Int. J. Cancer: **122,** 2594–2599 (2008)

Mean sojourn time and effectiveness of mortality reduction for lung cancer screening with computed tomography

Chun-Ru Chien[1,2] and Tony Hsiu-Hsi Chen[1]*

[1]*Institute of Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan*
[2]*Division of Radiation Oncology, Department of Oncology, National Taiwan University Hospital, Taipei, Taiwan*

This study aimed to estimate the mean sojourn time (MST) and sensitivity of asymptomatic lung cancer (ALC) detected by computed tomography (CT) or chest X-ray (CXR). Translation of early diagnosis into mortality reduction by 2 detection modalities and inter-screening interval was projected using a Markov model. On the basis of systematic literature review, data from 6 prospective CT screening studies were retrieved. The MST in association with the natural history of lung cancer depicted by a 3-state Markov model was estimated with a Bayesian approach. To project mortality reduction attributed to screening, the model was further extended to 5 health states for the inclusion of prognostic part. The analysis was run with a 10-year time horizon of follow-up, mimicking the Dutch-Belgian randomized lung cancer screening trial (NELSON). Screening for lung cancer with CT had high sensitivity (median: 97%) and may advance 1 year earlier than CXR in detecting ALC. By simulating the scenario similar to NELSON study, CT screen may gain an extra of 0.019 year of life expectancy per person, yields 15% mortality reduction (relative risk (RR): 0.85, 95% confidence interval [95%CI: (0.58–1.01)]. Approximate 23% [RR: 0.77, 95%CI: (0.43–0.98)] mortality reduction would be achieved by annual CT screening program. The mortality findings in conjunction with higher sensitivity and shorter MST estimate given data on prevalent and incident (2nd) screen may provide a tentative evidence, suggesting that annual CT screening may be required in order to be effective in reducing mortality before the results of randomized controlled studies available.

Key words: lung cancer; computed tomography; mean sojourn time; Bayesian approach

Lung cancer is the leading cause of cancer death in the world with 14% of 5-year survival rate.[1] To reduce mortality, different screening modalities have been applied to detect asymptomatic patients with lung cancer since 1980. There is suggestive evidence that less long-term mortality reduction for lung cancer screening targeted to smoker with chest X-ray (CXR) and sputum cytology has been demonstrated in previous studies.[2,3] An ongoing trial for average-risk subjects with CXR has been undertaken.[4]

With the advent of high-resolution computed tomography (CT), early detection of lung cancer become promising. Several randomized trials have been under way to assess the effectiveness of CT for screening lung cancer.[5,6] As CT can detect early stage tumors which are hardly visible in CXR,[5] it may have higher sensitivity than CXR.[7] From the viewpoint of disease natural history, this also implies that the MST based on CT may be longer than that based on CXR. However, there is lacking of empirical data supporting this postulate. The related previous studies reported a wide range between 7–8 months and 4 years. However, all of these estimates were based on CXR modality.[8,9]

Since MST is highly correlated with sensitivity, it is very difficult to disentangle both estimates using data from interval cancer, which are composed of newly diagnosed cancer and false negative cases.[10] The former is determined by a rapid progression whereas the latter is affected by the detectability of screening tool.

Whether the reported high sensitivity of CT[7] is attributed to long MST or high detectability cannot be easily discerned. Information on MST provides an important parameter for constructing the disease natural history without being interrupted by screening program and is a useful indicator for the determination of inter-screening interval.[11] The incorporation of sensitivity also makes contribution to estimating effectiveness given different screening schedules. The purpose of our study was to estimate the MST of lung cancer by screening CT with a Bayesian approach based on data reported from literatures as well as to apply these MST parameters in conjunction with other parameters relating to prognosis to predict mortality reduction of lung cancer given a series of scheduled screening programs of CT or CXR.

Material and methods

Search for literatures

We used the keywords including "lung cancer," "screen*" ("* depicts wildcard"), and "CT" to look up relevant literatures *via* PUBMED system (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi) until March 2007. To reduce bias inherent from retrospective study design, only studies with the prospective study design were included. We identified 18 prospective studies that are of potential for estimating MST.[12–29] To develop the likelihood function for estimating MST, we included studies reporting exact number of screen-detected lung cancer at prevalent screen, incident screen and interval cancers diagnosed between screens.

Our definition of prevalent screen and incident screen follows the conventional use in cancer screening. Although the terms used in these articles are different from those used in the context of conventional screening papers they are consistent, however. Baseline screening (ELCAP,[14] Diederich *et al*.,[16,30] Pastorino *et al*.,[19] Novello *et al*.,[29] Gohagan *et al*.[13,31]) or initial screening (Sone *et al*.[17]) corresponds to prevalent screen (first screen). Prevalent screenees in each study have been defined as either asymptomatic subjects (ELCAP,[14] Diederich *et al*.,[16] and Novello's *et al*.[29] study) or subjects free of lung cancer history (Pastorino *et al*.[19] and Gohagan *et al*.[13] study). Among these prevalent screenees, those identified to have lung cancer in each study were defined as the prevalent cases.

