Lung Cancer 82 (2013) 426–430

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Computed tomography screening for lung cancer: Results of ten years of annual screening and validation of cosmos prediction model

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ARTICLE INFO

Article history:
Received 8 July 2013
Received in revised form 28 August 2013
Accepted 31 August 2013

Keywords:
Lung cancer
Screening
Computed tomography
Treatment
Risk model
Overdiagnosis

ABSTRACT

Introduction: It is unclear how long low-dose computed tomographic (LDCT) screening should continue in populations at high risk of lung cancer. We assessed outcomes and the predictive ability of the COSMOS prediction model in volunteers screened for 10 years.
Materials and methods: Smokers and former smokers (>20 pack-years), >50 years, were enrolled over one year (2000–2001), receiving annual LDCT for 10 years. The frequency of screening-detected lung cancers was compared with COSMOS and Bach risk model estimates.
Results: Among 1035 recruited volunteers (71% men, mean age 58 years) compliance was 65% at study end. Seventy-one (6.95%) lung cancers were diagnosed, 12 at baseline. Disease stage was: IA in 48 (66.6%); IB in 6; IIA in 5; IIB in 2; IIIA in 5; IIIB in 1; IV in 5; and limited small cell cancer in 3. Five- and ten-year survival were 64% and 57%, respectively, 84% and 65% for stage I. Ten (12.1%) received surgery for a benign lesion. The number of lung cancers detected during the first two screening rounds was close to that predicted by the COSMOS model, while the Bach model accurately predicted frequency from the third year on.
Conclusions: Neither cancer frequency nor proportion at stage I decreased over 10 years, indicating that screening should not be discontinued. Most cancers were early stage, and overall survival was high. Only a limited number of invasive procedures for benign disease were performed. The Bach model – designed to predict symptomatic cancers – accurately predicted cancer frequency from the third year, suggesting that overdiagnosis is a minor problem in lung cancer screening. The COSMOS model – designed to estimate screening-detected lung cancers – accurately predicted cancer frequency at baseline and second screening round.

1. Introduction

The US National Lung Screening Trial (NLST) [1] found that low-dose computed tomography (LDCT) screening reduced lung cancer mortality, however only three screening rounds were offered to high risk individuals and it is unclear how long screening should continue [2]. No long-term results of periodic screening are available, and most published trials screened for no longer than five consecutive years [3–8].

While ample data are available on the long-term survival of patients with screening-detected lung cancer [9,10], no information is available on long-term outcomes in entire populations of individuals undergoing protracted periodic screening. A risk model [11] based on a screened population has been published, but has not so far been validated on an independent population. In the present study we assessed long-term overall survival and cancer detection rate, and compared model-predicted with observed lung cancer detection frequencies over ten years, in an ongoing single-center pilot screening study of volunteers at high risk of developing lung cancer.

2. Methods

A total of 1035 high-risk asymptomatic volunteers (smokers and former smokers, >50 years, mean age 58 years, 71% men) were

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http://dx.doi.org/10.1016/j.lungcan.2013.08.026

enrolled in 2000–2001 and followed for 10 years with annual LDCT (verification set). Study methods and protocol are described in detail elsewhere [6]. Briefly, to be eligible volunteers had to be over 50 years of age, have a smoking history of more than 20 pack-years and give written informed consent. At study entry, spirometry was performed, a self-reported questionnaire on smoking habits and other risk factors was compiled, and blood samples were collected for molecular analyses. A single detector CT scanner was used. In the subsequent COSMOS study (training set) a single detector CT scanner was used to 2003, for an 8- or 16-detector scanner was used subsequently. In both the verification set and training set, nodules ≤5 mm underwent repeat scan at 1 year; nodules 5.1–8 mm underwent CT 3 months later; lesions >8 mm received combined CT-positron emission tomography (CT-PET). The pre-COSMOS and COSMOS studies were approved by the ethical committee of the European Institute of Oncology. After five years, an Ethical Committee amendment allowed the pre-COSMOS study to continue for a further five years.

