APPENDIX

ESR-ERS Joint Position Paper on Lung Cancer Screening

I. Overview of Lung Cancer Screening activities in Europe

The current status of lung cancer screening (LCS) in individual European countries is presented. Table 1 provides an overview of population, smoking prevalence and annual lung cancer deaths in Europe.

Austria

Currently, there is no organised nation-wide lung cancer screening programme in Austria. Opportunistic screening is covered by some regional insurance companies. Screening should follow the consensus paper of the Austrian Pulmonological Society (ÖGP) and the Austrian Society of Roentgenology (ÖRG) published in 2013, which intended the inclusion criteria of the NLST [1]. The follow-up of screen-detected nodules should follow the nodule management protocol of the NELSON trial. A pilot study is in preparation which aims to get an estimate on the cost-effectiveness of lung cancer screening in Austria.

Belgium

Belgium participated in the NELSON trial through one institution, enrolling a small number of participants. Currently, there are no further lung cancer screening initiatives. Cancer screening in Belgium is organised on a population-based level with the different Belgian regions each having independent operational responsibility. Since cancer screening programmes (breast, cervical and colorectal cancer) were previously implemented only following European regulations, this will be no different for lung cancer screening. During parliamentary questioning, at the occasion of the presentation of the NELSON data, the Flemish minister of Health Care stated that cost-effectiveness and the possible harms of screening would be important issues in considering possible implementation in the future [2].

France

Lung cancer screening is not currently organised in France and it remains opportunistic [3]. Following NLST results, a taskforce from several academic groups published a statement favouring annual lung cancer screening using NLST eligibility criteria and NELSON-derived nodule management [4]. However, in 2016, French health authority stated that lung cancer was not ready for an active and organised screening policy, and encouraged research in this field [5]. Recently, intermediate results of a real-life experience of annual low-dose CT-scan in a French area (*Somme*) were released [4, 6]. Participation rate was 65%, 6.7% were screened positive, and 2.2% overall were diagnosed with cancer (82% stages I-II). Only one false-positive was investigated with surgical procedure [6]. Several trials were rejected from public granting, and some cohort studies are in preparation but still need public grant approval. Following NELSON results, the academic taskforce met again and released a statement advocating for LCS experimentation. New national guidelines are underway and discussions with health agencies are ongoing.

Germany

The single-site German randomised controlled lung cancer screening trial (LUSI) recruited 4,052 screenees [7]. The results show a statistically significant reduction in lung cancer mortality among women, but not among in the CT arm after 8.8 years [8].

The novel official German lung cancer guideline recommends screening using low-dose CT (LDCT) and encourages the use of a risk model [9]. The new radiation protection legislation also opens the way to apply for the establishment of a program for individualised early detection of lung cancer. Such programs will be strictly quality-controlled, and probably associated with certified lung cancer centres throughout the country. Discussions are ongoing regarding details and financial considerations.

Greece

Smoking is highly prevalent in Greece. The proportion of daily smokers is one of the highest in Europe, at 27% of the general population. Among daily smokers, heavy smokers are the majority, with almost 1 in every 7 adults being heavy smokers [10]. As a result, lung cancer is responsible for more than 8,000 deaths in Greece per year. Men are affected predominantly, having the highest percentage of deaths due to lung cancer in Europe, at 9.8 % [11]. Despite the high impact of smoking habits and lung cancer in the Greek population, there is currently no active LCS programme.

Israel

In Israel, the rate of smoking varies significantly based upon ethnicity and is 22 / 44% in males (Jewish / Arab) and 15 / 7 % in women respectively. Israel has 2,400 new cases of lung cancer every year. Screening programmes are emerging through private services; however, reimbursement has so far been rejected. Recently, upon a multi-disciplinary consensus statement, the ministry of health adopted the recommendation for screening and built a national programme in line with the NLST eligibility criteria. As the incidence of lung cancer is lower than that expected for the rate of smoking, and in order to increase the cost/benefit ratio from screening, reimbursement may be approved this year for those above the age of 60.