Regarding incident screen, 2 studies (ELCAP,[14] Gohagan *et al*.[13]) have reported the design of 2 rounds of screen [prevalent screen and incident (2nd round) screen]. Another study (Pastorino *et al*.[19]), although designed to have annual repeated screen for 5 years, has so far reported the results on 2 rounds of screen. The similar information has been reported in Diederich *et al*.,[16] study but their repeated screening is subject to several considerations such as age and funding. In original Sone *et al*.[17] and Novello *et al*.[29] papers, although they reported several rounds of screen, *i.e*., annual repeated screening, information after 2nd follow-up screening was not taken into account in order to be consistent and reduce the heterogeneity across studies as possible as we can. The incident screen used in meta-analysis in our study has been defined as the 2nd round of screening. Among these incident

This article includes supplementary material, available online at http://www.interscience.wiley.com/jpages/0020-7136/suppmat.

***Correspondence to:** Institute of Preventive Medicine, College of Public Health, National Taiwan University, Room 521, No. 17 Hsuchow Road, Taipei 100, Taiwan. Fax: +886-2-2358-7707. E-mail: stony@episerv.cph.ntu.edu.tw

Received 12 August 2007; Accepted after revision 3 December 2007
DOI 10.1002/ijc.23413
Published online 26 February 2008 in Wiley InterScience (www.interscience.wiley.com).

TABLE I – CHARACTERISTICS OF TRIALS INCLUDED IN MEAN SOJOURN TIME ESTIMATION[1,2]

Author	Gohagan *et al.*[133]	Henschke *et al.* [14]	Diederich *et al.* [16]	Sone *et al.* [17]	Pastorino *et al.* [19]	Novello *et al.* [29]
Trial period[4]	2000	2001	1997	1999	2000	2001
Country	USA	Multi-national	Germany	Japan	Italy	Italy
Gender (male %)	59	NA	72	52	71	74
Age (y)[4]	65	61	53	64	58	59
Non-smoker (%)	0	10[5]	0	54	0	0
Screen interval (y)	1	1[4]	1	1	1	1
Prevalent screen[6]	1,586	31,567	817	5,483	1,035	520
Incident (2nd) screen[6]	1,398	27,456	668	4,425	996	495
Prevalent cancer[6]	30	405	11	22	11	5
Interval cancer[6]	2	5	5	1	0	0
Incident cancer[6]	8	74	9	25	11	3
Double reading	NA	NA	NA	NA	Required	Required

NA, not available; Y, year.
[1]Major criteria for positive screen: >4 mm noncalcified,[13] >5 mm solid noncalcified or >8 mm nonsolid noncalcified,[14] >10 mm noncalcified,[16] Categorical classification (denoted as probable or possible),[17] >5 mm noncalcified[19,20].–[2]Subsequent work-up: Referred to personal health care provider[13] and Protocol specific recommendation.[14,16,17,19,20]–[3]Arm of computed tomography only.–[4]Median.–[5]Other risk factors required.–[6]Number.

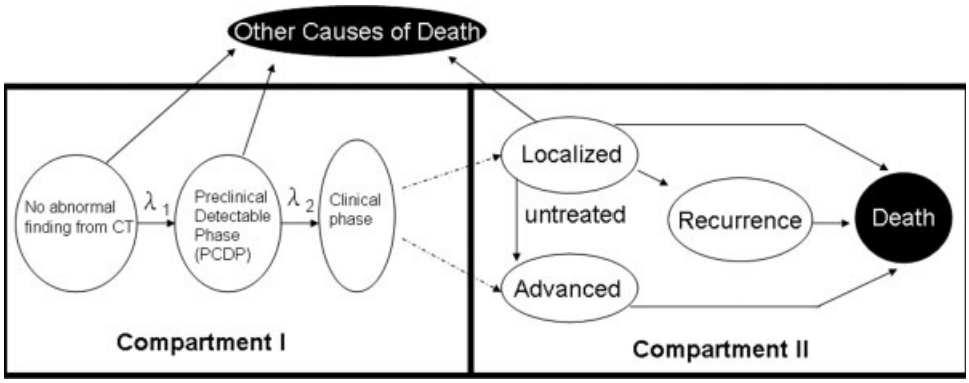

FIGURE 1 – The conceptual framework on state transitions using Markov model. A simulated patient spends time in a Markov state every cycle until he/she dies. Arrows means transitions that are made with each cycle.

screenees, those identified to have lung cancer by incident (2nd round) screen in each study was defined as the incident cases.

