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Commentary

UKLS trial: looking beyond negative results

Marie Darrason[1,2], Emmanuel Grolleau[1,3], Julie De Bermont[1,*], Sébastien Couraud[1,3]

[1] Service de Pneumologie et oncologie thoracique, Hôpital Lyon Sud, Hospices Civils de Lyon, Pierre Bénite, France
[2] Institut de Recherches Philosophiques de Lyon, Université Jean Moulin Lyon 3, France
[3] Center for Innovation in Cancer of Lyon, Lyon 1 University, Oullins, France

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In this issue of *The Lancet Regional health – Europe*, John K. Field and colleagues report the results of the UKLS trial [1]—the last of the European lung cancer CT screening trials to report outcomes. The purpose of this randomized study with a LDCT (low-dose computed tomography) arm and a control arm (usual care) was to demonstrate the usefulness of lung cancer screening among high-risk population (determined by the LLPv2 score). They found that this single-screen program results in a non-significant impact on lung cancer mortality (RR 0.65 [95% CI 0.41-1.02]). Some would consider these results as an additional argument against lung cancer screening. However, we should interpret them by looking beyond their negative components.

The trial was unfortunately underpowered for its main outcome—lung cancer mortality—since it was prematurely stopped at its pilot step. Thus, only 3,968 participants on the 16,000 planned were included in this analysis. Similarly, many other trials on lung cancer screening were also not powered enough to evaluate mortality outcome (Fig. 1). This is why the meta-analysis approach – added in this paper - is particularly interesting, to put these results into perspective. Taking together, all these trials (except DEPISCAN which did not publish mortality data) showed an improvement in lung cancer mortality (0.84 [0.76-0.92]) as well as in overall mortality (0.97 [0.94-1.00]).

Despite no significant results, this trial gives us many insights. First, while it is a single-screening strategy, the UKLS trial suggests an extended benefit, regarding lung cancer mortality, when performing a long-term follow-up (median 7.2 years). Although this strategy is not the recommended one in Europe [2], it could provide some interesting data for designing future screening programs. It also underlines the "power" of screening in this very-high risk population. Indeed, according to the existing trials, we know that new screen-detected lung cancers are discovered at each screening round. The COSMOS cohort demonstrated this phenomenon, with new lung cancers found each year between the baseline (N=12) and the 10th year (N=5) [3]. Therefore, lung cancer screening was mainly assessed with several round in randomized trials (see Fig. 1). No consensus exists, yet, for the optimal screening interval but it is clearly between one and two years. Indeed, we know from the optional 4th round of the NELSON trial that overpassing two years leads to a shift toward later stages of lung cancer [4]. By contrast, the MILD trial showed us that biennial screening are acceptable as compared to an annual strategy [5]. Finally, post-hoc analysis from the NLST trial found that interval should be individually adapted depending on personal medical history of chronic bronchitis or presence of emphysema at CT [6].

The UKLS trial is the first randomized trial with inclusion criteria based on a risk-score: the LLPv2 score. Optimized screening outcomes by enriching the population with high-risk individuals, is a key point [7]. Several scores are available but only two were prospectively tested: $PLCO_{m2012}$ [8] and LLPv2. Currently, we do not know if this approach using score leads to a better mortality outcome, since no trials, comparing, using score versus not, have been done. However, we do know that using score results in a highest proportion of eligible individuals with a screen-detected lung cancer [7]; in a decrease of the number needed to screen to avoid one death [9]; and, in a highest proportion of early stage screen-detected lung cancer [8]. By contrast, the use of score to assess eligibility may be problematic in the overall-population, particularly among individuals with the lowest socio-economic status. Indeed, self-assessing eligibility to screening of breast or colon cancer is less

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* Corresponding author.
E-mail address: julie.de-bermont@chu-lyon.fr (J. De Bermont).

