivo biologic parameters strongly supports the use of molecular imaging as a tool to guide therapy.

This review summarizes current and future applications of quantitative molecular imaging as a biomarker for cancer therapy, including the use of imaging to (1) identify patients whose tumors express a specific therapeutic target; (2) determine whether the drug reaches the target; (3) identify an early response to treatment; and (4) predict the impact of therapy on long-term outcomes such as survival. The manuscript reviews basic concepts important in the application of molecular imaging to cancer drug therapy, in general, and will discuss specific examples of studies in humans, and highlight future directions, including ongoing multi-center clinical trials using molecular imaging as a cancer biomarker.

Keywords: molecular imaging, PET, cancer biomarkers

INTRODUCTION

A "biomarker" characterizes disease status and/or predicts disease behavior[1]. Cancer biomarkers have become an increasingly important part of cancer care in the era of personalized "precision" medicine[2]. This review highlights use of molecular imaging as a cancer biomarker to direct targeted cancer therapy. We focus on applications where cancer imaging biomarkers could be an important part of clinical trials and clinical practice, guiding patient selection,

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evaluating drug delivery to the target, evaluating early response, and relating therapeutic response to long-terms outcome such as progression-free and overall survival (PFS and OS)[3].

Molecular imaging can add to our toolset of cancer biomarkers, based upon several distinct features complementary to tissue-based methods[4]. Imaging is non-invasive and therefore better suited to serial assay. This is especially important in measuring early drug response. Imaging also assesses the entire patient and can therefore measure properties for the entire disease burden. This overcomes sampling error that occurs in tissue sample assays that typically sample a single disease site. Imaging directly measures the heterogeneity of both target expression and therapeutic response, increasingly recognized as a key factors in therapeutic resistance[5-7]. It should be noted, however, that imaging, by no means, is a substitute for tissue sampling and assay, but rather a complementary method for characterizing cancer biologic features. Imaging does not replace biopsy, it simply adds to the information that can be gleaned by biopsy.

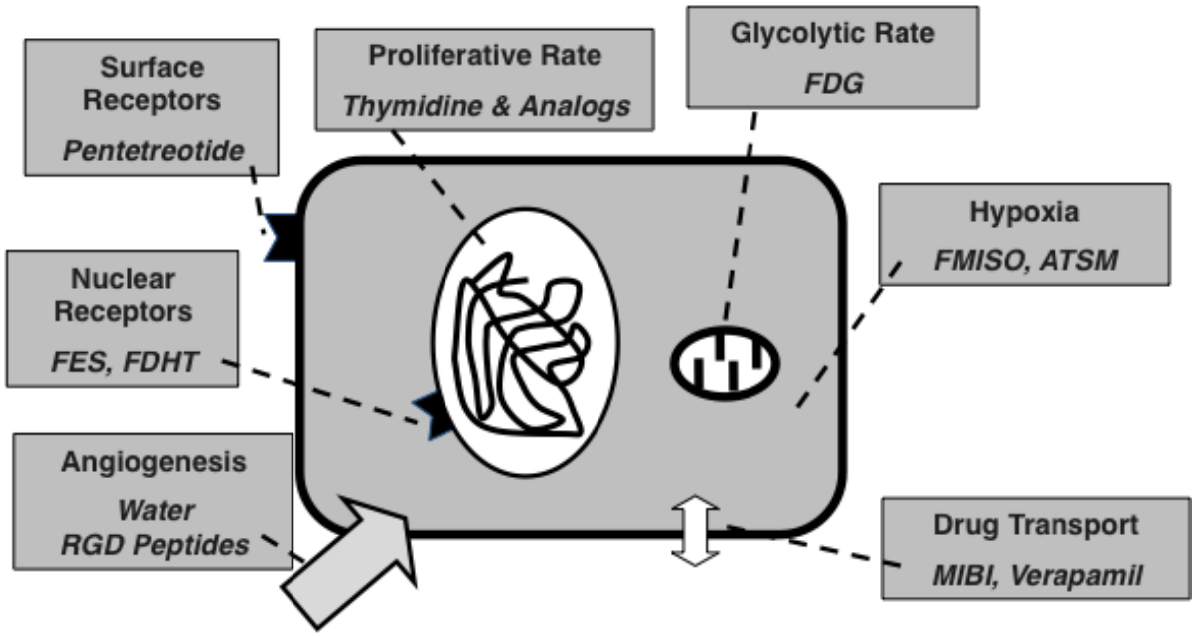

Figure 1 – Potential targets and imaging agents (italics) for molecular cancer imaging biomarkers.