2.1. Statistical methods

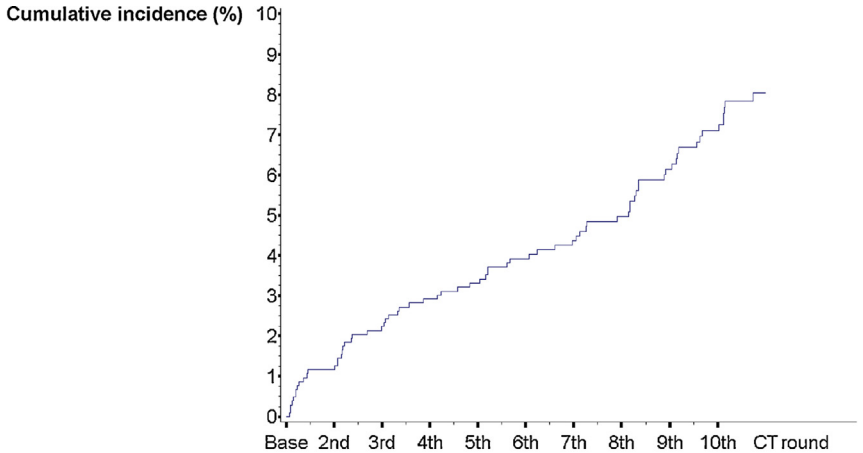
Lung cancer frequency and death rate were calculated dividing the number of events by the number of person-years of observation over the entire study period, from date of baseline screening to date of last follow-up or death. Overall survival and cumulative lung cancer incidence curves were constructed using, respectively, the Kaplan–Meier method and its compliment. The log-rank test was used to assess differences between curves. The expected numbers of lung cancers were calculated summing the risk of individual participants developing cancer as estimated by the Bach risk model [12] and the recalibrated model (COSMOS) proposed by Maisonneuve et al. [11]. Both models predict lung cancer based on age, sex, smoking history and exposure to asbestos. The COSMOS model used the number of screening-detected lung cancers at baseline among the 5203 asymptomatic participants of the COSMOS trial to recalibrate the original Bach model [11]. The numbers of cancers diagnosed in each of the 10 study years were compared with those predicted by the models, assuming that the observed cases followed a Poisson distribution. The analyses were performed with SAS version 8.2 (Cary, NC). All tests are two-sided. A P value <0.05 was considered statistically significant.

3. Results

Table 1 shows baseline characteristics of participants, together with outcomes. Eighty-four percent were current smokers at baseline. After 10 annual screening rounds and a median follow-up of 9.6 years, 71 lung cancers (6.9%) were diagnosed by screening (detection rate = 0.83 per 100 person-years) and 60 had died (mortality rate = 0.67 per 100 person-years). Compliance was good, with 671/1035 (65%) participants presenting for the tenth screening round. Death was attributed to lung cancer in 23 cases, other cancer in 12 cases, cardiovascular disease in 10 cases, and other causes in 15 cases. Twelve of the 71 lung cancers were detected at baseline and 59 subsequently; 78% were stage I. Histology was: squamous cell carcinoma, 14 (19.4%); adenocarcinoma or bronchioloalveolar carcinoma, 44 (61.1%); large cell carcinoma, 1 (1.4%); other non-small cell carcinoma, 1 (1.4%); small cell carcinoma, 7 (9.7%); and carcinoid, 5 (6.94%). The mean size of CT-detected non-small cell cancers was 12.5 mm. Stage breakdown was: IA, 48 (66.6%); IB, 6; IIA, 5; IIB, 2; IIIA, 5; IIIB, 1; IV, 5; limited small cell cancer, 3. Forty-three (70.5%) of the 61 non-small cell cancers were stage IA at diagnosis. Postoperative (30-day) morbidity was 31% (including 8% serious complications and 23% minor complications); there were no postoperative deaths.

Fig. 1 shows the cumulative incidence of screening-detected lung cancers over the ten-year period. The lung cancer detection rate was 1.1 per 100 person-years at the two first screening rounds and stable at around 0.7% per 100 person-years at following rounds.

The number of lung cancers detected during the first two screening rounds (n = 23) was higher (P < 0.001) than expected (n = 9.9) based on the risk prediction model of Bach et al. [12] to estimate incident lung cancers in high risk smokers, but close to that predicted (n = 25.9) by the COSMOS model [11] to estimate



	Base	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	Total
N receiving CT	1035	996	974	938	889	848	792	760	716	671	9,230
Lung cancers											
Detected	12	11	6	6	5	4	6	8	8	5	71
Expected (Bach model)†	4.8	5.1	5.4	5.7	5.8	6.1	6.2	6.3	6.4	6.5	58.3
Expected (Recalibrated model)‡	12.5	13.4	14.4	15.2	15.7	16.4	16.8	17.0	17.3	17.5	156.2
Deaths	-	4	4	7	7	14	5	8	8	3	60
Cumulative drop-outs (%)	-	35 (3.4)	53 (5.1)	82 (7.9)	124 (12.0)	151 (14.6)	202 (19.5)	226 (21.8)	262 (25.3)	304 (29.4)	304 (29.4)

Fig. 1. Cumulative incidence of lung cancer detected by annual CT. †Number of lung cancers expected calculated using the prediction model proposed by Bach et al. [12]. ‡Number of lung cancer expected calculated using the recalibrated prediction model proposed by Maisonneuve et al. [11] screening.