Utility of a Computer-Aided Diagnosis Program in the Evaluation of Solitary Pulmonary Nodules Detected on Computed Tomography Scans: A Prospective Observational Study

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A. Study Purpose and Rationale

Lung cancer is the most common cause of cancer death in the United States, accounting for approximately 160,000 deaths a year. Lung cancer carries a poor prognosis: the average five-year survival is less than 15%. Diagnosis often occurs late, contributing to the poor overall prognosis. Survival ranges from 70% for Stage I disease to less than 5% for Stage IV disease.[1] Early detection of lung cancer with computed tomography (CT) scans has the potential to find resectable tumors and thus improve prognosis.[2] However, as more chest CT scans are performed, whether for routine lung cancer screening or for symptoms, more non-cancerous pulmonary nodules are also detected.

Pulmonary nodules are found on 20% of CT scans performed for screening purposes, with likely an even higher incidence in CT scans obtained for symptoms. The differential diagnosis of the solitary pulmonary nodule (SPN) is broad, and includes neoplasm (primary lung cancer or metastasis) and benign entities (i.e. granuloma, hamartoma, and hemangioma). The incidence of malignancy in pulmonary nodules varies in the literature from 10-68%, but is approximately 30% for nodules less than three centimeters in diameter. Work-up of the SPN may include invasive measures, such as transbronchial biopsy, CT-guided fine needle aspiration, video-assisted thoracoscopic surgery, or thoracotomy. However, depending on clinical suspicion for malignancy, the SPN may be followed by serial imaging, typically CT scan initially every 3-6 months, with invasive procedures then utilized in the event of enlargement of the nodule. A nodule that is stable in size for two years is considered benign. The decision to "watch-and-wait" or to pursue diagnostic procedures (which carry significant risks) is informed by clinical data, imaging, and "gestalt." [3-7]

Computer-aided diagnosis (CADx) programs are designed to assist with this clinical decision. A CADx program can interpret nodules on CT scan and generate either a probability of malignancy or a preliminary yes/no diagnosis. Various groups have worked to develop CADx programs by retrospectively correlating CT characteristics of pulmonary nodules with known malignant or benign status.[8-10] These radiographic characteristics include nodule size and density, calcification patterns, and margin features. A previous study has shown that a CADx program can improve physicians' prediction of malignancy.[11] Li, et al, created a CADx program that produces a probability of malignancy (1-99%) for a pulmonary nodule. They utilized a collection of 59 CT scans with known malignant or benign nodules and asked a group of 16 radiologists to state the probability of malignancy for each CT and their planned diagnostic work-up (return to annual screening, follow-up in three months, follow-up in six months, or biopsy or surgery). The radiologists were then given the probability generated by CADx analysis and again asked to rate their own probability of malignancy and list their diagnostic work-up. They evaluated the performance of the CADx program

and of the physicians before and after learning the CADx result. By comparing receiver operating curves for the three groups, they determined that the CADx program performed better than the physicians, but physicians using CADx program were superior to either alone. A major drawback of this retrospective study is using radiologists to predict malignancy and determine diagnostic work-up, as this is typically the role of the pulmonologist or thoracic surgeon. This program now needs to be evaluated for clinical utility in a prospective study to determine if CADx can truly change physician practice.

B. Study Design and Statistical Analysis

This will be a prospective observational study evaluating the addition of a CADx program to the diagnostic work-up of solitary pulmonary nodules. We hypothesize that, when added to the routine diagnostic work-up, a CADx program can improve a physician's accuracy at predicting the malignancy of a nodule. We predict that this will be clinically significant, with more aggressive work-ups for malignant nodules and avoidance of unnecessary biopsies for benign nodules. In contrast to the Li, et al, study, the CADx program will be modified to produce a preliminary yes/no diagnosis and the physicians will be asked to make yes/no diagnoses.

The primary outcome will be the accuracy of physician prediction of malignancy with CADx input, as compared to their accuracy before this data is given. Several secondary outcomes are also of interest: the accuracy of physicians using standard-of-care work-up, the accuracy of the CADx program, change in physician decisions regarding probability of malignancy and diagnostic work-up, number of invasive procedures avoided or performed unnecessarily, number of cancers "missed" (found by enlargement on later serial imaging instead of aggressive initial work-up), and physician perception of CADx as an adjunct to clinical decision-making.

