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REPORT

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REPORT

Recommendations from the European Society of Thoracic Surgeons (ESTS) regarding computed tomography screening for lung cancer in Europe

Jesper Holst Pedersen[a,*], Witold Rzyman[b], Giulia Veronesi[c], Thomas A. D'Amico[d], Paul Van Schil[e], Laureano Molins[f], Gilbert Massard[g] and Gaetano Rocco[h]

[a] Department of Thoracic Surgery RT 2152, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark
[b] Department of Thoracic Surgery, Medical University of Gdansk, Gdansk, Poland
[c] Humanitas Research Hospital, Rozzano, Italy
[d] Thoracic Surgery, Duke University Medical Center, Durham, NC, USA
[e] Department of Thoracic and Vascular Surgery, Antwerp University Hospital, Edegem, Antwerp, Belgium
[f] Thoracic Surgery Respiratory Institute, Hospital Clínic, University of Barcelona, Barcelona, Spain
[g] Service de Chirurgie Thoracique, Hôpitaux Universitaires de Strasbourg, Strasbourg, France
[h] Division of Thoracic Surgery, Department of Thoracic Surgical and Medical Oncology, National Cancer Institute, Naples, Italy

* Corresponding author. Department of Cardiothoracic Surgery RT 2152 Rigshospitalet, University of Copenhagen, DK-2100 Copenhagen, Denmark. Tel: +45-35458014; e-mail: jesper.holst.pedersen@regionh.dk (J.H. Pedersen).

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Summary

In order to provide recommendations regarding implementation of computed tomography (CT) screening in Europe the ESTS established a working group with eight experts in the field. On a background of the current situation regarding CT screening in Europe and the available evidence, ten recommendations have been prepared that cover the essential aspects to be taken into account when considering implementation of CT screening in Europe. These issues are: (i) Implementation of CT screening in Europe, (ii) Participation of thoracic surgeons in CT screening programs, (iii) Training and clinical profile for surgeons participating in screening programs, (iv) the use of minimally invasive thoracic surgery and other relevant surgical issues and (v) Associated elements of CT screening programs (i.e. smoking cessation programs, radiological interpretation, nodule evaluation algorithms and pathology reports). Thoracic Surgeons will play a key role in this process and therefore the ESTS is committed to providing guidance and facilitating this process for the benefit of patients and surgeons.

Keywords: Lung Cancer • CT screening • Recommendations • Implementation

INTRODUCTION

Early diagnosis of lung cancer by computed tomography (CT) screening has in the USA lead to a significant reduction in lung cancer mortality of 20% in the National Lung Screening Trial [1, 2]. This was followed by an extensive evaluation of benefits and harms of CT screening and recommendation for its implementation by the US Preventive Service Task Force [3, 4] and subsequent approval by Medicare [5]. Recommendations for CT screening have been published by many organizations involved in the diagnosis and treatment of lung cancer: The American Association for Thoracic Surgery [6], Society of Thoracic Surgeons [7], American Lung Association [8], National Comprehensive Cancer Network [9], American Cancer Society [10], International Association for the Study of Lung Cancer (IASLC) [11], American Society of Clinical Oncology [12] and also patient advocacy groups [13]. As a consequence of these initiatives lung cancer CT screening is now being implemented on a wide population based scale in the US [5, 13] and in some parts of China [14, 15].

Status for implementation of computed tomography screening in Europe

In Europe, around 269 000 deaths from lung cancer are expected in 2016 and it now seems clear that screening and early detection can contribute to reducing lung cancer mortality. Lung cancer screening is yet to be implemented of a large scale, and remains a public health priority for Europe. CT screening is recommended in a white Paper by European Society of Radiology and European Respiratory Society (ERS) [16], in a statement from the Swiss University Hospitals [17] and European Society of Medical Oncology [18]. Decisions regarding implementation are under the jurisdiction of the national health authorities and so far most European countries await mortality and cost-effectiveness data of the Dutch-Belgian NELSON CT screening trial in 2016 and from pooled European Union trials thereafter. It is stated that European trials should be continued and their results should be awaited before further decisions are made.