Studies excluded from the following analysis are those with the provision of abstract only, incomplete information such as lacking of interval cancers, indistinct detection modes between screens and small sample for estimation. After excluding these studies, 6 studies were included for the following analysis.[13,14,16,17,19,29] Information on study period, age at entry, gender, smoking status, number of prevalence and incident (2nd) screens, was extracted from these studies. Table I lists the details of these variables. To consider the heterogeneity across studies, major criteria for positive screen, subsequent work-up and the requirement for double reading are also specified in Table I. Five of the 6 studies had only 1 study arm and 1 was a randomized controlled study with 2 arm (CT scan *vs*. CXR).[13]

Markov model specification

Two compartment models were formulated, including the disease natural history model for tumor progression and the prognostic model for recurrence and death. We modeled the natural history of progression of lung cancer by using a 3-state Markov model depicted in Compartment I of Figure 1, which has been already used in the previous study.[32] The natural history model gives a dynamic description of how a patient with or without lung cancer evolves with time after checking with CT. The model therefore begins with the status "showing no abnormal finding from CT," passes through preclinical screen-detectable phase (PCDP), and leads to "clinical phase" with symptoms or signs. The diagnosis of lung cancer either in the PCDP or clinical phases were made by positive findings of CT in combination with subsequent confirmatory clinical diagnosis. Patients staying in the PCDP are often occult and asymptomatic. We used 1 annual transition rate denoted as λ_1 to model the force of entering the PCDP phase given patients who underwent CT scan (in year) and the other one denoted as λ_2 to estimate annual progression rate from the PCDP to clinical phase, which is an inverse of MST, assuming a constant transition rate. The Compartment II model in Figure 1 is related to the prognosis of recurrence and death from lung cancer by different stages. For feasibility, we classified lung cancer in the PCDP or clinical phase into 2 types, localized and advanced cancers. In addition to modeling annual death rate by local and advanced types, our prognostic model can also capture the transition from the localized tumor, *i.e*., operated Stage 1 nonsmall cell lung cancer, to the recurrence, which is treated as advanced cancer.

MST estimation

For the first part on the disease natural history, we are interested in estimating the MST, the average duration of the PCDP, which is a useful indicator for the rate of progression as well as a crucial factor in the determination of inter-screening interval and the program sensitivity,[33,34] both of which may affect the effectiveness of screening. In the three-state Markov model proposed earlier, the MST can be calculated by taking the inverse of λ_2 if the constant rate is assumed. However, as the preclinical incidence rate of tumor in the PCDP is related to the MST we have to estimate both estimates simultaneously. To do so, it is necessary to consider different detection modes for detecting lung cancers, including prevalent and incident screen-detectable cases and interval cancers. For example, lung cancers diagnosed at first screen is different

TABLE II – PARAMETERS USED IN DECISION ANALYSIS

	Base case	Range: low end	Range: high end	Reference
Annual incidence(per 1,000 person-year)	4	–	–	Estimated from Refs. 1 and 6
λ_2 (Inverse of mean sojourn time) of CT:		Gamma distribution (α: 11.8; β: 25.1)		This report
λ_2 of CXR		Gamma distribution (α: 2.21; β: 1.86)		This report
Sensitivity of CT	0.85	0.8	0.9	Ref. 7 and estimation
Sensitivity of CXR	0.69	0.54	0.84	Ref. 37 and estimation
Specificity of CT	0.94	0.79	0.97	7
Specificity of CXR	0.945	0.9	0.99	Ref. 37 and estimation
Probability of localized disease by CT	0.85	0.53	1	Refs. 7,14
Probability of localized disease by CXR	0.46	0.42	0.5	Ref. 37 and estimation
Probability of localized disease: by clinical symptoms/signs	0.16	0.15	0.17	38
Adverse events: mortality from diagnostic work up for false positive screen	0.0001	0	0.0003	Estimated from Refs. 7 and 13
Operative death	0.035	0.01	0.076	7
Competing mortality	0.0127	0.00635	0.01905	Ref. 38 and estimation
Annual probability of recurrence after operation for Stage I lung cancer	0.057	0.0285	0.0855	39
Rate of treatment for localized disease	0.91	0.8	1	Refs. 7,14
Rate of treatment for advanced disease	0.41	0.205	0.615	Ref. 40 and estimation
One-year survival rate for advanced disease	0.35	0.3	0.4	Ref. 41 and estimation
Difference in 1-year survival rate for advanced disease due to untreated	0.1	0.05	0.15	Ref. 42 and estimation

from those diagnosed at subsequent screen because different lengths of natural history may affect the detection of the PCDP cancer to a great extent in the first screen but, to a less extent, at subsequent screen. Thus, it is very likely to disproportionately sample tumor with long duration of PCDP, so-called length-bias sampling. To model information on such different detection modes, we developed a statistical program using Bayesian underpinning. The details of program are specified in Appendix A.

The statistical program was implemented by using an acyclic graphic Bayesian model programmed with WinBUGS computer software.[35] Baseline λ_1 was based on a recent study.[36] Posterior distributions, from which we drew inferences on λ_2, MST and sensitivity, were derived from 5,000 iterations after 1,000 burn-in. By using the 5,000 samples, we computed the median value and 2.5th and 97.5th percentiles as the lower- and upper-bounds of the 95% credible intervals (95%CI). On the basis of the data from the CXR arm of the randomized study,[13]the λ_2 and MST of lung cancer by CXR was estimated in a similar way.

