



Can We Improve Detection of Early Stage Lung Cancer by Using Automated Image Analysis (ClearSign™ Test) of Sputum?

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During the last few years Automated Image Analysis of sputum (ClearSign™ test) has evolved into a valuable diagnostic and prognostic tool in cytopathology. A good portion of the utility of Automated Image Analysis comes from its ability to detect and quantify the DNA amount and distribution in cell nuclei which cannot be done using conventional stain in routine cytology screening. Furthermore, the collection of sputum is a highly tolerated, non-invasive procedure for the collection of a clinical sample.

We have employed Automated Image Analysis of several thousand sputum cell nuclei per subject. The nuclei were stained by DNA specific stain which enables the quantitative assessment of over one hundred features that describe the amount and distribution of DNA, as well as the shape of the individual nuclei.

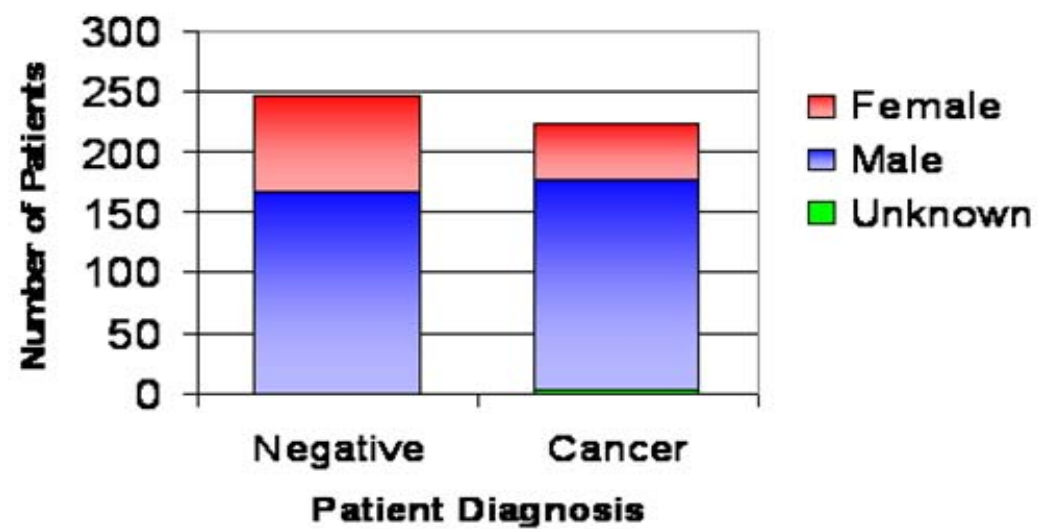


1043 high risk individuals aged 45 and over were enrolled in the pre clinical and clinical study during four year period (2000-2004). High risk negative group was comprised of COPD patients; patients exposed to asbestos and long term smokers or ex smokers. For each patient's groups pack years were collected.

Out of the 1043 high risk patients, 248 negative and 225 lung cancer specimens came from the pre-clinical study. The clinical study has not been un blinded therefore the remaining clinical specimens are not included in the data analysis.

