Lung cancer screening with low dose computed tomography: Where do we stand today?

R.J. van Klaveren

Department of Pulmonology, Erasmus MC, Rotterdam, The Netherlands

When lung cancer is intercepted in its early stages, lung cancer can be treated with a surgical resection. However, most patients present when they are symptomatic and in an advanced disease stage. The hypothesis is that if a larger proportion of the lung cancer cases could be detected in an early stage, this might translate into an improved outcome. Randomised controlled trials in the 1970s and 1980s did not validate this principle. The intervention and control arms in these studies had the same frequency of advanced cancer diagnoses and death from lung cancer, despite the fact that in the screened populations more cancer cases were diagnosed. However, these studies used chest-X-ray and sputum cytology for early diagnosis. With the advent of new technology and the introduction of low-dose multidetector computed tomography (MDCT), new hopes have been raised. In order to address the effectiveness and cost-effectiveness of low dose computed tomography (LDCT) screening for lung cancer, several observational cohort studies and randomised clinical trials have been launched. Four systematic review papers on this topic have recently been published [1–4]. Yau and colleagues conclude that, based on all relevant data on LDCT lung cancer screening between 1966 and 2006, on average 80% of the lung cancer cases detected by LDCT screening were stage I cancers [1]. The sensitivity, specificity, positive predictive and negative predictive values of these LDCT screening trials were 81%, 81%, 8% and 99%, respectively [1]. A major drawback of current screening regimens is, however, that they lead to a high rate of false positive test results and to low positive predictive values. This translates into high rates of subsequent work-ups, costs, loss of quality of life, potential morbidity and low acceptance of these screening programmes among the public. Although lung cancer screening and surgical resection for early stage lung cancer may offer a potential curative treatment, it is not free of complications. Therefore, the number of participants with a false positive test result in a screening programme should be as low as possible. Consequently, it is essential to make evidence-based decisions on whether a nodule is benign or malignant and what the most optimal follow-up regimen should be in order to avoid the potential harm from excess radiation exposure, anxiety and costs. Apart from demonstrating a lung cancer mortality reduction, improvement of the screening regimen with a reduction in the rate of false positive test results is, therefore, needed to increase acceptance of possible future screening programmes. In the Dutch-Belgian low dose MDCT lung cancer screening trial (NELSON), a novel screening strategy has been used based on the size of new nodules and the volume doubling times of existing nodules with growth. Growth was defined as a percentage volume change of at least 25% over at least a 3-month period [5]. The results of this strategy will be presented at the 2009 ECCO-ESMO meeting.

The detection of more stage I disease will only lead to a reduction in lung cancer mortality if we accept the assumption that screen-detected lung cancers behave essentially the same as lung cancers that present clinically with aggressive, rapidly progressing conditions. There is, however, doubt about the validity of this assumption. There is no evidence that size always correlates with biologic behaviour and that small lesions are always equivalent to early-stage disease [6]. In patients with lung cancer who undergo surgical resection for early stage I or II disease only 60–70% will be cured while the others, despite having early stage disease and complete surgical resections, have recurrence of their disease and ultimately die. One of the concerns around LDCT screening for lung cancer is the issue of overdiagnosis, but if this is really an issue then it needs to be established. In LDCT screening trials there are many more adenocarcinomas detected than in the general practice today, and in Japanese studies that also included non-smokers, the cancer detection rate was as high in smokers as in non-smokers, which is not in accordance with our current experience where more than 80% of all

tumours arise in smokers. Peripheral adenocarcinomas may have a different clinical behaviour and might probably, outside a screening programme, not have been recognised. This might suggest overdiagnosis if we adhere to the current growth paradigm which assumes that malignant nodules will continue to develop and grow unless they are surgically removed. Yet it may be the case that some will stabilise, shrink or grow so slowly that even if left *in situ* they will not all develop into lethal lesions. Multi-step carcinogenesis may not be able to account for dramatic cases of lung cancer that develop in very short intervals. This suggests that although the current paradigm is well supported and might be applicable for a certain subset of cancer cases, it does not explain all lung cancer biology. Therefore, we believe that it is inappropriate to assume that lung cancer cases with a volume doubling time (VDT) >400 days are by definition overdiagnosed cases based on the argument that it would take more than 30 years to grow from a 1 cm lesion to a size which is usually lethal, because it is based on the simplified assumption that cancers double at a constant rate, which is without doubt inaccurate. Recent advances in knowledge on the potential role of cancer stem cells in the natural history of lung cancer and its interaction with the micro-environment and the immune system may provide alternative explanations for the observed biological behaviour of lung cancer that does not always fit into the multi-step carcinogenetic model. It is, therefore, too premature to conclude that all lung cancer cases with a VDT >400 days are overdiagnosed cases [6].

Based on the first study results on the impact of MDCT screening on health related quality of life (HRQOL) we may conclude that the effect is minimal or even absent. In the NELSON trial we investigated the impact of participation in a lung cancer screening programme and the effects of undergoing a CT scan on HRQOL [7,8]. Eighty-seven percent of the participants in the screening arm experienced no discomfort from undergoing a CT scan. For those who did experience discomfort it was, in 75%, related to waiting for the CT scan results, in 17%, related to the prospect of undergoing a CT scan, and in 7%, related to undergoing the CT scan. When we evaluated the changes in HRQOL over time (1 day before the CT scan, 1 week after and 6 months after the CT scan), no changes in mental or physical health have been observed with only small, but not clinically relevant, changes in self-reported health and anxiety. Only lung cancer specific distress showed a significant decrease over time, but the differences were very small and the scores for distress very low. More lung cancer specific distress was observed in those with a higher risk perception for developing lung cancer. When the changes in HRQOL were evaluated for those with a negative and an indeterminate test result in comparison to a neutral time point before randomisation, no clinically relevant differences in HRQOL have been observed over time. In conclusion, LDCT screening should be regarded as investigative and needs to be confirmed in well-designed randomised controlled trials before LDCT screening is ready for implementation on a large scale.

Conflict of interest statement

None declared.

References

1 Yau G, Lock M, Rodrigues G. Systematic review of baseline low-dose CT lung cancer screening. *Lung Cancer* 2007;**58**:161–70.
2 Black WC. Computed tomography screening for lung cancer: review of screening principles and update on current status. *Cancer* 2007;**110**:2370–84.
3 Black C, de Verteuil R, Walker S. Population screening for lung cancer using computed tomography, is there evidence of clinical affectiveness ? A systematic review of the literature. *Thorax* 2007:**62**:131–8.
4 Read C, Janes S, George J, Spiro S. Early lung cancer: screening and detection. *Prim Care Resp J* 2006;**15**:332–6.
5 Van Iersel CA, de Koning HJ, Draisma G, et al. 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**(4):868–74.
6 Van Klaveren RJ, van't Westeinde SC, de Hoop BJ, Hoogsteden HC. Stem cells and the natural history of lung cancer: implications for lung cancer screening. *Clin Cancer Res* 2009;**15**(7):2215–8 [Epub 2009 Mar 17].
7 Van den Bergh KA, Essink-Bot ML, Bunge EM, et al. Impact of computed tomography screening for lung cancer on participants in a randomized controlled trial (NELSON trial). *Cancer* 2008 Jul 15;**113**(2):396–404.
8 Bunge EM, van den Bergh KA, Essink-Bot ML, van Klaveren RJ, de Koning HJ. High affective risk perception is associated with more lung cancer-specific distress in CT screening for lung cancer. *Lung Cancer* 2008;**62**(3):385–90 [Epub 2008 May 12].