Probabilistic decision analysis for effectiveness of screening for lung cancer

We developed another Markov model tracking yearly patients' transitions between 5 health states (disease free, asymptomatic disease (denoted as "PCDP"), local disease with treatment (denoted as "Localized"), advanced lung cancer [denoted as "recurrence" or "advanced"), and death] (Fig. 1) and implemented with a decision tree (TreeAgePro, TreeAge Software, Williamstown, MA) comparing effectiveness among different screening strategies (CT, CXR and observation). The details of program are specified in Appendix B. Base estimate and range of parameters used in modeling were adapted from recent reports, review, guideline and this study such as the MST estimate[1,6,7,13,14,37–42] as listed in Table II. Triangular distribution was adopted for the majority of the parameters save that gamma distribution was adopted for λ_2. The screening schedule of our simulation was analogous to that of Dutch-Belgian randomised lung cancer screening trial (NELSON) (*i.e.*, screening at Year 1, 2 and 4 with follow-up for 10 years),[6] but other scenarios such as 3-yearly or annual programs were also simulated. Given 90% statistical power and 5% Type 1 error, ~5,000 subjects per study arm are required[43] by assuming stage distribution (early/advanced) is 85%/15% for CT screening and 46%/54% for CXR screening[14,37] and stage-specific survival rate being 60% for early stage and 1% for advanced stage (estimated from Ref. 1).

The reliability on parameter regarding survival is contiguous on accuracy of stage-specific cases and stage-specific survival in addition to competing death. Therefore, the stage-specific distribution of cases ascertained and stage-specific survival were simulated and compared to previous reports.

To validate the stage-specific cases, we simulated the scenario of I-ELCAP trial (the largest prospective study of screening CT published so far)[14] with the program mentioned earlier. The parameter λ_1 was estimated to be 0.003 assuming the study population being 61-years-old smoker with 38 pack-year smoking history (the median status of I-ELCAP participants).[14,44] The stage-specific distribution of detected lung cancer cases was compared to the observed data.

To validate the stage-specific survival, we assigned the initial probabilities for local or advanced stage mentioned in Appendix B. Then 1- and 5-year survival rate of early stage or advanced stage was simulated and compared to recent review and report.[1,45]

After model validation, we projected the effect of screening CT, CXR or observation along with 10-year follow-up similar to the NELSON trial.[6] The life expectancy after 10-year follow up, cases detection rates, and lung cancer death and cumulative mortality rates were simulated and compared across 3 arms (CT, CXR, observation). Relative risk (RR) of lung cancer mortality and number to screen per 1 lung cancer death averted were also estimated. To investigate the impact of different inter-screening intervals on effectiveness of mortality reduction, we also compared annual screening program with 3-yearly screening program with CT. The median values as an overall summary data and 95% CI were reported after 1,000 times of Monte Carlo simulations.

Results

MST estimation by modality

The baseline characteristics of each individual study are shown in Table I. The total number of screenees was 41,008. Number of lung cancer cases from prevalent and incident (2nd round) screen is also given in Table I.

All studies were conducted between 1997 and 2001. Most (4/6) of them were conducted in western countries for smokers.[13,16,19,29] The study from Japan was the only one including nonsmoker/average risk population.[17] The updated International Early Lung Cancer Action Project, which was the largest study (n = 31,567), consisted of more than 20% Asian patients.[14] Most (5/6) studies were

TABLE III – ESTIMATED MEAN SOJOURN TIME AND SENSITIVITY OF INDIVIDUAL TRIALS

Author	Gohagan *et al.*[13 1]	Henschke *et al.*[14]	Diederich *et al.*[16]	Sone *et al.*[17]	Pastorino *et al.*[19]	Novello *et al.*[29]
MST (year)[2]	2.53	3.86	1.38	1.68	2.02	2.13
MST: 95%CI	1.50–3.88	3.42–3.99	0.63–3.18	1.06–3.02	1.06–3.63	0.96–3.75
Sensitivity (%)[2]	97	99	89	97	97	96
Sensitivity: 95%CI	70–99	97–99	51–99	80–99	74–99	63–99

95% CI, 95% confidence interval.
[1]Arm of computed tomography only.–[2]Means sojourn time, median.

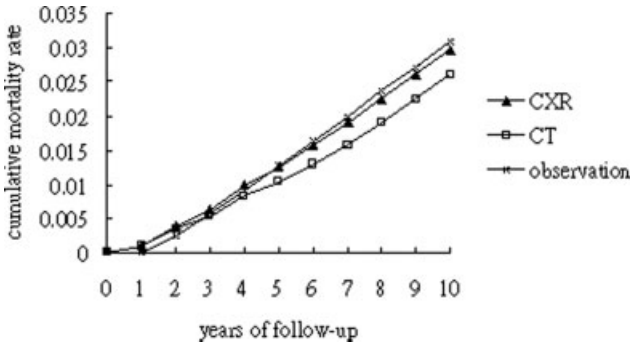

FIGURE 2 – Cumulative mortality rate among 3 study arms in NELSON-like setting.

