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The Importance of Biopsy in the Era of Molecular Medicine

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Abstract

Recent advances in the molecular characterization of cancers has triggered interest in developing a new taxonomy of disease in oncology with the goal of using the molecular profile of a patient's tumor to predict response to treatment. Image-guided needle biopsy is central to this "Precision Medicine" effort. In this review, we first discuss the current role of biopsy in relation to clinical examples of molecular medicine. We then outline important bottlenecks to the advancement of precision medicine and highlight the potential role of image guided biopsy to address these challenges.

Keywords

Molecular medicine; image-guided needle biopsy; "precision-medicine"

Introduction

Over the past decade a tremendous amount of effort has been invested into translational research programs geared toward the advancement of "molecular medicine" (or "personalized medicine" or "precision medicine"). Broadly speaking, the goal of this research is to define a new taxonomy of disease, in which patients receive tailored treatments based on specific molecular characteristics of their tumor(1). Whether meritorious or perilous (2), there is little doubt regarding plans for continued investment. In 2015 President Obama announced a research initiative "that aims to accelerate progress toward a new era of precision medicine...[driven by] extensive characterization of biologic specimens (cell populations, proteins, metabolites, RNA, and DNA)"(3). Accurate and informative tissue biopsies are essential in this new era.

In oncology, biopsies are used to establish diagnosis of malignancy, identify tumor histology, and confirm presence of metastases for staging(4). With the advent of advanced imaging and image-guidance technologies, there has been an increase in the number of biopsies, largely performed by radiologists (5). In the era of molecular medicine, the role of image-guided percutaneous biopsies is now expanding as a growing compendium of molecular assays and biomarkers are used to determine prognosis, to predict treatment response, and to detect disease progression or treatment resistance. Biopsies are integral to

clinical trials, particularly adaptive clinical trials that attempt to study drug effects and identify relevant biomarkers (6). Recognizing this tremendous growth, the Society of Interventional Radiology (SIR) recently convened a research consensus panel comprised of a multidisciplinary group of experts to address how the field should evolve in the coming years(7). In this article we first review the current utility of image-guided biopsy in relation to molecular medicine and then discuss some unresolved issues and open questions facing the community.

The current role of image guided biopsy in molecular medicine

Biopsy in the era of molecular medicine: success stories

Advances in molecular medicine over the past 15 years represent a paradigm shift in oncology. One of the most striking examples of this is in lung cancer. In 2002, the Eastern Cooperative Oncology Group published results of a large randomized study comparing four different chemotherapy regimens in patients with advanced non-small-cell lung cancer.(8) The authors reported that none of the regimens provided an advantage over the others with abysmal response rates (19%) and median survival (7.9 months). Response rates of drugs that targeted epidermal growth factor receptor (EGFR) were known to produce dramatic responses, but were also limited to a small percentage of patients. However, it was soon recognized that these responses were seen in patients that carried activating EGFR mutations in their tumors(9, 10). Patients receiving EGFR inhibitors with biopsy-proven EGFR mutations demonstrated much higher response rates compared with traditional chemotherapy(11). Just three years later, investigators identified a subset of lung tumors with chromosomal aberrations in the anaplastic lymphoma kinase gene (ALK) (12). Targeted therapies with ALK inhibitors also improved response rates in this patient population.(13, 14) Over the course of the past decade, the classification of lung adenocarcinomas has moved from histology-based to *clinically relevant molecular subsets* (Figure 1). Biopsies for somatic mutation testing to guide patient management has become routine practice (15).

Examples of molecular prognostic and predictive biomarkers abound in other cancer types. In patients with breast cancer, erb-b2 receptor tyrosine kinase 2 (ERBB2) amplification (or protein overexpression) has long been known to be associated with poor prognosis (16). These patients frequently respond to trastuzumab, an antibody that blocks the ERBB2 receptor (17). Breast cancer tissue ERBB2 testing is now commonly performed alongside estrogen and progesterone receptor status assessment, and multiple diagnostic multi-gene assays are used to predict recurrence (18, 19). Patients with melanoma are tested for BRAF V600E mutations to identify potential responders to vemurafenib (20). Patients with colorectal cancers are examined for KRAS (and possibly other downstream effectors of the EGFR signaling pathway) to determine candidates for EGFR inhibitors (21–23). Metastatic bladder cancer patients with TSC1 mutations show durable remission when treated with everolimus (24). BRCA mutation carriers with various solid tumors show response to PARP inhibitors.(25) In some cases of rare and understudied tumors, treatment options may be derived from the presence of common mutations (26). Histologically unclassifiable cancers, or those without a known primary site, may be particularly amenable to such a strategy (27). Over-expression of programmed death ligand-1 (PD-L1) in tumor cells is associated with

objective response in patients treated Anti-PD-1 antibody, suggesting a role for biopsy to select patients best suited for immunotherapy.(28)