Italy

Italian randomised controlled LCS trials by LDCT recruited some 10,000 screenees, and a further 9,000 were recruited in LDCT single arm trials [12]. These figures were scattered over four independent centres, resulting in underpowered small cohorts [13]. Data pooling by two centres showed a reduction of overall mortality by LDCT, yet this was not statistically significant [14]. Significant 39% reduction of lung cancer mortality was recently reported by the Multicentric Italian Lung Detection (MILD) trial, with further specific emphasis on long-term effects beyond 5 years [15]. Noteworthy, smoking cessation was confirmed a pivotal component to the final outcome of overall mortality control [16]. The ongoing Italian LCS trials aim to prospectively test plasmatic micro RNA biomarkers and to select low-risk subjects for low-intensity screening (e.g. LDCT every 3 years) [17-19].

Netherlands

There is currently no organised lung cancer screening in The Netherlands. The authorities have indicated that they are unlikely to make recommendations or decisions regarding implementation until the results from the Dutch-Belgian NELSON trial have been published. This large trial involved 7,900 participants in the CT screening arm and compared them to 7,892 participants in the control arm between 2003 and 2015 [20]. The announcement in September 2018 of the positive NELSON results immediately led to a debate in Dutch media on the need for screening implementation. Several initiatives were announced that are preparing requests to the Dutch regulatory authorities on population screening to establish an implementation programme.

Portugal

Portugal lags behind the tobacco epidemic, presenting lower lung cancer mortality compared to other European countries. Over recent decades, the progressive increase in tobacco use among females has been followed by a late steady rise in women lung cancer mortality even though it is still comparatively rather low. In contrast, tobacco consumption in males has decreased but not consistently in all age groups [21]. Trends in lung cancer mortality until 2005 depict stabilisation among males [22]. More recently, cancer incidence estimates in the north of Portugal (2009-2020) predict a steep rise in lung cancer, especially among women. This is mostly attributable to increased risk of developing lung cancer rather than demographic changes [23]. Notably, lung cancer mortality is alarmingly high in the Azores

region [24]. Currently, there is no organised lung cancer screening programme in Portugal. While medical societies look forward to evidence-based guidelines on LCS, a population-based survey in mainland Portugal shows that most participants (62.3%) believe that organised LCS should be implemented after a specific age [25].

Russian Federation

Russia is still predominantly using "fluorography" for population screening for lung diseases, primarily tuberculosis. However, the effectiveness and efficiency of this approach is very controversial as the majority of tuberculosis cases are diagnosed in high-risk groups. In 2016, an LDCT screening programme was launched in Moscow. In 2018, baseline screening was completed: 5310 individuals (53% men, 47% women) aged 18 to 92 years (average 62 years) participated. The final risk-group cohort included 4,762 persons. The detected lesions were: Lung-RADS 3 in 291 (6.1%) patients, 228 (4.8%) Lung-RADS 4A, and 196 (4.1%) Lung-RADS 4B/4X. All 4B and 4X patients were referred to oncologists. Malignant neoplasms were diagnosed in 84 cases (1.76% of the cohort), with 40.3% of stage I-II lung cancers. The number needed to screen (NNS) to identify one lung cancer patient was 57, and 207 to detect one Stage I lung cancer. The results of the study will be published in early 2019. This LDCT programme has initiated a movement to reject fluorography screening in Russia, and to initiate similar screening programmes in other regions of Russia. It has also increased the demand for Picture Archiving and Communication Systems (PACS), as well as interest in artificial intelligence services for the radiologists' augmentation. The LDCT screening programme continues in Moscow.

United Kingdom

Lung cancer screening is not currently recommended as a national programme in the UK. The UK Lung Screen Trials (UKLS) previously reported on the baseline findings of CT screening in approximately 2,000 participants [26]. Currently there are a number of ongoing early lung cancer detection pilot projects underway in many parts of the UK using low-dose CT [27]. While these projects are being delivered at a local level, including the use of community-based mobile low dose CT scanners, they share many similarities including the use of risk-prediction models to recruit participants, the use of standardised nodule management guidelines based on volumetry, and the incorporation of lung health checks at the time of patient visit.