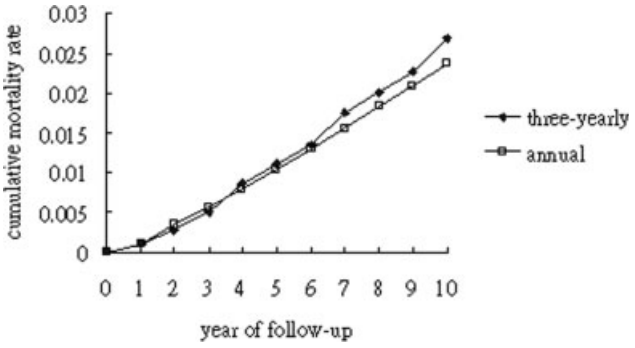

FIGURE 3 – Comparison of cumulative mortality rates between 2 different screening schedules (3-yearly program *vs.* annual program) by CT.

nonexperimental study that only addressed lung cancer screening with CT. There is only one randomized controlled study conducted to compare CT scan with CXR.[13]

The simultaneous estimated median and 95% CI of MST and sensitivity by each study are shown in Table III. The estimated MST (year) (95%CI) ranged from 1.38 (0.63–3.18) to 3.86 (3.42–3.99). The median sensitivity was higher than 95% except 89% in a small (n = 817) study.[16] The median and 95% CI of MST as a whole was estimated as 2.06 (0.42–3.83) years.

Using the reported outcome from randomized controlled study with 2 arms (CT scan *vs.* CXR),[13] the median (95% CI) MST of lung cancer by CXR was estimated as 1.01 (0.3–3.64) year, which was shorter than that from CT-arm (2.53, 1.5–3.88).

Validation of effectiveness of decision analysis model

Our estimated lung cancer cases detection rate & 95% CI for early stage (Stage I) and all lung cancer in the I-ELCAP setting[14] were 1% (0.6–1.4) and 1.4% (1.1–1.7), close to the observed detection rate (1.3 and 1.5%).

Regarding stage-specific survival, the estimated 1- or 5-year survival rate (95% CI) of early and advanced stage lung cancer were 0.97 (0.91–1)/0.71 (0.6–0.84) and 0.29 (0.2–0.37)/0 (0–0.02) respectively, which are comparable to reports in recent review and report (0.87–0.94/0.54–0.73 for early stage and 0.2–0.37/0.01–0.07 for advanced stage).[1,45]

Projection of effectiveness by screening CT and CXR

The life expectancy (standard deviation) (year) was 9.292 (0.121) for CT, 9.269 (0.124) for CXR and 9.275 (0.119) for observation. The median (95%CI) estimates of incremental life expectancy were 0.019 (−0.056 to 0.087) year for CT and −0.003 (−0.099 to 0.071) year for CXR, compared to observation after 10-year follow-up. The simulation reported 1.22% local cancers and 2.22% all lung cancer cases in CT arm, 0.5% local cancer and 2% all lung cancer in CXR arm and 0.3% local cancers and 1.9% all lung cancer cases in controlled arm after 5-year follow-up. The corresponding numbers for 10-year follow-up were 1.46% and 3.76% in the CT arm, 0.8% and 3.7% in CXR arm and 0.6% and 3.66% in the controlled arm, respectively. Although the cumulative mortality was initially higher in screening arm, the long-term cumulative mortality was lower in the CT arm as seen in Figure 2. The relative risks (95%CI) for being death from lung cancer would be 0.85 (0.58–1.01) in CT arm and 0.97 (0.7–1.16) in CXR arm, compared to observation. The number needed to screen per 1 death from lung cancer averted by CT screening would be 208. Regarding the influence of different inter-screening interval, 10-year cumulative mortality rate was lower for annual program compared to 3-yearly program (Fig. 3). This yielded 0.9 (95%CI: 0.58–1.06) of relative risk of being death from lung cancer. Opposed to the observation arm, the relative risk (95%CI) of death from lung cancer by annual screening program is 0.77 (0.43–0.98).

Discussion

As the increased demand for using CT as screening tool for early diagnosis of lung cancer, it is of primary interest to have a better understanding of how early asymptomatic lung cancer (ALC) patients can be detected by CT compared to the conventional method, *i.e.*, CXR, and to what extent such early diagnosis as a result of CT screen can reduce mortality from lung cancer, which have been never elucidated before. By using meta-analysis with the inclusion of 6 studies, we found CT can advance the diagnosis of ALC patients by 1 year or so compared to CXR. Translation of such early diagnosis resulting from CT yields an additional gain of life expectancy by 0.019 year/subject, which in turn gives a 15% lung cancer mortality reduction in NELSON-like setting.[6] Annual screening program using CT may lead to 23% mortality reduction compared to observation.

