Malignancy Associated Change and The LuCED® Test for Detection of Early Stage Lung Cancer

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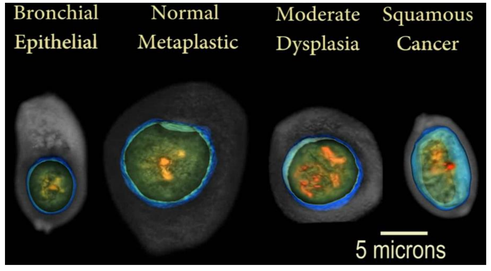
Background

Sputum Prep: Dissolves mucous, stains chromatin, enriches for bronchial epithelial cells
Cell-CT® Platform Processing: Automatically analyzes cells in true 3D with isometric, sub-micron resolution



Motivation:
Early detection remains by far the most reliable and potent strategy in curing lung cancer. Many current approaches, however, are limited by poor sensitivity or specificity that increase health care costs and potentially risk patient health through unneeded and invasive procedures. The Cell-CT™ platform and LuCED® test represent a promising new method for detecting lung cancer with high (92%) sensitivity and (95%) specificity that is based on alterations in cellular morphology.
The association between cell morphology and cancer has been established in the cytology literature. However, the tumor field effect potentially introduces subtle changes into non-tumor cells that reside in the tumor microenvironment. This phenomenon has given rise to the malignancy associated change (MAC) hypothesis.
We present a study of 3D morphological alterations in non-tumor cells obtained from sputum of healthy subjects and biopsy confirmed lung cancer patients.

Methods

Study Materials:

- Non-invasive sputum specimens from 235 patients with and without biopsy confirmed lung cancer were processed using the Cell-CT™ platform
- 3D cell images from these patients were examined to find squamous intermediate, macrophages and bronchial epithelial columnar cells that were within the normal range by cytology:

Cell Type	Number of cells from cancer patients	Number of cells from normal patients
Squamous Intermediate	2316	684
Macrophages	4960	5040
Columnar cells	3227	3234

Hierarchical Clustering Analysis:

- Heatmap of 3D morphological features of macrophage cells
- The first 200 features with most discriminatory power between normal and cancer cases are shown
- Features were selected based on statistical significance (p-value) of differentiation between normal and cancer samples
- Clustering highlights 'dissimilar cells' (macrophages) obtained from normal subjects and cancer patients

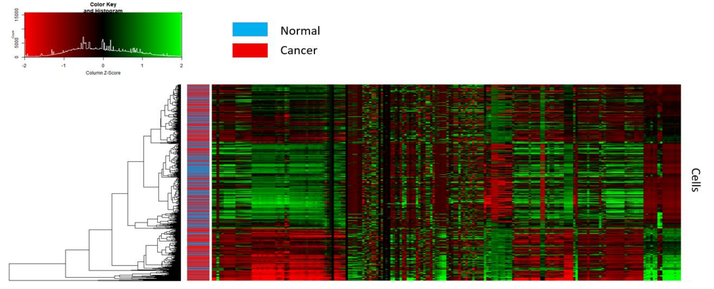
Classifier Development:

- Over 700 morphometric biosignatures for each 3D cell image:
  - Nuclear, cell and cytoplasm segmentation
  - Texture – chromatin arrangement, distribution within nucleus
  - Nuclear/Cytoplasm volume ratio
  - Nuclear Grooves
- Ground truth defined by the biopsy status and dissimilar clusters
- Adaptively boosted logistic regression
- Three separate classifiers for each of the above cell types

Results and Conclusions

Results:

Cell Classifiers	Area Under ROC
Squamous Intermediate	0.94
Macrophages	0.94
Columnar	0.92



Heatmap analysis indicates distinct features distribution patterns of macrophage cells correlated with normal vs. malignant diagnosis.

Conclusions:
Our results suggest that the Cell-CT platform can discriminate cell features that are too subtle to distinguish by a human. The study suggests that detection of cells with Malignancy Associated Changes may be used to further enhance the LuCED test's performance beyond published levels.

Cell-CT™ 3D cellular imaging shows promise as a means of identifying patient lung cancer based on malignancy associated change, without the need to detect actual cancer cells

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