Conclusion

LCS by LDCT reduces specific mortality in some clinical trials but, but several concerns remain: cost-effectiveness, eligibility optimisation, service implementation, balance of benefits and harms, gender, or participation rate. First-released outcomes of screening programmes in the US (for 2016 and 2017) are contrasted: 90% of screened individuals were eligible, but only 2 to 3% of the eligible population attended a screening CT scan [28]. However, this programme is not nationally organised, and lacks quality assurance measures. By contrast, most organised trials showed higher participation rates. This contrast should highlight to the scientific community, as well as health policy makers, that national organisation of lung cancer screening - as for breast or colon cancer - should be highly encouraged in all European countries.

Appendix Table A1. Population, smoking prevalence and annual lung cancer deaths in Europe.

Overview of Lung Cancer Screening activities in Europe

Area	Country[A]	Population >15 yo, in 2016[B]	Prevalence of current tobacco smoking in >15yo, in 2016 (%)[C]			Estimation[D] of current smokers(N)	Number of lung cancer deaths in 2018 (N[E]		
		Both	Both	Females	Males	Both	Both	Males	Females
ALL	**Europe[F]**	**623 686 886**	**29.4**	**20.7**	**38.1**	**192 632 135**	**387 136**	**266 727**	**120 409**
East	Belarus	7 920 202	28.3	10.5	46.1	2 241 417	2 944	2 563	381
	Bulgaria	6 126 450	37.3	30.1	44.4	2 285 166	3 867	2 987	880
	Czech Republic	8 995 819	34.4	30.5	38.3	3 094 562	5 217	3 427	1 790
	Hungary	8 353 228	30.8	26.8	34.8	2 572 794	8 893	5 358	3 535
	Poland	32 565 516	28.2	23.3	33.1	9 183 476	26 509	17 135	9 374
	Republic of Moldova[1]	3 421 545	25.3	5.9	44.6	865 651	1 326	1 058	268
	Romania	16 749 517	30	22.9	37.1	5 024 855	10 277	7 838	2 439
	Russian Federation	119 070 212	40.9	23.4	58.3	48 699 717	54 595	44 543	10 052
	Slovakia	4 611 322	30.4	23.1	37.7	1 401 842	2 436	1 757	679
	Ukraine[2]	37 670 123	30.5	13.5	47.4	11 489 388	15 295	12 600	2 695
North	Denmark	4 764 023	19.1	19.3	18.8	909 928	4 058	2 117	1 941
	Estonia	1 099 883	31.9	24.5	39.3	350 863	722	531	191
	Finland[3]	4 602 248	20.5	18.3	22.6	943 461	2 322	1 408	914
	Iceland	265 423	14.8	14.3	15.2	39 283	143	69	74
	Ireland	3 700 349	24.4	23	25.7	902 885	2 060	1 101	959
	Latvia	1 670 202	38.3	25.6	51	639 687	930	685	245
	Lithuania	2 480 985	29.7	21.3	38	736 853	1 363	1 098	265
	Norway[4]	4 317 947	20.2	19.6	20.7	872 225	2 386	1 252	1 134
	Sweden	8 125 842	18.9	18.8	18.9	1 535 784	3 849	1 844	2 005
	United Kingdom	54 197 417	22.4	20	24.7	12 140 221	37 688	19 918	17 770
South	Albania	2 407 729	29.2	7.1	51.2	703 057	1 021	859	162
	Bosnia & Herzegovina	3 016 713	39	30.2	47.7	1 176 518	2 174	1 730	444
	Croatia	3 593 837	37.1	34.3	39.9	1 333 314	2 879	2 097	782