Our report was the first study to estimate the MST of lung cancer by CT for screening. In addition to estimation from individual study, we further estimated the MST as a whole based on meta-analysis from 6 identified studies. By simultaneously estimating the sensitivity of CT and the parameter of MST, we confirmed the high sensitivity of CT in detecting lung cancer. The high sensitivity may account for why CT can lead to a mortality reduction compared to small benefit of screening with CXR even the MST is shorter.

Since the results of randomized control studies on the effectiveness of CT for screening have not been available yet, some researchers had used several mathematical models to estimate the potential effectiveness of screening CT. Patz *et al.*,[46] used a deter-

ministic model based on reported stage distribution of published CT screening studies and stage-specific 5-year survival rates obtained from the literature to estimate lung cancer mortality rate for each study. This study reported that CT screening did not reduce mortality as prior CXR screening studies did. As the authors compared the estimated results for study conducted in 1971–1983 with studies conducted in late 1990, background variables may be different between the 2 periods.

Bach *et al*.,[44] predicted stage-specific lung cancer incidence and mortality among smokers based on age- and sex- specific stage distribution obtained from SEER database by simulating a scenario that combined 3 CT screening studies. There was lacking of evidence showing a decline in the number of diagnoses of advanced lung cancers or deaths from lung cancer. Note that the follow-up period for these 3 studies is relatively short (only 33% were followed up over 4 years) whereas 10 years horizon was used in our study. As revealed in the Bach's study, over-diagnosis by screening may exist, but it tends to be smaller after longer follow-up. In our simulation, the percentages of lung cancer diagnosis after 5-year follow-up were 2.22% for CT, 2% for CXR and 1.9% for observation, respectively. The corresponding figures after 10-year follow-up were 3.76, 3.7 and 3.66%. As shown in Figure 2, although there was also more lung cancer death at the inception of screening, long term mortality reduction as a result of CT seems promising.

The remarkable disparity between our study and 2 studies mentioned earlier is that our study is to estimate mortality reduction as a function of MST and detectability of lung cancer by CT as well as the prognostic part of the diagnosed lung cancer. The incorporation of MST into modeling makes the estimation more flexible in assessing the effect of inter-screening intervals on mortality, which has been not considered in previous studies.[44,46]

One concern in our study is that the credibility of results may be subject to the uncertainty of parameters related to the performance of screening program with same schedule but different criteria applied to assessing positive screen and to determining the subsequent details of work-up. The reliability of finding such early lesions is affected by the definition of positive screen, the skill of the reader or whether quality control procedures such as double readings were employed. However, as 95% confidence interval of MST estimates overlapped across studies (Table III), the effect of such variation may not be substantial. Furthermore, a random effect was incorporated (as specified in Appendix A) and probabilistic approach was applied to capturing this heterogeneity. Such uncertainty has been taken into account in our study. Finally, the estimated stage-specific cases and survival after disease onset were close to published reports. All these evidence and arguments make our results reliable. However, because of this concern, we still regard our prediction on mortality reduction as an interim analysis before the results of randomized controlled studies are available. This suggests that our simulated approach and results cannot displace the randomized trials but would provide useful formation for follow-up policies and the interpretation of trials.

Our study shows screening for lung cancer with CT have high sensitivity and may advance 1 year earlier than CXR in detection of ALC. By simulating the scenario similar to the NELSON study, CT screen may gain an extra of 0.019 year of life expectancy per person, which, in turn, yields 15% mortality reduction. Approximately 23% mortality reduction could be achieved by annual CT screening program opposed to observation, Our mortality findings in conjunction with higher sensitivity and shorter MST estimate given data on prevalent and incident (2nd round) screen may provide a tentative evidence, suggesting that annual CT screening may be required in order to be effective in reducing mortality before the results of randomized controlled studies available.