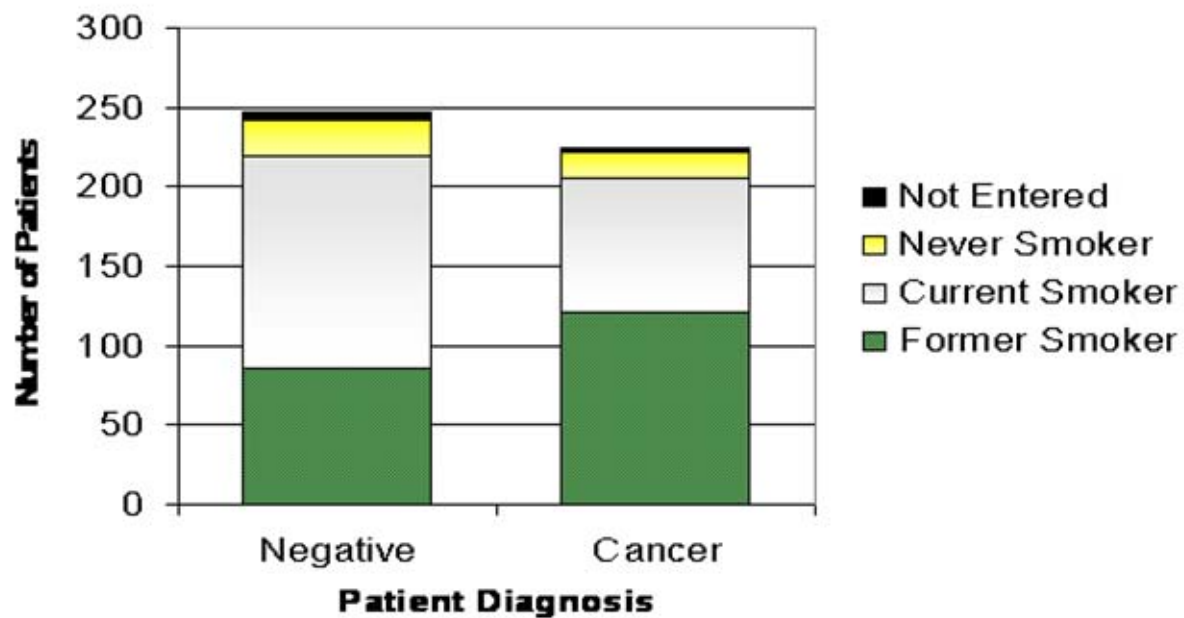


Number of Male and Female Patients in the Pre-Clinical Study





Smoking status of the negative and lung cancer patients in the pre-clinical study

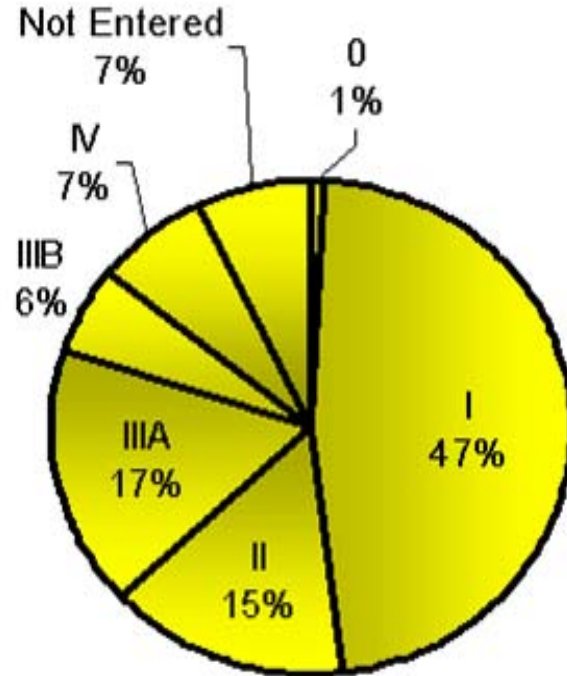




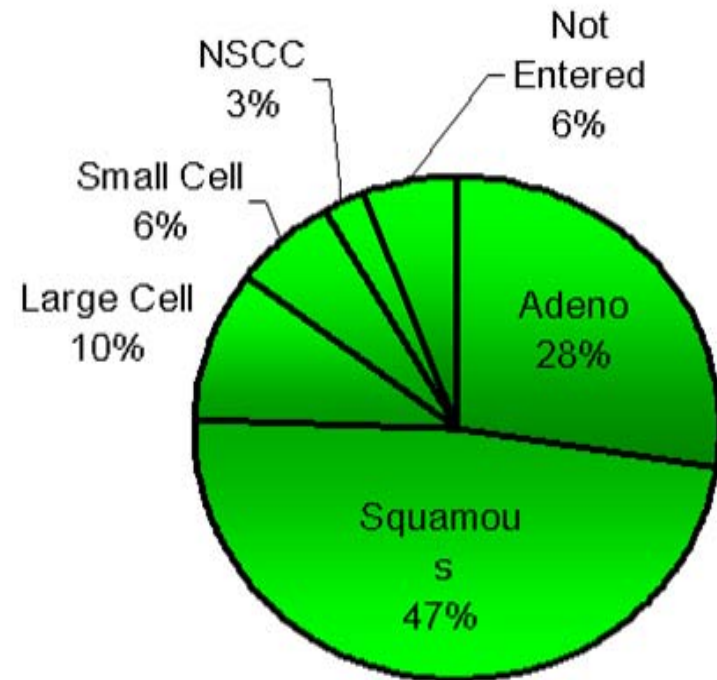
	Negative	Lung Cancer
Mean Pack-Years	36	41
Median Pack-Years	34	38