	Greece	9 579 222	43.7	35.3	52	4 186 120	8 343	6 688	1 655
	Italy	51 342 604	23.8	19.8	27.8	12 219 540	34 512	24 034	10 478
	Malta	367 499	25.6	20.9	30.2	94 080	188	151	37
	Montenegro	513 800	46	44	47.9	236 348	344	268	76
	Portugal	8 933 939	23.2	16.3	30	2 072 674	4 671	3 654	1 017
	Serbia[5]	7 358 318	39	37.7	40.2	2 869 744	6 811	4 824	1 987
	Slovenia	1 769 909	22.6	20.1	25	399 999	1 282	841	441
	Spain[6]	39 498 395	29.4	27.4	31.4	11 612 528	22 896	17 559	5 337
	TFYR Macedonia	1 731 874					947	761	186
West	Austria	7 484 052	29.7	28.4	30.9	2 222 763	4 389	2 648	1 741
	Belgium	9 423 906	28.3	25.1	31.4	2 666 965	7 037	4 676	2 361
	France	52 958 172	32.9	30.1	35.6	17 423 239	37 459	26 156	11 303
	Germany	71 192 481	30.7	28.2	33.1	21 856 092	50 560	32 168	18 392
	Luxembourg	481 230	23.5	20.9	26	113 089	232	154	78
	Netherlands	14 168 902	25.9	24.4	27.3	3 669 746	11 008	6 096	4 912
	Switzerland	7 156 051	25.8	22.6	28.9	1 846 261	3 503	2 074	1 429

1. Including Transnistria.
2. Including Crimea.
3. Including Åland Islands.
4. Including Svalbard and Jan Mayen Islands.
5. Including Kosovo.
6. Including Canary Islands, Ceuta and Melilla.

A. List of country and region is from UNStats (available at https://unstats.un.org/unsd/methodology/m49/)

B. Data are for 2016. United Nations, Department of Economic and Social Affairs, Population Division (2017). World Population Prospects: The 2017 Revision, custom data acquired via website available at https://population.un.org/wpp/DataQuery/

C. Age-standardized prevalence of current tobacco smoking among persons aged 15 years and older , 2016 from Global Health Observatory data repository, Prevalence of current tobacco use, Data by country, available at http://apps.who.int/gho/data/view.main.GSWCAH20v

D. Calculated from the ratio provided and the population number.

E. Data are for 2018, International Agency for Research on cancer, Global Cancer Observatory, available at http://gco.iarc.fr/today/home

F. Data for Europe are calculated as the sum of all other data in the row.

Yo: Years-Old ;

II: Tobacco Cessation

Appendix Table A2. Impact of Lung Cancer Screening on smoking behaviour change. Main findings from prospective cohort studies and randomised control trials

					Baseline prevalence Tobacco use (%)		Quit attempt (%)		Smoking Abstinence (%)			Relapse in former Smokers (%)		
First Author / Date	N Total	% Men	Study Type	Cessation Intervention	LDCT	CG	LDCT	CG	LDCT / Interve ntion	CG	total	LDCT	CG	total
Schnoll / 2002 [29]	55	0	PC	100	-	-	-	-	16	-		-	-	
Cox / 2003 [30]	1475	53	PC	none	61	-	-	-	14	-		10	-	
Clark / 2004 (1) [31]	85	54	PC	web program	61	-	68	-	5	-		-	-	-
Clark / 2004 (2) [31]	86	48	PC	Self-help materials	61	-	48	-	10	-		-	-	-
MacRedmond / 2006 [32]	449	49%	PC	Limited counselling	69	-	-	-	19	-	-	2	-	
Anderson / 2009 [33]	2083	45	PC	Limited counselling	35	-	-	-	29	-	-	4	-	-
Ashraf / 2009 [34]	4104	55	RCT	Limited counselling	75	77	-	-	11	10	11	10	11	9
Styn / 2009 [35]	2094	49	PC	Limited counselling	100	-	59	-	16	-		-	-	
Van der Aalst / 2010 [36]	1248	100	RCT	Brochure	91	78	-	-	14	16		-	-	-
Ashraf / 2014 [37]	4104	55	RCT	Limited counselling	75.3	76.9	-	-	-	-	24	-	-	10
Pozzi/ 2015 [38]	187		PC *(sub-set MILD)*	Varenicline+ counselling	100	100	-	-	19.8	-	-	-	-	-
Marshall/ 2016 [39]	55	-	RCT	Counselling + quit aids (web/print) + quit line info vs print aids + quit line info	-	-	-	-	14.3	18.5	16.4	-	-	-
Brain/ 2017 [40]	4055		RCT		49	51			24.0	21.0	-	-	-	-
Taylor/2017 [41]	92	43.5	RCT	Telephone counselling	100	-	-	-	17.4	4.3	-	-	-	-

				+MI+ quit aids										

Info- information; LDCT – Low dose computerized tomography; CG – Control group; PC - prospective cohort; RCT - randomised control trial MI – Motivation interview
Adapted from Leone et al. [42].