References

1. Spira A, Ettinger DS. Multidisciplinary management of lung cancer. N Engl J Med 2004;350:379–92.
2. Manser RL, Irving LB, Byrnes G, Abramson MJ, Stone CA, Campbell DA. Screening for lung cancer: a systematic review and meta-analysis of controlled trials. Thorax 2003;58:784–9.
3. Marcus PM, Bergstralh EJ, Zweig MH, Harris A, Offord KP, Fontana RS. Extended lung cancer incidence follow-up in the Mayo Lung Project and overdiagnosis. J Natl Cancer Inst 2006;98:748–56.
4. Oken MM, Marcus PM, Hu P, Beck TM, Hocking W, Kvale PA, Cordes J, Riley TL, Winslow SD, Peace S, Levin DL, Prorok PC, et al. Baseline chest radiograph for lung cancer detection in the randomized prostate lung colorectal and ovarian cancer screening trial. J Natl Cancer Inst 2005;97:1832–9.
5. Mulshine JL, Sullivan DC. Clinical practice. Lung cancer screening. N Engl J Med 2005;352:2714–20.
6. van Iersel CA, de Koning HJ, Draisma G, Mali WP, Scholten ET, Nackaerts K, Prokop M, Habbema JD, Oudkerk M, van Klaveren RJ. Risk-based selection from the general population in a screening trial: selection criteria, recruitment and power for the Dutch-Belgian randomised lung cancer multi-slice CT screening trial (NELSON). Int J Cancer 2007;120:868–74.
7. Black C, Bagust A, Boland A, Walker S, McLeod C, De Verteuil R, Ayres J, Bain L, Thomas S, Godden D, Waugh N. The clinical effectiveness and cost-effectiveness of computed tomography screening for lung cancer: systematic reviews. Health Technol Assess 2006;10: 1–90 (iii-iv, ix-x).
8. Walter SD, Kubik A, Parkin DM, Reissigova J, Adamec M, Khlat M. The natural history of lung cancer estimated from the results of a randomized trial of screening. Cancer Causes Control 1992;3:115–23.
9. Flehinger BJ, Kimmel M. The natural history of lung cancer in a periodically screened population. Biometrics 1987;43:127–44.
10. Myles JP, Nixon RM, Duffy SW, Tabar L, Boggis C, Evans G, Shenton A, Howell A. Bayesian evaluation of breast cancer screening using data from two studies. Stat Med 2003;22:1661–74.
11. Duffy SW, Chen HH, Tabar L, Day NE. Estimation of mean sojourn time in breast cancer screening using a Markov chain model of both entry to and exit from the preclinical detectable phase. Stat Med 1995;14:1531–43.
12. Garg K, Keith RL, Byers T, Kelly K, Kerzner AL, Lynch DA, Miller YE. Randomized controlled trial with low-dose spiral CT for lung cancer screening: feasibility study and preliminary results. Radiology 2002;225:506–10.
13. Gohagan JK, Marcus PM, Fagerstrom RM, Pinsky PF, Kramer BS, Prorok PC, Ascher S, Bailey W, Brewer B, Church T, Engelhard D, Ford M, et al. Final results of the lung screening study, a randomized feasibility study of spiral CT versus chest X-ray screening for lung cancer. Lung Cancer 2005;47:9–15.
14. Henschke CI, Yankelevitz DF, Libby DM, Pasmantier MW, Smith JP, Miettinen OS. Survival of patients with stage I lung cancer detected on CT screening. N Engl J Med 2006;355:1763–71.
15. Sobue T, Moriyama N, Kaneko M, Kusumoto M, Kobayashi T, Tsuchiya R, Kakinuma R, Ohmatsu H, Nagai K, Nishiyama H, Matsui E, Eguchi K. Screening for lung cancer with low-dose helical computed tomography: anti-lung cancer association project. J Clin Oncol 2002;20:911–20.
16. Diederich S, Thomas M, Semik M, Lenzen H, Roos N, Weber A, Heindel W, Wormanns D. Screening for early lung cancer with low-dose spiral computed tomography: results of annual follow-up examinations in asymptomatic smokers. Eur Radiol 2004;14:691–702.
17. Sone S, Li F, Yang ZG, Honda T, Maruyama Y, Takashima S, Hasegawa M, Kawakami S, Kubo K, Haniuda M, Yamanda T. Results of three-year mass screening programme for lung cancer using mobile low-dose spiral computed tomography scanner. Br J Cancer 2001;84:25–32.
18. Swensen SJ, Jett JR, Hartman TE, Midthun DE, Sloan JA, Sykes AM, Aughenbaugh GL, Clemens MA. Lung cancer screening with CT: mayo clinic experience. Radiology 2003;226:756–61.
19. Pastorino U, Bellomi M, Landoni C, De Fiori E, Arnaldi P, Picchio M, Pelosi G, Boyle P, Fazio F. Early lung-cancer detection with spiral CT and positron emission tomography in heavy smokers: 2-year results. Lancet 2003;362:593–7.
20. Nawa T, Nakagawa T, Kusano S, Kawasaki Y, Sugawara Y, Nakata H. Lung cancer screening using low-dose spiral CT: results of baseline and 1-year follow-up studies. Chest 2002;122:15–20.
21. MacRedmond R, Logan PM, Lee M, Kenny D, Foley C, Costello RW. Screening for lung cancer using low dose CT scanning. Thorax 2004;59:237–41.
22. Tiitola M, Kivisaari L, Huuskonen MS, Mattson K, Koskinen H, Lehtola H, Zitting A, Vehmas T. Computed tomography screening for lung cancer in asbestos-exposed workers. Lung Cancer 2002;35:17–22.

