Editorial Commentary

Predicting progression of *in situ* carcinoma in the era of precision genomics

Monica Cheng[1], Nasser H. Hanna[2], Darrell D. Davidson[3], Richard B. Gunderman[1]

[1]Department of Radiology and Imaging Sciences, [2]Department of Medicine, Division of Hematology/Oncology, [3]Department of Pathology, Indiana University School of Medicine, Indianapolis, Indiana, USA

Correspondence to: Monica Cheng. Indiana University School of Medicine, 702 Barnhill Drive, Indianapolis, Indiana 46202, USA. Email: mocheng@iu.edu.

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Cancer control depends on early detection, a discipline formalized in the 1950s by widespread use of the Papanicolaou test for detecting pre-invasive squamous epithelial neoplasia of the uterine cervix (1-3). Studies growing out of that public health initiative have revealed a long latency between the earliest cellular abnormalities and invasive cancer. Pre-invasive or intraepithelial neoplasia arises in predisposed benign tissue, often influenced by metaplasia or inflammation (4,5). These precursor lesions can be reliably diagnosed by the microscopic appearance, but the biological behavior of these lesions is difficult to predict by histology alone. In situ carcinoma of the cervix or breast has only a 50% probability of eventually becoming invasive cancer (1-3).

Lung cancer is the leading cause of cancer-related death worldwide. Due to the late stage of diagnosis, patients with lung cancer often face poor prognosis with limited treatment options despite recent advances in cancer therapeutics (6,7). Early detection is therefore of critical importance, and a National Lung Screening Trial revealed that low-dose computerized tomography screening of 54,454 high risk individuals reduced lung cancer mortality by 20% (8).

Squamous cell carcinoma accounts for 30% of all lung cancers and is strongly associated with bronchial injury from smoking (9-11). Ongoing repair and regeneration of the airway epithelia results in squamous metaplasia with subsequent dysplasia, carcinoma *in situ*, and eventual transformation to squamous cell carcinoma (12,13). Although advances in immunotherapy and the development of multimodal therapies have augmented and improved treatment outcomes for patients with non-small cell lung cancer (NSCLC) (14,15), there remains no consensus on the management of precancerous lesions (1-3).

Squamous cell carcinoma of the lung begins as carcinoma *in situ* (CIS) in metaplastic epithelium of the bronchus, and has about 50% probability of becoming invasive squamous cell carcinoma within 2 years (16). Longitudinal studies using autofluorescence bronchoscopy to identify and biopsy areas of CIS have found that 30% of CIS lesions regress to benign or low-grade epithelial change, while 20% remain non-invasive for years under active surveillance (1,16). The ability to predict progression of CIS lesions therefore has the potential to significantly impact lung cancer prevention and treatment.

The recent *Nature Medicine* study by Teixeria and colleagues [2019] represents the first reported systematic whole genome sequencing analysis of lung CIS. This study aims to use molecular profiling to predict which CIS lesions will regress or progress to carcinoma (17). Whole genome sequencing, epigenetic profiling, and chromosomal instability analysis were applied to 129 CIS biopsy samples obtained from 85 patients who were followed for 5 years post-biopsy (17). All CIS samples that progressed to carcinoma possessed tumor suppressor *TP53* mutations and chromosomal amplifications and deletions characteristic

of squamous cell carcinoma (17). Although five of ten CIS lesions with *TP53* mutation appeared to regress, three of these subsequently developed recurrent CIS or cancer. Moreover, five genes associated with chromosomal instability (*ACTL6A*, *ELAVL1*, *MAD2L1*, *NEK2*, *OIP5*) were upregulated in progressive lesions compared to regressive samples. Progressive lesions had accrued significantly more mutations and copy number alterations than regressive CIS specimens. Principal component analysis of gene expression and methylation also revealed significant differences between progressive and regressive samples (17).