III. State-of-the-art treatment of early stage (1A) lung cancer

Stage 1A lung cancer detected at LCS will pose specific challenges to organ-sparing treatment options. While lobectomy and systematic lymph node dissection is the standard surgical procedure [43], there are data supporting sub-lobar resection vs. lobectomy. When compared to lobectomy in stage I Non-small-cell lung carcinoma (NSCLC), sub-lobar resection had a higher risk of local recurrence, but fewer peri-operative pulmonary complications and similar cancer-related mortality [44]. Wedge resection was associated with an increased risk of loco-regional recurrence. In a different study, lobectomy and sublobar resection groups had similar 5-year overall survival (61.8% vs 55.6%) with the sublobar group having an increased risk of recurrence [45]. In patients with NSCLC <2 cm, the 5- and 10-year survival rates after segmentectomy were 83% and 83%, respectively, versus 81% and 64% after lobectomy ($p = 0.66$) [46]. El-Sherif et al [47] showed a similar recurrence rate after sub-lobar vs. lobectomy in stage IA, but slightly worse in stage IB. Investigating 294 lobectomies and 53 sub-lobar resections, Altorki et al showed that 10-year survival rates were 86% and 85%, with recurrence rates of 19% vs 12%, respectively (NS) [48].

For inoperable patients, stereotactic radiotherapy (SBRT) is reported to be as effective as surgical resection, particularly for peripheral lesions [49]. SBRT was equivalent to lobectomy in the endpoints of loco-regional control and cancer-specific survival. In tumours up to 5 cm, the rates of disease-free and overall survival at 3 years were 48.3% and 55.8% respectively [50]. Radiofrequency ablation (RFA) is another possible treatment option for inoperable patients with a local recurrence rate of 40% at 2 years after RFA [51]. Local control was marginally better for tumours <2 cm, but it was still not close to the rates of SBRT or sublobar resection. However, in a recent prospective multicentre study of RFA in stage IA lung cancer, local control rate at 1 year was 84% and 81% at 3 years. The OS rate was 92% at 1 year and 58% at 3 years [52]. The forced expiratory volume was stable in most patients and there was no significant change in the global health status or in the quality of life following RFA. It is important to note that patients who are not candidate for surgery were not eligible for LDCT based screening studies. Interestingly enough, Tanner et al [53] explored this issue of patients with multiple co-morbidities within NLST and compared them with elderly patients with both with and without comorbidities. Those who could not undergo surgery had very poor outcomes.
Due to the lack of evidence in this important field of the therapeutic options in stage 1A lung cancer detected at LCS, ERS and ESR have liaised with ESTS and ESTRO to produce a joint statement paper.

IV. Incidental Findings

In LCS, clear algorithms should be in place regarding which findings will be reported and which require further evaluation, based on the following principles:

- The finding should be real (i.e. there should be general agreement with minimal inter-observer variation as to the presence of the finding).
- The finding must be clinically significant (i.e. it should usually be associated with an important or adverse impact on the patient).
- There should be an established intervention associated with the observation that leads to patient benefit.
- The reporting of incidental findings should be accompanied by specific recommendations for intervention.

The management of incidental findings can thus be broadly categorised as follows:

- Findings that require immediate action (e.g. pneumothorax), prompting emergency referral.
- Findings indicating a likelihood of non-pulmonary cancer, which requires further investigation (e.g. breast mass), prompting referral to a specialist.
- Other non-cancer findings requiring further investigation or that may lead to beneficial interventions (e.g. significant diffuse parenchymal lung or dilated ascending aorta), prompting referral to a specialist or a notification of general practitioner.
- Findings which are usually clinically insignificant, which may be prone to observer variation and for which there is no established beneficial intervention do not need to be reported (e.g. minor atelectasis, renal or liver or thyroid cysts), needing no communication.

Screening programmes should use these principles to develop locally agreed protocols for management of incidental findings. A list of examples of incidentals findings that can be encountered in LCS is set out in Table A3.

Appendix Table A3. Examples of incidental findings that may be identified in low dose CT screening for lung cancer.