[19–21]. The structure of the health care systems varies greatly between European countries, and the adoption of CT screening may vary from country to country. In several European countries (Netherlands-Belgium, UK, Denmark, Italy, Germany, Poland, Spain, Switzerland) both observational and randomized CT screening studies have been performed within the last 10 years., and all have provided valuable results and experiences that may be used in the future refinement and improvement of the National Lung Screening Trial screening protocols in order to reduce false positive rates and to improve cost effectiveness. Results from the NELSON [22, 23] and DLCST [24] trials demonstrated ways to achieve low false positive rates. In NELSON, important results regarding the optimal screening interval were also achieved [25]. In the UK, the United Kingdom Lung Screening trial, showed that risk stratification of participants was possible in a screening setting to select a high-risk cohort with minimum 5% risk of getting lung cancer within the next 5 years [26]. This and other reports suggests that COPD may be an important selection criteria for lung cancer screening [27, 28], but also other risk factors included in risk prediction models may be of benefit [29].

In Europe, implementation of CT screening will most likely follow traditions from other screening programs as for example breast and colorectal cancer which are already implemented in many European countries. This implies that CT screening for lung cancer would be implemented in a form with complete public financing and public screening centres with population-based recruitment to allow equal access for all eligible citizens [30]. The financial burden of this may be considerable and in some countries public radiology services may be at a shortage. It is therefore expected that some countries may integrate private operators and perhaps private financing in this process. Under these circumstances, it will be important to have evidence-based guidelines or recommendations to guide the implementation process in Europe.

A lung cancer screening program with low-dose CT (LDCT) screening is a complex endeavour with the purpose of identifying persons without symptoms with lung cancer in an early stage allowing curative treatment, at the same time avoiding causing harm to the persons that do not have the disease. To achieve this during large scale implementation requires that the screening program is performed according to a systematic, structured, standardized and validated protocol, and that the quality of the performance is monitored continuously.

Thoracic surgeons will play a key role in the implementation of CT screening in Europe. Therefore they also carry a major responsibility for the safety and well-being of persons enrolled in the CT screening programs in which they take part. The ESTS is committed to providing guidelines and facilitating this process for the benefit of patients and surgeons. The ESTS Executive Committee reviewed and endorsed the final content of this document.

THE GOALS OF THE ESTS WORKING GROUP

Provide recommendations on the following issues in relation to CT screening for Lung Cancer**:**

1. Implementation of CT screening in Europe
2. Participation of thoracic surgeons in CT screening programs
3. Training and clinical profile for surgeons participating in screening programs.
4. Use of minimally invasive thoracic surgery and other relevant surgical issues.
5. Associated elements of CT screening programs (i.e. smoking cessation programs, radiological interpretation, nodule evaluation algorithms and pathology reports).

SPECIFIC RECOMMENDATIONS REGARDING SURGICAL ISSUES IN RELATION TO COMPUTED TOMOGRAPHY SCREENING PROGRAMS

Recommendation no. 1

Implementation in Europe

The ESTS recommendations are based on the likely scenario that, in Europe, CT screening for lung cancer will have to be implemented within the next few years. Accordingly, it is envisaged that each country makes preparations to accommodate and facilitate the process according to specific cultural, political and socioeconomic circumstances. In order to successfully implement high-quality screening programs, it is therefore important that local conditions are taken into account. As an example, smaller countries are encouraged to establish partnerships with bordering countries and international organizations in order to maximize their access to research opportunities and the attendant potential benefit from lung cancer screening programs. The European Commission (EC) is expected to implement publicly mandated quality assurance in cancer screening programs but lung cancer screening is not included among EC health programs [31]. It is recommended that the European Union should warrant financial support for designing and implementing early diagnosis programs, and include lung cancer among priorities in initiatives such as Horizon 2020.

Countries without previous experience with CT screening for lung cancer are encouraged to establish demonstration projects with CT screening for lung cancer in one or two centres, in order to get experience with the organization and daily practice of CT screening. These centres should have multi-disciplinary team (MDT) capabilities (as described elsewhere in this document), and a minimum screening population of 2000 individuals in order to have a sufficient yield of screen detected nodules and lung cancers to rapidly create enough expertise. Central data registration and quality evaluation is essential for this resource to be of benefit for the further planning and implementation of screening.

Countries with previous or ongoing screening centres/trials are encouraged to prepare a joint protocol and organization for the national implementation of CT screening, based on these local experiences. This could be combined with a parallel application for and initiation of demonstration projects evaluating specific issues in relation to screening. This could for example be: (i) an evaluation of the safety and cost effectiveness of biannual screening, (ii) an evaluation of risk prediction models for selection of the high-risk cohort for CT screening, (iii) an evaluation of safety and effect of different nodule size cut-offs for the rate of false positive test results, (iv) an evaluation of individualized screening protocols based on findings on base line CT screening and (v) value of biomarkers in CT screening.