The study will be powered to detect an improvement in accuracy from 70 to 80% with CADx input. Power calculations must incorporate the possibilities of physicians switching their answers both correctly and incorrectly. Here we assume that physicians will change their answer from wrong to right 20% of the time and from right to wrong 10% of the time; it will be unchanged in 70%. This is generous for our calculations, since the Li, et al, study demonstrated that the physicians rarely changed their prediction when confronted with an incorrect CADx calculation. Using a chi-square test, 230 participants are needed to achieve a power of 80% with a p-value of 0.05.

C. Study Procedure

Patients with newly discovered pulmonary nodules are typically referred to pulmonary or thoracic surgery clinic. Fliers will be posted in these clinics and pulmonologists and thoracic surgeons will be encouraged to participate by referring their patients with solitary pulmonary nodules 0.5-3.0 cm found on non-contrast chest CT. Informed consent will be obtained from the patients and their physicians for participation in the study. The physicians and their patients will be informed that the study is designed to evaluate the addition of a new computer program for diagnosis of pulmonary nodules. Physicians will be told the sensitivity and specificity of the CADx program (80% and 75%, respectively, in the prior study).

The physicians will complete their usual work-up (history, physical, review of the radiologic imaging including chest X-ray, CT scan, and possibly PET scan), and then fill out a questionnaire, making an informed guess about the nodule (cancer/benign). They will also state the next step in their diagnostic work-up (repeat CT scan in 12, 6, or 3 months; biopsy via bronchoscopy, CT-guided FNA, or VATS; or thoracotomy). The CADx program will be applied to the CT scan and will also give a designation benign or malignant. The physicians will be given this information and then be asked to repeat the questionnaire. On the second questionnaire we will also ask if the CADx information assisted their decision-making process.

The patients will undergo diagnostic work-up; the pulmonary nodule will ultimately be diagnosed as malignant or benign. There are several possible endpoints: (1) the nodule is biopsied and found to be cancer; (2) the nodule is biopsied and found to be benign; (3) the nodule is stable for two years and designated benign; (4) the nodule grows, is biopsied, and found to be cancer; (5) the nodule grows, is biopsied, and found to be benign. The intervening work-up is not relevant to the primary endpoint; we are evaluating the physician's initial impression of malignancy with and without CADx input with respect to the ultimate diagnosis (made up to two years later).

D. Study Drugs

Not applicable.

E. Medical Device

Not applicable.

F. Study Questionnaires

Physicians involved will fill out a questionnaire before and after acquiring the CADx program results.

Nodule is:
___ malignant
___ benign

Plan for initial work-up:
___ serial CT scan
- ___ return in 12 months for repeat CT scan
- ___ return in 6 months for repeat CT scan
- ___ return in 3 months for repeat CT scan

___ biopsy
- ___ transbronchial biopsy
- ___ CT-guided FNA
- ___ VATS

___ thoracotomy

Does CADx input help you make this clinical decision?
[included only on second questionnaire]
___ yes
___ no

G. Study Subjects

Participants will be patients aged 40-75 years with no known cancer (excluding non-melanoma skin cancer), fit to undergo thoracic surgery, who are found to have a solitary pulmonary nodule 0.5-3.0 cm on non-contrast chest CT.

H. Recruitment of Subjects

Patients presenting to pulmonary or thoracic surgery clinic who meet eligibility criteria will be recruited for the study.

I. Confidentiality of Study Data

Information about study participants will remain strictly confidential. All patients and physicians participating will receive unique code numbers; no personal identifiers will be used in the study.

J. Potential Conflict of Interest

The author of this study does not have financial interest in the CADx software.

K. Location of the Study

The study will take place at Columbia-Presbyterian Hospital.

L. Potential Risks

It is possible that the CADx program may incorrectly diagnose a malignant nodule as benign and that this information may convince a physician to forego aggressive initial work-up, delaying the diagnosis of cancer. It is also possible that a benign nodule may be designated as malignant by CADx, thus convincing a physician to pursue an invasive diagnostic procedure with its potential morbidity. Study participants will be informed of these possibilities.

M. Potential Benefits

Of our hypothesis is true, study participants may benefit from more accurate determination of the malignancy of pulmonary nodules, and thus have earlier diagnosis of lung cancer or avoid unnecessary invasive procedures.

N. Alternative Therapies

The alternative to adding CADx to the diagnostic work-up is to continue with the standard-of-care workup as per the study participant's physician.

O. Compensation to Subjects

There will be no compensation to subjects for participating in this study.

P. Costs to Subjects

There will be no costs to subjects for utilizing the CADx program.

Q. Minors as Research Subjects

No minors will be involved in this study.

R. Radiation or Radioactive Substances

Not applicable.

S. References

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