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Trial (country)	Control arm	CT schedule (years) 0	1	2	3	4	5	6	7	8	N exp. N cont.	Age On.	End	Tobacco	Other	Nodule interpretation model	Follow-up	Result Lung cancer mortality (Overall mortality)		Ref.
DEPISCAN	CXR										385 380	50	75	>15cig/d > 20y Form. <15y		NELSON like	<2y	*Not reported*		Blanchon T et al. Lung Cancer. 2007;58(1):50-8.
LSS	CXR										1660 1658	55	74	>30 PY Form.< 10y		NLST >4mm	5.2y	1.24 [0.74-2.08] (1.20 [0.94-1.54])		Doroudi M et al. JNCI Cancer Spectr. 2018; 2(3): pky042.
NLST	CXR										26722 26732	55	74	>30 PY Form.< 15y			6.5y	0.8 [0.73-0.93] (0.93 [0.86-0.99])		National Lung Screening Trial Research Team, N Engl J Med. 2011;365(5):395-409.
DANTE	CXR baseline then observ.										1264 1186	60	75	> 20PY Form. <10y	Male only	NLST (≥10mm)	8y	***Pooled with MILD*** 0.83 [0.61-1.12] (0.89 [0.74-1.06])		Infante M et al. Eur J Cancer Prev. 2017;26(4):324-329.
MILD	Observ.										2376 1723	50	75			NELSON like	10y	0.61 [0.39-0.95] (0.8 [0.62-1.03])		Pastorino U et al. Ann Oncol. 2019;30(7):1162-1169
DLCST*	Observ.										2052 2052	50	70		FEV1 > 30%		5y	1.03 [0.66-1.6] (1.02 [0.82-1.27])		Saghir Z et al. Thorax. 2012;67(4):296-301.
ITALUNG*	Observ.										1613 1593	55	70				10y	0.70 [0.47-1.03] (0.83 [0.67-1.03])		Paci E et al. Thorax. 2017;72(9):825-831
LUSI*	Observ.										2029 2023	50	70	>15cig/d > 25y OR >10cig/d > 30y Form. <10y			8.8y	M: 0.94 [0.54-1.61] F: 0.31 [0.10-0.96]		Becker N et al. Int J Cancer. 2020;146(6):1503-1513
NELSON*	Observ.							OPTION			7907 7915	50	75				11y	M: 0.76 [0.61-0.94] F: 0.67 [0.38-1.14] (M: 1.01 [0.92-1.11])		De Koning HJ et al. N Engl J Med. 2020;382(6):503-513
UKLS	Observ.										1987 1981	50	75	-	LLPv2 > 4.5%		7.3	0.65 [0.41-1.02]		Field JK et al. Lancet Reg Health Eur. 2021

Fig. 1. Randomized controlled trials on lung cancer screening: design, eligibility and results. Y: year – cig.: Cigarette – PY: Pack-Year – CXR: Chest X-Ray – Observ.: Observation – exp.: Experimental arm – Cont.: Control arm – On.: Onset – Power: powered to assess a difference in lung cancer mortality: GREEN Yes, ORANGE No.

challenging because it depends only of age (and gender). Despite this simple process, participation rates are sometimes lower than expected, especially in population with lower socio-economic status. However, those individuals have a higher risk of cancer, and namely of lung cancer [7]. The use of NELSON eligibility criteria might be difficult in an overall population, because it necessitates some basic knowledge in mathematic (to conceptualize a mean or to calculate a duration). Using a score represents also some difficulties, as it requires reaching an internet page, and fulfilling a questionnaire. All these steps represent obstacles for many individuals, and particularly for the ones with the lowest socio-economic status.

Bypassing socio-economic barriers is a big challenge. There are many ways to do this. In another UK program, investigators have assessed the impact of using mobile CT-scan. While using the PLCOm2012 score as entry criteria, a very high proportion of participants were from lowest deprivation quintiles [10]. This result highlights that dedicated programs, such as those including mobile CT, are a way to lift inequalities in screening, to overtake difficulties related to complex entry criteria and, thus, to optimize individuals selection and finally improve screening outcomes.

Author contributions

EG, JD, MD and SC all contributed to literature search and writing.

Declaration of Interests

All authors declare no competing interests.

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