The use of molecular imaging in cancer thus far has largely been directed towards cancer detection and staging, and based largely upon the detection of aberrant glycolysis at sites of cancer using the PET probe ^{18}F-fluorodeoxyglucose (FDG)[8]. In this case, we expect FDG uptake to be elevated compared to background normal tissue for most tumors and most parts of the body. Cancer biomarker imaging departs form this model to include a larger array of targets (Figure 1), where the absence of a particular feature – for example, expression a therapeutic target – may be as important as it presence. Quantitative image analysis to measure the level of molecular probe uptake is a therefore key feature of cancer biomarker imaging. Imaging methods, especially PET, can provide highly accurate measures of regional probe concentration to enable robust quantification of regional molecular properties from molecular images[4]. The physics of nuclear detection enable more reliable estimate of concentration from annihilation pair imaging (i.e., PET) compared to single-photon counting (SPECT). Good quantitative imaging requires careful scanner maintenance and calibration, strict adherence to standard imaging protocols, and consistent approaches to quantitative image analysis[9]. In many cases simple uptake measures such as the Standardized Uptake Value (SUV) will suffice for image analysis, while more complex probe kinetics and biology may require more sophisticated image analysis, including compartmental modeling[10]. Emerging standards for image analysis will be important to the consistent application of molecular imaging as a cancer biomarker across centers[11]. Organizations devoted to quantitative cancer imaging, for example the NCI's Quantitative Imaging Network (QIN) help support quantitative imaging in clinical trials through research and the development of tools for robust image analysis[12]. More sophisticated methods to analyze the heterogeneity and textural features of molecular imaging probe uptake may offer even more predictive imaging biomarkers in the future[13].

In the remainder of the review, we provide examples of early results and ongoing work for 4 cancer biomarker goals (Table 1):

1. Choosing the right patient: Is the therapeutic target present, and if so, at what level?
2. Choosing the right drug: Is the drug delivered to the tumor and to the target?
3. Getting the right result: Is the tumor (and the patient) responding to the treatment?
4. Predicting outcome: Will drug treatment lead to better survival for the patient? Does the patient need additional and/or different therapy to assure a good outcome?

In each case we provide the rationale for using molecular imaging in the specific biomarker task, and provide one or more examples of the use of molecular imaging in that role.

Table 1 – Possible Imaging Biomarker Roles

- **Choosing the right patients**
  - **Is the therapeutic target present?**
- **Choosing the right drug**
  - **Does the drug reach the target?**
- **Getting the right result**
  - **Is there a pharmacodynamic response?**
- **Predicting the outcome**
  - **Will response lead to better patient survival?**

APPLICATIONS OF QUANTITATIVE MOLECULAR IMAGING AS A CANCER BIOMARKER

Choosing the right patients

Biomarkers that predict the likelihood of response a specific therapy are termed predictive markers. The use of molecular imaging to measure therapeutic targets is an example of a predictive cancer biomarkers[2,9]. In clinical practice, predictive assays that measure therapeutic target expression are commonly used to select treatment. An example of a widely used predictive marker is the use of estrogen receptor (ER) expression to direct breast cancer endocrine therapy in breast cancer[3]. In breast cancers expressing ER, the chance of response to endocrine therapy is as high as 75%, but in the absence of expression, clinical benefit occurs in less than 5% of patients. Molecular imaging can be complementary to tissue-based predictive biomarkers, especially for advanced disease, where imaging offers the ability to assess target expression across all sites of disease and to assess sites challenging to biopsy and assay.

An example of a molecular imaging predictive assay is PET imaging of ER expression using the positron-emitting probe, ^{18}F-fluoroestradiol (FES). FES uptake correlates with ER expression as measured by a variety of tissue assays[14,15]. In early trials, PET found a higher average FES SUV for responder versus non-responders, and low or absent uptake indicated that patients were unlikely to respond to endocrine treatment. As a predictive assay for endocrine therapy, the ability to characterize ER expression over the entire disease burden may offer advantages for patients with for more widespread and refractory disease. FES PET was able to demonstrate the evolution of ER-negative disease in over 30% of patients with endocrine-refractory metastatic breast[6,16], indicating the ability of imaging to direct therapy in advanced disease. These promising early results in single-center trials have spurred the development of multi-center trials to further test the use of FES PET in breast cancer and other diseases.