It is recommended that when establishing lung cancer screening programs—checklists are utilized in order to guarantee high-quality standards, even in the temporary absence of large numbers. It is also recommended that the ESTS should prepare a checklist for high quality lung cancer screening programs in

Europe, followed by approaches to the UEMS to have endorsement of this checklist at a national level.

Recommendation no. 2

Involvement of thoracic surgeons in preparation of screening programs

Surgeons should be involved in structuring and implementing of all screening programs. With the increasing rate of detection of early lung cancer through screening LDCTs, surgeons will be called to provide the necessary expertise to obtain both diagnosis and treatment of screen-detected nodules. According to the checklist concept of a high-quality lung cancer screening program in the USA, the surgeon plays a leading role within the lung cancer screening MDT, especially with a view to apply the principle of adopting the least invasive diagnostic and surgical approach to achieve the minimal harm and maximal parenchymal preservation [13, 32].

Major goals of surgical participation in lung cancer screening programs include [7, 33]:

1. Optimization of the management of screen detected nodules
2. Reduction of false positive rates of surgical biopsies
3. Reduction of surgical incision-related trauma
4. Implementation of national or international risk assessment guidelines
5. Implementation of a smoking cessation policy
6. Active education of primary care physicians towards lung cancer screening programs

Accordingly, it is recommended that the surgeon involved in lung cancer screening programs possess the qualifications and requirements described in recommendation 5 [33, 34].

In order to provide an optimal profile of safety for the surgical candidates, the thoracic surgical unit belonging to the institution participating to the lung cancer screening program must possess the minimum requirements stated in the ESTS document on structure and qualification of general thoracic surgery [35].

In addition, thoracic surgeons must demand appropriate pathologic reporting in line with the most recent World Health Organization classification and be prepared to provide adequate tissue for biomolecular characterization [34].

Recommendation no. 3

Multi-disciplinary capabilities and requirements to a screening centre

A lung cancer screening (LCS) centre should be a centre of excellence based on multi-disciplinary teamwork. In fact, the Lung Cancer Screening MDT (LCSMdT) should include thoracic radiologists, pathologists, pulmonologists, thoracic surgeons, medical oncologists, radiation oncologists and nurses who are experienced in lung cancer management and are trained in the process of screening. An expert in smoking cessation counselling should be a mandatory member of such a team [36]. The LCSMdT should ensure standardization of the lung cancer screening pathway according to established quality assurance protocols as well as timely and uniform reporting system [37, 38].

All participants of the LCSMdT must be dedicated clinicians with recognized expertise in the diagnosis, management and follow-up of screen detected lung nodules and the use of currently published, evidence-based algorithms and care pathways [7].

The adoption of a tobacco cessation program and the emphasis on a close cooperation with other specialties managing population diseases (i.e. pulmonologists, cardiologists) are essential. In fact, a tobacco cessation program is potentially associated to a reduction in lung cancer specific mortality that exceeds that from lung cancer screening as well as to an improvement of the cost-effectiveness of a LCS program [39, 40]. A comprehensive individualized smoking cessation program should be offered to all participants. Precise data collection on interventions like enrolment, completion, and 'quit' rates are of utmost importance to monitor the outcomes of the LCS program [41].

In this setting, LCS programs should participate in national or international registries of all aspects of screening such as risk assessment protocols and biological samples collection for the study of e.g. biomarkers.

Recommendation no. 4

Diagnostic protocols

One of the major topics related to CT screening is the precise diagnostic algorithm used for management of screen-detected nodules, the vast majority of which are not malignant [7]. Obviously, it is important not to overlook any early stage lung cancer and in this way, a high sensitivity is required. Also, an acceptable specificity is important to limit the number of false-positive diagnoses which may give rise to unnecessary invasive procedures [42, 43]. Moreover, the introduction of a new pathological classification for lung adenocarcinoma and its radiological correlation has had a profound impact on diagnosis and management of early stage lung cancer [44, 45].