Molecular characterization of CIS lesions may clarify field cancerization mechanisms, elucidate the early processes of lung carcinogenesis, and guide the development of novel biomarkers for early detection and intervention (12,13). Previous studies have reported upregulation of chemokines including CXCL8-10 in preinvasive lung lesions, as well as dysregulated expression of stem cell associated genes such as *SOX2*, *SSBP2*, *RASGRP3*, and *PTTG1* (18). The PI3K/AKT signaling pathway is associated with the early pathogenesis of squamous cell carcinoma, and homozygous inactivation of *KEAP1* or *TP53* promotes clonal expansion of mutant airway basal stem cells (18). While Teixeria and colleagues suggest a predictive role for *TP53* mutations to identify progressive CIS lesions, the *TP53* point mutation has been known for decades to have widespread presence in the bronchi of smokers due to "field cancerization" (9,19,20). This effect cannot be overlooked in a study of subjects with smoking histories ranging from 30 to 100 pack years. Exposure to smoking-related carcinogens induces mutations in *TP53*, *KRAS*, and *EGFR* genes in addition to epigenetic alterations to mRNA and miRNA expression; these aberrancies contribute to the initial stages of lung carcinogenesis by increasing susceptibility to dysplasia and subsequent transformation to carcinoma (9,19,20). Studies have shown that p16 methylation is consistently induced by tobacco-specific carcinogen 4-methylnitrosamino-1-(3-pyridyl)-1-butanone in lung squamous cell carcinomas and 75% of adjacent CIS lesions (21).

Cancer is an evolving disease that interacts with a dynamic and heterogeneous tumor microenvironment, complicating efforts of early detection, treatment, and monitoring (22). By uncovering the molecular underpinnings of precursor lesions, it becomes possible to elucidate the common origins of tumorigenesis and improve preventive therapies through early detection tailored to the probability of disease progression. Combining molecular signature knowledge with recent advances in medical imaging and minimally invasive biomarkers can further enhance our ability to detect early disease and deliver targeted therapy to patients in the era of precision medicine (22).

Liquid biopsies, which analyze circulating tumor DNA, represent one method which enable real time monitoring of disease progression or regression (23). Cell free DNA is utilized to capture novel targetable mutations for the development of new treatments. Another noninvasive, *in vivo* approach to characterizing the malignant potential of neoplasms is molecular imaging (24-27). Although conventional imaging techniques such as CT revolutionized the diagnosis, staging, and monitoring of tumor progression and response to therapy, it did so by focusing on features such as size, macroscopic morphology, density, and water content. As evermore biomarkers associated with malignancy are identified, molecular imaging offers the promise of higher degrees of precision and functional characterization of neoplasms (28,29). Such improvements may manifest as targeted MRI contrast agents, optical agents that rely on chemical traits such as fluorescence and bioluminescence, and single photon emission computer tomography imaging using radiopharmaceuticals. As these examples indicate, progress in the field will depend on the development of appropriate biological probes. Furthermore, radiomic image feature extraction and deep learning have the potential to augment clinical diagnostics through quantification of radiographic features (e.g., shape, size, texture) and assessment of intratumor heterogeneity. These capabilities can translate to radiometric biomarkers that inform and complement clinical expertise and screening tests.

Recent breakthroughs in immune checkpoint blockade, along with a deeper understanding of tumor immune biology, have further added to the repertoire of targeted cancer therapeutics, but only for a subset of patients (14,15). Radiomic biomarkers represent a minimally invasive method to characterize tumor hallmarks easily complemented by genomic data for early detection and treatment monitoring. Together with genomic data, radiomic biomarkers can help predict response to immunotherapy and guide patient selection for treatment (27,28). A recent study showed that radiomic features—region dissimilarity and entropy—significantly predict overall survival of patients with NSCLC who received anti-PD1 treatment (nivolumab) (26). These results reveal a heterogeneous tumor landscape that eludes traditional tissue biopsies, yet is captured by radiomic imaging data. Combining

radiomic analysis with molecular data enables the development of treatment tailored to the distinctive features of each tumor or pre-invasive lesion (27-29).

Together, these advancements spanning molecular, pathological, and image-derived radiomic and deep learning data greatly enrich the evolving landscape of cancer diagnostics and therapeutics in the era of precision medicine.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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