Neck
Thyroid gland -nodule -cysts -calcifications **Lymphadenopathy**
Thoracic cavity
Trachea, bronchi, bronchioles ***Trachea:*** -tracheal stenosis -tracheomalacia -mass ***Bronchi:*** -bronchial thickening -bronchiectasis -secretion/foreign bodies **Lungs** -linear opacities

-increased lung attenuation (diffuse ground glass opacity, consolidation) -decreased lung attenuation (cyst(s), emphysema)
-combined pattern (honeycombing, crazy-paving pattern)
-interstitial opacities with or without traction bronchiectasis
Pleura
-pleural effusion, unilateral or bilateral
-pneumothorax
Heart
-left ventricular hypertrophy or dilatation
-valvular calcifications
-right ventricular hypertrophy or dilatation
-coronary artery calcifications
Pericardium
-pericardial effusion
-pericardial calcifications
Oesophagus
-diverticulum/diverticula
-achalasia or dilatation
-oesophageal mass
Mediastinum
-pneumomediastinum
-lymphadenopathy
-masses
Vessels:
-aorta/arteries: arteriosclerosis , aneurysms
-pulmonary arteries: enlarged main pulmonary arteries

Diaphragms

Hernia
-hiatal hernia
-other diaphragmatic hernias
Diaphragmatic elevation, unilateral or bilateral

Abdominal cavity

Liver
focal lesion(s):
-cyst(s), solitary or multiple
-masses
generalized lesion(s):
-liver cirrhosis/irregularity
Gallbladder, bile ducts
-biliary calculi
-choledocholithiasis
-cholestasis, intrahepatic or extrahepatic
-aerobilia
Pancreas
focal lesion(s):
-cyst(s), solitary or multiple
-masses
generalized lesion(s):
-calcifications
-pancreatic atrophy
-pancreatitis, acute or chronic
Stomach
-masses
Spleen
focal lesion(s):
-accessory spleen
-cyst(s), solitary or multiple
-masses
-calcifications
generalized lesion(s):
-splenomegaly
Peritoneum
-ascites

-pneumoperitoneum
-nodules/masses
Kidneys
focal lesion(s):
-cyst(s), solitaryor multiple
-masses
-calcifications, nephrocalcinosis
-urolithiasis
generalized lesion(s):
-atrophic kidney(s)
-hydronephrosis
Adrenal glands
-nodules
-masses
-hypertrophy
Retroperitoneum
Vessels:
-aorta/arteries: arteriosclerosis, aneurysms or stenosis

Skeleton, joints, ligaments, tendons

-osteoporosis
-diffuse idiopathic skeletal hyperostosis (DISH)
-spondylosis
-spondylodiscitis
-lytic or sclerotic lesions

Skin, subcutaneous tissue, muscular system

-lipoma
-sebaceous cysts
Breast
-nodules
-masses
Obesity
Cachexia, sarcopenia

Previous surgery

V. The psychological impact of lung cancer screening

Selection bias has been revealed as a problem in an RCT: the participants in the Danish Lung Cancer Screening Trial (DLCST) had a more favourable socio-demographic profile and were more psychologically robust compared to the general population of heavy smokers [54]. Therefore, selection bias could have resulted in underestimating the actual psychosocial consequences [54].

In lung cancer CT screening, several studies about health-related quality of life, psychological and psychosocial have been conducted. Two systematic reviews have been identified regarding this topic and neither included an assessment of the measurement properties of the PROMs used nor properly assessed the presence of selection and attrition [55, 56].

The patient-reported outcome measures on the consequences of screening in lung cancer (PROM COS-LC) was developed and validated using qualitative interviews in focus groups and psychometrically analysing survey data [57]. One study, using the COS-LC as a primary outcome and investigating the first two screening rounds in the DLCST, concluded that participation in the DLCST experienced negative psychosocial consequences for all participants, worst for the control group [58]. Another study, also using COS-LC as the primary outcome, investigated all DLCST's five screening round, concluding that these negative psychosocial consequences persisted throughout the trail's four years: both the intervention group and the control reported higher negative consequences compared to the baseline measurement, again worst for the control group [59].

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