23. Miller A, Markowitz S, Manowitz A, Miller JA. Lung cancer screening using low-dose high-resolution CT scanning in a high-risk workforce: 3500 nuclear fuel workers in three US states. Chest 2004;125:152S–153S.
24. Stephenson SM, Mech KF, Sardi A. Lung cancer screening with low-dose spiral computed tomography. Am Surg 2005;71:1015–17.
25. Picozzi G, Paci E, Lopez PA, Bartolucci M, Roselli G, De Francisci A, Gabrielli S, Masi A, Villari N, Mascalchi M. Screening of lung cancer with low dose spiral CT: results of a three year pilot study and design of the randomised controlled trial "Italung-CT". Radiol Med (Torino) 2005;109:17–26.
26. Shaham D, Breuer R, Copel L, Agid R, Makori A, Kisselgoff D, Goitein O, Izhar U, Berkman N, Heching N, Sosna J, Bar-Ziv J, et al. Computed tomography screening for lung cancer: applicability of an international protocol in a single-institution environment. Clin Lung Cancer 2006;7:262–7.
27. Abe Y, Hanai K, Nakano M, Ohkubo Y, Hasizume T, Kakizaki T, Nakamura M, Niki N, Eguchi K, Fujino T, Moriyama N. A computer-aided diagnosis (CAD) system in lung cancer screening with computed tomography. Anticancer Res 2005;25:483–8.
28. McWilliams AM, Mayo JR, Ahn MI, MacDonald SL, Lam SC. Lung cancer screening using multi-slice thin-section computed tomography and autofluorescence bronchoscopy. J Thorac Oncol 2006;1:61–8.
29. Novello S, Fava C, Borasio P, Dogliotti L, Cortese G, Crida B, Selvaggi G, Lausi P, Brizzi MP, Sperone P, Cardinale L, Ferraris F, et al. Three-year findings of an early lung cancer detection feasibility study with low-dose spiral computed tomography in heavy smokers. Ann Oncol 2005;16:1662–6.
30. Diederich S, Wormanns D, Semik M, Thomas M, Lenzen H, Roos N, Heindel W. Screening for early lung cancer with low-dose spiral CT: prevalence in 817 asymptomatic smokers. Radiology 2002;222:773–81.
31. Gohagan J, Marcus P, Fagerstrom R, Pinsky P, Kramer B, Prorok P. Baseline findings of a randomized feasibility trial of lung cancer screening with spiral CT scan vs chest radiograph: the Lung Screening Study of the National Cancer Institute. Chest 2004;126:114–21.
32. Chen TH, Kuo HS, Yen MF, Lai MS, Tabar L, Duffy SW. Estimation of sojourn time in chronic disease screening without data on interval cases. Biometrics 2000;56:167–72.
33. Walter SD, Day NE. Estimation of the duration of a pre-clinical disease state using screening data. Am J Epidemiol 1983;118:865–86.
34. Day NE. Estimating the sensitivity of a screening test. J Epidemiol Community Health 1985;39:364–6.
35. The BUGS Project [homepage on the internet]. Winbugs software [cited: June 2007]. Available at: http://www.mrc-bsu.cam.ac.uk/bugs/winbugs/contents.shtml.
36. Manser R, Dalton A, Carter R, Byrnes G, Elwood M, Campbell DA. Cost-effectiveness analysis of screening for lung cancer with low dose spiral CT (computed tomography) in the Australian setting. Lung Cancer 2005;48:171–85.
37. Gavelli G, Giampalma E. Sensitivity and specificity of chest X-ray screening for lung cancer: review article. Cancer 2000;89:2453–6.
38. Mahadevia PJ, Fleisher LA, Frick KD, Eng J, Goodman SN, Powe NR. Lung cancer screening with helical computed tomography in older adult smokers: a decision and cost-effectiveness analysis. JAMA 2003;289:313–22.
39. Ginsberg RJ, Rubinstein LV Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group. Ann Thorac Surg 1995;60:615–22 (discussion 22–23).
40. Potosky AL, Saxman S, Wallace RB, Lynch CF. Population variations in the initial treatment of non-small-cell lung cancer. J Clin Oncol 2004;22:3261–8.
41. NCCN Clinical Practice Guidelines in Oncology [homepage on the internet]. Non-small cell lung cancer v. 1.2007 [cited May 2007]. Available at: http://www.nccn.org/professionals/physician_gls/PDF/nscl.pdf.
42. Non Small Cell Lung Cancer Collaborative Group. Chemotherapy for non-small cell lung cancer. Cochrane Database Syst Rev 2000: CD002139.
43. Chen HH, Prevost TC, Duffy SW. Evaluation of screening for nasopharyngeal carcinoma: trial design using Markov chain models. Br J Cancer 1999;79:1894–900.
44. Bach PB, Jett JR, Pastorino U, Tockman MS, Swensen SJ, Begg CB. Computed tomography screening and lung cancer outcomes. JAMA 2007;297:953–61.
45. Goldstraw P, Crowley J, Chansky K, Giroux DJ, Groome PA, Rami-Porta R, Postmus PE, Rusch V, Sobin L. The IASLC lung cancer staging project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. J Thorac Oncol 2007;2:706–14.
46. Patz EF, Jr, Swensen SJ, Herndon JE, II. Estimate of lung cancer mortality from low-dose spiral computed tomography screening trials: implications for current mass screening recommendations. J Clin Oncol 2004;22:2202–6.