Computed Tomography Screening
The International Early Lung Cancer Action Program Experience

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KEYWORDS

• CT screening • Lung cancer • Assessment of benefit • Screening study design
• Diagnostic performance • Cure rate • Curability

KEY POINTS

- The Early Lung Cancer Action Project (ELCAP) was the first study of computed tomography (CT) screening for lung cancer when it started in 1992. It was designed to provide the relevant quantitative *diagnostic and prognostic* performance measures of annual CT screening using an innovative design.
- The ELCAP design recognized the profound difference between the baseline round and all subsequent rounds of annual screening and also that the annual rounds can be pooled. ELCAP also recognized that the *regimen of screening* is a critical component that determines the diagnostic and prognostic performance measures. The initial regimen was chosen to understand growth of small lung cancers, and the resulting data were used to continuously assess and update the regimen for the successor projects of the New York ELCAP and the International ELCAP (I-ELCAP).
- Key metrics of diagnostic performance are the proportion of participants diagnosed with stage I lung cancer, tumor size at diagnosis, and time from initial identification of the abnormality to treatment. The key prognostic performance measure is the *curability gain* that is achieved by early diagnosis followed by early treatment. The curability gain is defined by the proportional reduction in the case-fatality rate of lung cancer under optimal CT screening, diagnostic workup, and treatment as compared with the case-fatality rate in the absence of screening, whereby the case-fatality rate is equal to 1 minus the cure rate.

BACKGROUND

Stimulated by the technologic advances in computed tomography (CT) scanning that made it possible to image the lungs in a single breath, the Early Lung Cancer Action Project (ELCAP) was developed to assess the benefit of annual CT screening for lung cancer. The study design provided both a low-dose chest CT and a chest radiograph (CXR) to participants at high risk of lung cancer to obtain *diagnostic* information on the frequency of nodule detection and that of diagnosed lung cancers on both imaging modalities as well as prognostic information on predictors of cure and ultimately the estimated cure rate of

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lung cancers diagnosed *under* screening—the screen-diagnosed cases as well as the symptom-prompted cases of lung cancer that come to attention before the next round of annual repeat screening (**Fig. 1**).[1] Critical to the diagnostic and prognostic performance is the *regimen of screening* (how to do the screening), which specified the required imaging technique, definition of a positive result, clinical workup and its timing for positive results, and the pathologic confirmation of the diagnosis.

ELCAP was started in 1992 when the initial funding was obtained. Its goal was to enroll 1000 participants, and for this it later received additional funding from a National Cancer Institute (NCI) grant.[2] The results of the baseline round of screening were reported in 1999[3] and those of annual rounds were reported in 2001.[4] ELCAP demonstrated that a high proportion of the patients with lung cancer were diagnosed in stage I with low-dose CT scans together with a shift to smaller tumor sizes, particularly on annual repeat screening. Of the participants diagnosed with stage I lung cancer in the baseline round, 83% were missed on CXRs performed at the same time[3]; thus, CXR was not provided in annual repeat screening rounds.[4]

The baseline results were widely publicized[5] and stimulated renewed public debate about the merits of screening for lung cancer. To provide further information and discuss future research projects, the ELCAP investigators organized the First International Conference on Screening for Lung Cancer in New York City in October 1999.[6] In addition to the established ELCAP investigators and others following their original paradigm,[7–11] the conference was attended by investigators from Japan who had developed their own screening programs,[12,13] representatives from the American Cancer Society, the NCI, and many other organizations, physicians, statisticians, epidemiologists, and experts in imaging and other related disciplines. The public interest in CT screening led to multiple discussions at the NCI Advisory Board meetings beginning in 1999 and led the director of the NCI to call for a Lung Cancer Progress Review Group Report[14] to establish the future research agenda. In regard to CT screening for lung cancer, the report recommended that *multiple approaches* be pursued to address all relevant questions. "Several meetings co-sponsored by NCI and the American Cancer Society have determined that several study designs in addition to a mortality endpoint-randomized trial (the gold-standard approach) are important and valid.[14]"

At the second International Conference on Screening for Lung Cancer,[6] the consensus recommendation was to pool data on CT screening from different institutions to allow for rapid assessment of its effectiveness rather than waiting for later meta-analyses of individual screening projects. To this end, a common protocol for screening was developed that was unanimously adopted at the third International Conference and that also allowed for inclusion of data from the CT screening arm of randomized controlled trials.[15,16] Subsequently a common protocol for pathology was also developed.[17]

After the initial publications[3,4] and the development of the common protocol in 2000,[16,17] ELCAP expanded to a trial of 6295 participants involving 12 institutions in the state of New York (NY-ELCAP) using the same enrollment criteria as the original ELCAP.[18] At the same time, other national and international sites expressed interest in joining ELCAP leading to the formation of the International Early Lung Cancer Action Program (I-ELCAP) collaboration in 2000, which provided further expansion to 31,567 participants who had annual CT screening and resulted in the publication of the survival benefit of CT screening.[19] According to the common I-ELCAP protocol, the research sites were permitted to set their own enrollment criteria as to age and smoking history in order to broaden the knowledge base for determining the indications for screening.[15,16] Ultimately, the goal of the ELCAP design was to provide quantitative estimates of relevant diagnostic and prognostic parameters.

DIAGNOSTIC MISSION

The ELCAP design can provide the relevant *diagnostic* information to any desired precision by

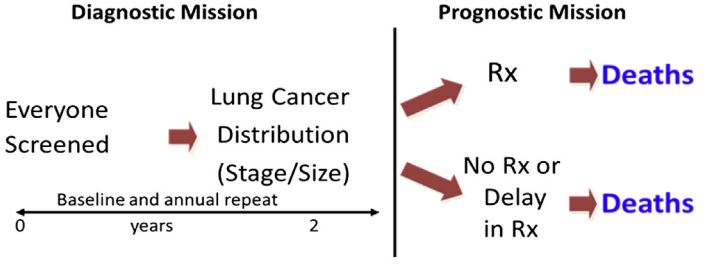

Fig. 1. In ELCAP, the diagnostic and prognostic missions are evaluated separately. The diagnostic mission is to determine the distribution of diagnosed lung cancers by relevant prognostic indicators (eg, stage and size). The prognostic mission is to determine the cure rate of the diagnosed and treated cases of lung cancer under screening. R_x, treatment.