When considering diagnostic protocols several aspects are important: First of all, the target population has to be clearly identified showing an increased risk of developing lung cancer. The National Lung Screening Trial criteria; Age: 55–74, Tobacco exposure of > 30 pack years and no more than 15 years since quitting smoking [1, 2] have been endorsed by all organisations engaged in screening [9–12, 16, 18]. Some have expanded the criteria to include ages over 50 years in combination with other risk factors [6, 7, 9]. Inclusion of higher risk groups: age up to 80 and additional risk factors [3, 4, 9, 16] or risk models selecting individuals with LC risk > 5% [26] or 2% [28, 29] over the next 5 years may be justified in order to increase cost effectiveness [26, 29]. Secondly, consideration should be given to the radiation exposure generated by the CT screening protocol. This has been achieved by using LDCT with an effective dose of 1 mSv per scanning, as recommended both in the US [9, 36, 38] and Europe [16]. Lastly, size and nodule characteristics are important to determine follow-up examinations or referral for other noninvasive or invasive tests to determine the indication for surgical excision [35]. Size can be measured and reported as unidimensional, bidimensional or volumetric assessment, and consecutive scans can enable an evaluation of growth and calculation of nodule volume doubling time [46, 47]. The lower cut-off size for defining a positive nodule has great impact on the false positive rate, and a change to higher cut-offs has been shown to be possible without a major reduction in sensitivity [36, 48]. Also the distinction between findings at baseline and at subsequent incidence screenings is important, both with regards to expected findings and the

REPORT

false positive rate, which in most European trials was only 1–2% at incidence screenings [19, 21, 24, 25, 49]. This has important implications for the implementation of CT screening.

At the present time, no universally accepted protocol for management of screen-detected nodules exists, and in several of the prospective randomized trials different protocols were used. The National Lung Screening Trial defined a positive test result as any non-calcified nodule measuring at least 4 mm in any diameter, and consequently had high false positive rates in up to 24% of the participants [1]. In the USA, an increased cut-off rate from 4 to 6 or 7 mm in diameter has been suggested [36, 38].

In the Dutch-Belgian NELSON and the United Kingdom Lung Screening trials volumetric measurements with specific volume criteria were used [16, 26, 46]. The positive screenings had a predictive value of 40.6% reducing false-positive results to 59.4% [47]. Selective use of volumetric assessment of higher risk nodules may further reduce false-positive results [50] and is included in the recent guidelines from the British Thoracic Society [51]. The incorporation of PET in the risk model using a 4-point intensity scale may further improve accuracy [52–54].

The criteria of the Fleischner Society for solid nodules and subsolid (pure ground-glass and part-solid lesions) nodules [55, 56], are used in the National Comprehensive Cancer Network guidelines [9]. A revision of the Fleischner guidelines will be published in late 2016 (Fleischner Society, personal communication H. MacMahon). Accurate criteria were proposed by the Pan Canadian (PanCan) screening research group and these are the only ones that have been validated in independent cohorts [57]. Predictors of cancer include older age, female sex, family history of lung cancer, emphysema, larger nodule size, location in the upper lobe, part-solid nodule, lower nodule count and spiculation [58].

The ESTS Working Group on Lung Cancer Screening strongly recommends that every screening centre utilizing LDCT should adopt a specific diagnostic protocol with a high sensitivity and adequate specificity in order to reduce the number of false-negative and false-positive screening results. Based on the experiences gained during the last 10 years it is now possible to plan diagnostic protocols with satisfactory sensitivity and the low false positive rates necessary for implementation.

Recommendation no. 5

Qualifications of participating surgeons

Early detection is essential for successful lung cancer treatment [58]. LDCT screening is an effective way of detecting early stage lung cancer [1, 42, 59, 60]. However, many screening-detected lesions are benign and may require invasive investigations—with attendant increased costs and risk of complications—to demonstrate non-malignancy [1, 59]. This poor specificity may constitute an obstacle to the large-scale implementation of screening. However, several studies have shown that by applying an effective diagnostic algorithm together with multi-disciplinary discussion of positive cases detected by CT screening, the frequency and extent of surgery for non-malignant disease can be minimized while a high-cure rate for individuals diagnosed with lung cancer can be obtained [16, 42, 60] .

Thoracic surgeons involved in LCSMdT have the important responsibility to minimize the risk of useless invasive procedures for benign disease and avoid overtreatment of very early cancers or precancerous lesions [7, 42].

As for the avoidance of overtreatment, the role of sublobar resection, anatomical segmentectomy and wide-wedge resections in the management of very early lung cancers detected in the context of CT screening programs is being re-evaluated. Non-solid or part-solid ground glass opacities (GGOs) have particularly favourable prognoses and appear to be ideal lesions for treatment by sub-lobar resection [61, 62].