Choosing the right drug

Molecular imaging can measure drug transport and kinetics through a variety of approaches. Labeled versions of drugs, typically labeled with ^{11}C or ^{18}F can measure dynamic drug biodistribution and provide key insights in drug clearance and transport to the site of disease. While powerful, this approach requires considerable labor to label and validate drugs labeled with a short-lived positron emitter. An alternative approach is to label a surrogate marker for drug properties- for example, drug transport- that can be used for classes of drugs. An example is ^{11}C-verapmil to measure transport of the efflux protein, P-glycoprotein (p-gp)[17]. This approach has been successfully used to demonstrate the impact of a p-

gp inhibitor on drug transport across the blood-brain-barrier[18]. Imaging drugs can also be used to demonstrate the ability of a drug to reach the target in sufficient quantity to carry out its desired action. For example, studies have shown that that FES PET performed before and after the administration of ER-blocking drugs such as tamoxifen and fulvestrant in breast cancer can help guide drug dosing and reveal patient-to-patient variability in drug penetrance[19,20].

Getting the right result

The standard clinical approach to the assessment of response in cancer patients undergoing treatment for advanced disease is measurement of the size of the tumor typically every two months (usual range: 6 weeks to 3 months) using standard anatomic imaging with CT or MRI[21]. This allows enough time for a tumor to shrink in responding patients or to grow in those with progressive disease. Size-based methods are widely used for response assessment but may not be well suited as early-response indicators. Biochemical and molecular changes will typically precede subsequent changes in tumor size and can provide a much better indictor of whether or not the drug has an effect on the tumor. This principal underlies considerable research and future promise for molecular imaging as an early response indicator. A number of approaches to molecular imaging early response markers have been developed and tested. The most successful thus far have targeted biologic processes that relatively are ubiquitously affected by successful treatment, including processes such as glycolysis and cellular proliferation.

FDG PET has been shown to be a good predictor of early response for a number of several cancers and treatment types[22]. One of the most dramatic examples is the impact of drug such as imatinib and sunitinib on GI stromal tumors, where dramatic declines in FDG uptake are seen within 24 hours of drug administration[23]. An early decline in FDG uptake has also been a robust indicator of breast cancer response to HER2-directed therapy, confirmed in the recent Neo-ALTTO study, where serial FDG PET performed in the setting of a randomized drug trial comparing the efficacy of two different HER2-directed regimens indicated that a decline in FDG uptake with treatment was a robust indicator response to combined HER2-targeted therapy/chemotherapy[24]. Besides FDG, other radiopharmaceuticals applicable to early response have been tested, including tracers of cellular proliferation and cell death. Thus far, cellular proliferation has been the most successful PD marker tested, mostly using labeled thymidine and analogs[25]. The thymidine analog ^{18}F-fluorothymidine (FLT) has shown promise in early trials, including studies indicating an ability to demonstrate response to both chemotherapy and targeted agents as early as a single dose of therapy and as early as a few days after treatment[26,27]. These studies have prompted several multi-center FLT PET trials, most commonly testing early breast cancer response to chemotherapy in the neo-adjuvant setting. Although results have been somewhat mixed, at least one trial, ACRIN 6688, has indicated an ability of serial FLT PET pre- and one week after chemotherapy to predict pathologic response post-neoadjuvant chemotherapy[28].

Predicting Outcome

The earliest studies of molecular imaging to measure cancer response showed it to be quite predictive of established measures of therapeutic outcomes, such as pathologic response[29]. In vivo molecular cancer properties can provide evidence of residual active tumor post-therapy, yielding incremental information beyond anatomic imaging spredictive of key patient outcomes such as disease-free and overall survival (DFS and OS). The value of FDG PET in predicting survival has been best demonstrated in lymphoma, where the presence of absence of residual FDG uptake post therapy, independent of the presence or absence residual anatomic abnormalities by CT, is a strong predictor of relapse and survival[30]. FDG PET is widely used in clinical practice for Hodgkin's and aggressive non-Hodgkin's lymphomas, and PET has been accepted as a surrogate endpoint and integral marker in lymphoma clinical trials[31]. It is likely that PET molecular imaging could provide a similarly robust endpoint for other cancers, with FDG or other probes of cancer biology.

SUMMARY AND CONCLUSIONS

The considerable potential for molecular imaging as a biomarker to help direct cancer clinical trials and clinical practice is only just beginning to be realized. Future progress will depend upon a concerted effort by academia, industry, and governmental authorities and close collaboration between imagers and oncologists. An infrastructure for clinical trials that can support novel molecular imaging cancer biomarkers in the setting of therapeutic trials will be essential to

validating and supporting molecular imaging biomarkers and guiding their use in the clinic. The key role of quantitative image analysis is recognized by many investigators, and collaborative organizations such as the NCI's Quantitative Imaging Network (QIN) have been formed to provide guidelines and tools to direct quantitative biomarker imaging[12]. Future progress in the field will require the efforts of imaging scientists to improve the quantity and reliability of information gleaned form quantitative molecular imaging biomarkers in order to realize the full potential of the promising area of investigation.

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