Stage of the 225 Lung Cancer cases



Histological Types of the 225 lung cancer cases





All subjects were given chest x-rays and sputum samples were acquired by induction using ultrasound nebulizers. All patients were also examined by either spiral CT or by bronchoscopy, and some were examined by both of these methods. The majority of cancers were confirmed by surgical biopsies. Sputum samples were processed for both conventional qualitative cytology and Automated Image Analysis. A fully automated, high resolution image cytometer (ClearSign™ Test - Perceptronix Medical Inc., Vancouver, Canada) was used to establish the probability for the presence or absence of lung cancer based on measurements of DNA amount and nuclear distribution in populations of cells.

In the pre-clinical study, of the 224 lung cancer patients 46 gave their sputa before and after lung cancer surgery performed with curative intent.



The table below show the results of ClearSign™ test set at 90% specificity. The test has correctly classified 53% of the lung cancer patients, and 87% of the negative patients. Interestingly ClearSign™ was better able to classify early stage cancers than late stage. It also showed higher sensitivity on centrally located squamous cell carcinomas.



Histology	Number of Specimens	Sensitivity (%)
Adenocarcinoma	57	45 ± 9
Squamous Cell	91	50 ± 8
Small Cell	12	29 ± 14
Other*	33	54 ± 13

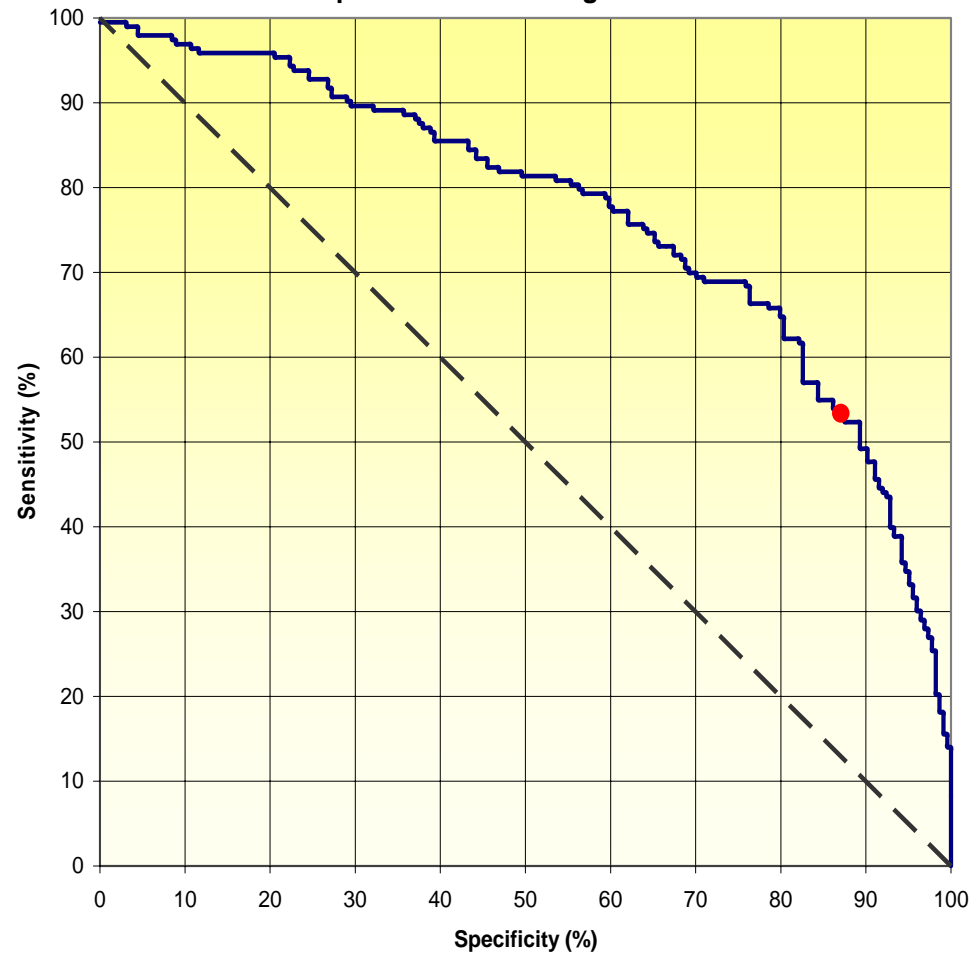
Other* (this group includes Large cell, NSCC –not specified or mixed squamous cell and adenocarcinoma.