In this setting, minimally invasive techniques should be used, either in the context of video-assisted thoracoscopic surgery (VATS) or robot-assisted surgery. We recommend that surgeons involved in lung cancer screening be familiar with minimally invasive thoracic surgery techniques within Thoracic Surgical Units where VATS or robotic equipment is used routinely to perform lobar and sublobar anatomical resections.

Thoracic surgeons involved in the LCSMdT must have a crucial role in tailoring the treatment to the screen detected lesion and the individual patient prognostic factors including age, comorbidities, performance status and life expectancy. In addition, thoracic surgeons involved in LCS must have extended experience in the interpretation of lung cancer imaging and related tumour variables such as volume doubling time, standardized uptake value at CT/PET, and nodule density (i.e. solid, partially solid and non-solid) [63]. In addition they should have received specific training in the diagnosis and management of screen-detected nodules so as to be able to recognize potentially false positive and false negative lesions and be aware of the incidence and features of interval cancers. Needless to say, thoracic surgeons should also be aware of potential harms, mortality, cost effectiveness and quality of life LCS- related issues.

Accordingly, it is recommended that the surgeon involved in lung cancer screening programs possess the following requirements [33, 34];

1. National certification as a Specialist Thoracic Surgeons—also called Board Certification.
   The European Board of Thoracic Surgery Certification is a preferred requirement.
2. Demonstrable experience as minimally invasive thoracic surgeon and in the interpretation of thoracic radiologic investigations. Moreover, he/she should be familiar with the use of different diagnostic options, along with alternative methods of diagnosis and treatment of lung cancer.
3. Participation as individual surgeon and/or unit to the ESTS European Database or a national equivalent in order to comply with international standards in terms of morbidity and mortality [43].
4. A good knowledge and regular practice of thoracic oncology is mandatory as well; the ERS-HERMES certification in thoracic oncology offers an opportunity for credential [64].

Surgeons involved in screening should have propensities to consider follow-up instead of immediate surgery for indeterminate nodules. In selected cases with comorbidities, multi-focal disease, or with previous lung lobectomy, non-surgical treatments include stereotactic ablative radiotherapy need to be contemplated [65].

Moreover, the ESTS Working Group on Lung Cancer Screening emphasizes that, since individuals receiving an indeterminate or positive result for a baseline screening CT develop increased anxiety, fear of cancer, and lung cancer-specific distress compared to those with a negative result [66], thoracic surgeons should possess the necessary skills to communicate LDCT results, in a face-to face meeting before the written report is sent out.

Recommendation no. 6

The use of minimally invasive surgery for small (<3 cm) screen-detected nodules

Lung cancer screening with LDCT detects approximately 80% of screening-detected cases are at stage I or II [49, 67]—compared to 16% at this stage in historical data on unscreened individuals [68]—and the resection rate is approximately 80–90%, with overall 5 years survival >70% [49, 66].

As a consequence of the increased detection of small-sized lung cancers at an earlier and potentially curable stage, it has become increasingly crucial to choose the most advantageous treatment strategy, including minimally invasive approach and sublobar resections for selected cases.

As with any screening modality, LDCT screening has potential inherent risks, which include [9, 69, 70]:

1. False-positive results, leading to unnecessary testing and/or invasive procedures (including surgery)
2. Complications from diagnostic workup
3. Detection of indolent disease (i.e. overdiagnosis), which would never have harmed the patient who subsequently undergoes unnecessary therapy [71].

Every effort must be made to minimize invasive interventions (diagnostic or therapeutic) on nodules that prove to be benign [4, 6]. Furthermore, when it is decided to proceed with a surgical therapeutic intervention, it is imperative that the vast majority of procedures be performed using minimally invasive techniques [72].

Thoracoscopic resections, also termed VATS, have been demonstrated to be associated with fewer complications [73], lower cost [74], and at least equivalent oncologic results [75] when compared with open procedures.

Thoracoscopic procedures are defined by the following criteria [72]: visualization is achieved using a camera and a video monitor, an access incision must be < 8cm in length, and no rib retraction, rib spreading or rib resection is employed. Minimally invasive resections include the use of manual thoracoscopic procedures as well as robotic procedures [76], as long as rib spreading is avoided.