Clinical trials and biopsies

Promising exemplars have spurred many centers to develop and institute multiplexed genomic profiling with the intent of expediting relevant clinical trial enrollment (29). Indeed, the role of biopsies has expanded with more frequent incorporation of biomarker studies into clinical trials.(30), (31, 32) Predictive biomarkers offer the opportunity to streamline drug development by (a) enabling smaller trial designs and (b) identifying biologically based targets (6). Serial biopsies of the same or different tumors may be obtained throughout the course of treatment for these purposes (33).

Interventional oncology procedures

In the field of interventional oncology, there is a growing interest in identifying both prognostic and predictive markers of treatment response. Predictors of loco-regional cancer treatment efficacy, such as after tumor embolization or ablation, have traditionally focused on technical variables such as ablation margin and tumor size (34, 35). However, paralleling a shift toward molecularly guided systemic treatments, several investigators have recently focused on molecular biomarkers of local tumor response. For example, KRAS status prior to lung adenocarcinoma ablation was an independent predictor of local recurrence (36); thus prior knowledge of mutation status could influence decision-making regarding thermal ablation size, or possibly result in triage to a different treatment modality. Similar advances in biomarker discovery are being pursued with colorectal liver metastases where KRAS mutation status was found to predict poor prognosis after radio-embolization(37). Gaba et al, recently reported hepatocellular carcinomas with complete response to trans-arterial chemoembolization demonstrated upregulation in genes associated with pre-treatment chemotherapy-sensitivity and mitosis (38), although they did not report any correction for multiple testing. Further studies such as these are certain to shed light on the role of biomarkers in interventional oncology therapies. In the near future, compendiums of tissue biopsy profiles linked to patient outcomes are likely to guide best practices in oncology.

Histopathology

Conventional histopathology remains central to tumor classification.(39) For example, some cancers share mutations but respond differently to the same targeted therapy. In melanoma patients, BRAF V600E mutations are common and demonstrate excellent response rates to BRAF inhibitors. Yet, colorectal cancer patients with the same mutation show poor response rates (40). Another example is seen in the lung cancer literature. In 2011, the International Association for the Study of Lung Cancer, the American Thoracic Society, and the European Respiratory Society proposed a new classification system for lung adenocarcinoma.(41) Invasive lung adenocarcinoma tumor was subdivided into lepidic, acinar, papillary, micropapillary, solid, colloid, and invasive mucinous adenocarcinoma. Multiple studies in the surgery literature have since validated the prognostic utility of this classification with respect to recurrence patterns and post-recurrence survival, confirming the role of micropapillary and solid histologic subtypes as predictors of poor prognosis and high local recurrence even in completely resected early-stage lung adenocarcinomas(42, 43). The

molecular correlates of these subtypes remain poorly understood, underscoring the continued relevance of histology.

Open questions and challenges

Despite the advances in molecular characterization of tumors, there are several unresolved issues that represent critical bottlenecks to the advancement of molecular medicine (Table 1).

Specimen quality

A large phase II precision medicine trial was recently paused after an interim analysis showed only 87% of cases submitted completed tumor testing, largely due to poor sample quality.(44) Biopsy specimens were inadequate for testing in 26% of cases in a multicenter study of driver mutations in lung adenocarcinomas.(45) Given the patient risk and financial cost of biopsy, specimen quality and sufficiency are essential to the oncology community.

Currently there are no standard guidelines for tissue acquisition and preparation. Variables in tissue acquisition include technique (fine needle aspiration, core biopsy), needle gauge, number of samples, spatial sampling method within a tumor, number of sites, site location, primary vs metastasis. Formalin-fixed paraffin-embedded is the most widely used tissue preparation method and multiple molecular methods for DNA, RNA, and protein extraction have been developed.(46) However, formalin induced degradation, especially for RNA and protein is problematic. Additionally, standard decalcification methods in bone effects the quantity and quality of nucleic acids in the specimen.(47) Cellular and genetic preservation may become even more critical with the emergence of single cell analytic platforms.(48) Biopsy samples vary in tumor quantity; DNA, RNA, and protein quantity vary by organ and tumor. These issues may in part be offset by manual microdissection(46), but potentially important information about the tumor stroma may be ignored. Rapid on-site evaluation (ROSE) of imprint cytology or core biopsy touch preparation has been shown to improve diagnostic adequacy rate, (49) although it remains unclear whether ROSE can improve adequacy with respect to molecular characterization.