Stage	Number of Specimens	Sensitivity (%)
I	95	54 ± 7
II	25	41 ± 12
Other	73	43 ± 9

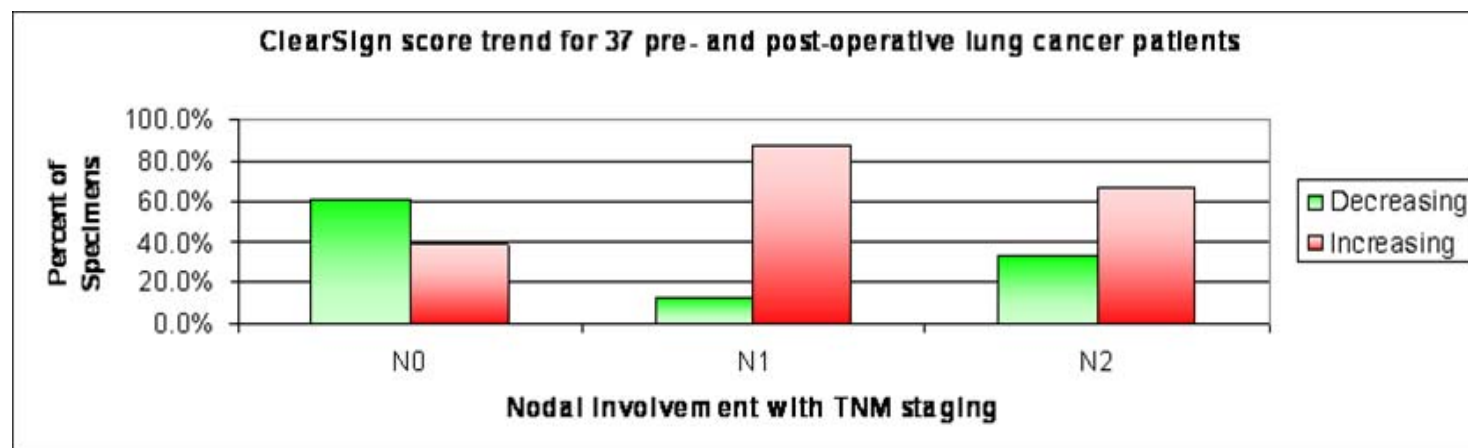


ROC Curve using 224 Negative Cases and 193 Positive Cases. Red point indicates operating point of the ClearSign test.





Of the 46 patients who gave samples before and after surgery, 37 produced satisfactory specimens both before and after. 17 scores decreased after surgery, 20 scores increased.





The discussion will also address the role of Automated Image Analysis of sputum in a comprehensive approach to detection and prevention of invasive lung cancer and its potential role in post-operative monitoring of lung cancer patients.

Analysis of score trends based on other measures that typically guide prognosis show that the score trends are related to nodal involvement and to cancer stage.





Clearly, the future use of Automated Quantitative Image Analysis (Clear Sign Test) is yet to be seen. We found these results to be promising and are expecting to gain much more knowledge once data from prospective study become available





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