To ensure adherence to standardized quality of practice, minimally invasive thoracic surgical procedures should be performed by board certified individuals in thoracic surgery; certification should be granted in any European Nation and/or confirmed by the European Board of Thoracic Surgery. Using thoracoscopic anatomic (lobar or sublobar) anatomic resections of screen-detected cancers that are less than 3 cm, it is expected that mortality would be less than 1%, major morbidity would be less than 5%, and the length of hospital stay should be approximately 3 days [72–74].

Prior to resection of screened-detected nodules, obtaining a preoperative diagnosis is the preferred approach. In patients with peripheral nodules with high likelihood of malignancy, VATS wedge resection prior to anatomic resection (VATS or open) is a reasonable strategy. In patients with larger or more central lesions, obtaining a preoperative diagnosis would be possible also with CT-guided transthoracic needle aspiration, trans-bronchial needle aspiration, navigational bronchoscopy, or endobronchial ultrasound guided aspiration. In any case, a diagnosis should be secured prior to proceeding with lung major resection. In case of suspicious lung lesions less than 2 cm with no preoperative diagnosis, resectable in the volume of an anatomical segmentectomy, it can be acceptable to perform a diagnostic and therapeutic minimally invasive segmental resection using both VATS or Robotics [77, 78] while diagnostic lobectomy should be avoided or limited to extremely rare cases.

REPORT

Recommendation no. 7

Pathology

ESTS working group on Lung Cancer screening express the importance of a standardized pathology reporting on surgical specimens and also recommends the set-up of a biobank to study biomarkers. Close cooperation of surgeon and pathologist with onsite verification of biopsy specimens is mandatory to enhance effectiveness of diagnostic work-up in order to minimize harms of screening [7].

Several key modifications were established in the 2011 IASLC/ATS/ERS Classification of lung adenocarcinoma [44]:

1. The term non-mucinous BAC was eliminated and described as lepidic;
2. Adenocarcinoma in situ for tumours 3 cm or less with completely lepidic growth and no invasion;
3. Minimally invasive adenocarcinoma for tumours 3 cm or less predominantly lepidic with invasion of 0.5cm or less;
4. Invasive adenocarcinoma with the predominant subtype mucinous BAC is now considered invasive mucinous adenocarcinoma.

The impact of sub-typing the lung adenocarcinoma according to the 2011 IASLC/ATS//ERS classification on patient survival is independent of other known prognostic factors such as TNM stage, similar to that breast and prostate cancer [79–81].

The resection of an adenocarcinoma in situ, minimally invasive adenocarcinoma and a lepidic-predominant adenocarcinoma have almost 100% 5-year survival rate. These figures can influence the surgical treatment of such patients in the near future as candidates for sublobar resection. The role of experienced lung pathologist is crucial. It is important to notice that in intraoperative frozen sections and/or small biopsies an invasive component cannot be always excluded [7, 45]. Pathology reports should adhere to the 2015 World Health Organization Classification of Tumors of the Lung, Pleura, Thymus and Heart recommendations.

Discovery and validation of biomarkers is central to segregate groups of patients by defining a diagnosis, prognosis and prediction. Ideally, the biomarkers in tissue are measured in formalin-fixed paraffin-embedded tissue, to avoid the use of 'snap-frozen' or 'fresh' specimens. Mutational analysis of NSCLC has become increasingly important and become the standard of care. The significant mutations in NSCLC are: EGFR, KRAS, BRAF, EML4-ALK and ROS1 Fusion Proteins, ERCC1 and RRM1 [82].

Recommendation no. 8

Specific surgical issues relevant to the screening situation

Lung cancers detected with LDCT screening will most often be in early stages and operable by minimal invasive techniques (VATS).

However, not all screen-detected nodules are easily diagnosed and therefore they require specific consideration:

Ground glass opacity lung nodules

In recent years, improvements in CT scanning resolution in combination with more frequent CT scanning use, has led to the detection of GGO lesions: often non- or minimally invasive adenocarcinoma type of lung cancer with a favourable prognosis [83–85]. GGO lesions may represent a wide spectrum of disease from benign lesions to invasive carcinoma, and the correlation between radiological appearance and histology may not be reliable [86, 87]. Therefore GGO nodules are a diagnostic challenge requiring a MDT approach to ensure correct work-up. Growing evidence indicates that the development and the size of a solid component is much more important than the nonsolid/lepidic component for the assessment of prognosis and risk of invasive carcinoma [88, 89], and this is reflected in the coming new (eighth edition) American Joint Committee on Cancer staging system [90]. Growth and solid transformation of GGO nodules may occur, however most GGO nodules remain unchanged. One study of 122 CT screening detected GGO nodules showed that 90% of nodules did not grow during long term follow-up of median 59 months [85, 91]. Most GGOs may therefore have an indolent clinical course [85, 92, 93], especially in a screening setting where the participants are without symptoms.