Heterogeneity

Tumor heterogeneity represents an important challenge for personalized medicine. Heterogeneity may be spatial within a single tumor, or occur across metastatic sites and time points. Gerlinger et al demonstrated that single biopsy specimens revealed only a minority of genetic aberrations when compared to the entire tumor(50) in renal cancer. Multiple biopsy sampling improved mutation detection, depending upon mutation prevalence.(51) In a cohort of lung adenocarcinomas, single-region sampling was sufficient to identify the majority of known cancer mutations(52). The role of spatial heterogeneity may therefore be dependent on the temporal evolution of the individual tumor. Differences in tumor grade between primary sites and synchronous/metachronous metastases have been reported in neuroendocrine tumors.(53) Studies systematically examining tumor heterogeneity are likely to inform treatment approaches in the coming years.

Assessing Resistance

Excitement regarding targeted therapies has been tempered by the inevitable development of treatment resistance.(54) For example, most lung cancer patients with activating EGFR mutations have median responses of approximately one year before therapeutic efficacy wanes. Resistance is attributed to a T790M point mutation in exon 20 in approximately one-half of such cases.(55) Several newer EGFR inhibitors are in development to overcome this resistance, commonly prompting re-biopsy to identify the T790M mutation.(56) Since resistance may only be seen in spatially localized subclonal populations in a tumor, mutationally representative tissue sampling remains a formidable challenge. Techniques that facilitate increase needle biopsy targeting specificity, such as real-time or multi-modal PET/CT fusion imaging, may be beneficial in this regard (7).

Assessing tumor response

The effectiveness of targeted therapies is generally evaluated using the standardized imaging-based Response Evaluation Criteria in Solid Tumors (RECIST). Fernandes et al contend that tumor size based response criteria do not directly measure what they define as meaningful progression (local invasion and metastasis) and should therefore be replaced (57). The authors' position is in part informed by the now well-established view of cancer as not a disease of abnormal cells, but a disease of abnormal cells within a tumor microenvironment (58). Quantitative and molecular imaging are offered as potential alternatives to assess tumor response, especially in the setting of targeted (non-cytotoxic) therapies (59–61). Correlative studies of imaging features with molecular changes via biopsies (e.g. radiogenomics (62)) will likely play an important role in this transition.

Liquid biopsies

Many investigators are seeking to develop biomarker analytics platforms based on blood samples rather than percutaneous tissue biopsies. So-called “liquid biopsies” denote the capture and extraction of circulating tumor cells (CTCs) or fragments of DNA (ctDNA). Since these methods are minimally invasive compared to other sampling alternatives, they have several potential advantages including lower patient risk and cost (7). Successful liquid biopsy technologies would simplify serial assessment of tumor response or acquired resistance. At the European Lung Cancer Conference (ELCC) 2016, several authors presented the feasibility of liquid biopsy to predict benefit in patients with lung adenocarcinoma. In one study, there was high concordance between T790M positive plasma and T790M tissue biopsies and in a second study there was high correlation between T790M-positive plasma and response rates to T790M-targeting EGFR inhibitor.(63, 64) However, unstable molecules such as RNA and protein are less likely to be reliably extracted and low volume disease may not be detectable. The fraction of ctDNA in a sample limits the sensitivity of such approaches. The previously discussed issue of tumor heterogeneity may also be relevant here, as it is unclear whether hematogenous tumor elements will be sufficiently representative to guide effective treatments. At least some of these issues may be addressed with systematic correlative studies between image guided biopsies and liquid biopsies.

Summary

We have reviewed the central role of image-guided biopsy in the era of molecular medicine. We have also highlighted several bottlenecks to the advancement of the field and which represent challenges and opportunities for interventional oncologists participating in image-guided biopsies.

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Figure 1.

Driver mutation profile of lung adenocarcinomas. Generated using data from cbio-portal based on 5 studies of lung adenocarcinoma(65). Targeted small molecule inhibitors are either approved or in development for all of the above mutations (66). “Other” category includes NRAS, FGFR1, and AKT1 which represent <1% of driver mutations.

Table 1

Bottlenecks to the advancement of molecular medicine	Relationship to image-guided biopsy
Sample Quality	Standardization
Heterogeneity	Spatial and temporal sampling
Tumor Resistance	Molecular imaging guidance
Assessing Response	Radio-genomics
Liquid Biopsy	Correlative studies

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