Currently it is recommended that:

- Persisting GGO nodules with size above 5 mm should be followed for at least 4 years [51, 94].
- PET-CT has limited value in the diagnostic work-up of GGO nodules [55, 95].
- Development of a solid component in a pure GGO nodule or growth of a pre-existing solid component in a part-solid GGO nodule is predictive of invasive malignancy. In these cases invasive diagnostic procedures should be considered [51].
- Careful consideration of the indications for surgery and longer follow-up, even for more than 4 years, of GGO nodules is crucial to insure safe management and reduce over diagnosis and overtreatment.
- Further research in this area is important for future practice

Treatment of invasive carcinoma even in stage I-II should be VATS lobectomy with systematic lymph node dissection [96]. Recent research from Japan has shown that some GGO lesions with low-consolidation/tumour ratios may be treated by sublobar resections [97]. However, final recommendations with regards to this must await results of the Japan Clinical Oncology Group (JCOG 0802) and Cancer and Leukemia Group B (CALGB 140 503) trials [98].

Surgery for benign lesions

It is an inherent risk in lung cancer CT screening that a suspicious but indeterminate pulmonary nodule may in fact be benign. Determination of malignancy will ultimately require either a biopsy or removal of the nodule in question. In all of the published studies of CT screening for lung cancer, surgery has been performed for some lesions in which pathology revealed benign histology. The reported extent varies from 2–45% [1, 9, 42, 43, 99–101], and current recommendations are to keep this rate below 15% [9]. In the majority of cases, surgery was performed as a minimally invasive procedure (43, 99), but also open procedures have been reported [43, 100, 101]. The extent of the resection for these benign nodules has most often been a sublobar resection [99], but also lobectomies for benign lesions have been reported [43, 99–101].

The best way to reduce surgery for benign lesions is to have an accurate preoperative/diagnostic biopsy algorithm, as this reduces the number of indeterminate nodules referred for surgery. Surgeons should be closely involved in development and maintaining a high quality diagnostic work-up to locate and mark or biopsy small indeterminate pulmonary nodules [102]. In addition, in difficult cases time should be allowed for watchful waiting to verify growth and calculation of tumour volume doubling time of the nodules and repeated biopsies to substantiate or verify a suspicion of malignancy [51]. In a screening setting a delay in diagnosis under close monitoring may be preferable to unnecessary surgery.

The extent of surgery for benign lesions during CT screening should be monitored and reported as an indication of surgical quality.

Recommendation no. 9

Quality monitoring and education

Quality monitoring and education of physicians are essential for safety issues within the framework of a screening program. While under diagnosis is limited with LDCT screening, there is a permanent threat of over diagnosis and potentially unnecessary surgical procedures for benign nodules. Mortality and morbidity of invasive diagnostic procedures should of course be kept as low as possible, especially in false positive cases [7, 42].

The fundament of quality control is materialized by an appropriate protocol, which needs to sharply outline [1]:

- Definition of the group at risk to be subjected to screening
- Technical means of screening and frequency of testing
- Strict criteria defining positive, negative and intermediate result of testing
- Algorithms for managing of positive, negative and intermediate results.
- Qualification of doctors involved
- Monitoring and re-evaluation of global results

Safety issues of a screening program concern both the individual and the collective level.

At the collective level, we should be concerned about the following:

- Information of the public
- Easy and equal access to the program for high-risk individuals
- Compliance to the program:
  - Number of refusal to join
  - Number leaving the program prematurely
  - Reasons to do so
- Monitoring of false positives/negatives and re-evaluation of criteria for evaluation of the results of testing (negative, positive, intermediate) [42]
- At the individual level, quality and safety issues concern the following:

- Use of LDCT to limit risk of irradiation [16, 36, 38, 103]
- Negative results: how long should screening be maintained and how often?
- Handling of positive results:
  - there should be no treatment without histology [7]
  - surgical exploration should be minimally invasive [7]
  - surgery should be performed in expert high-volume centres to keep mortality and morbidity in the lowest possible range [35, 102, 104]

As for confirmed lung cancer, multi-disciplinary handling of the results of screening tests should ascertain the best possible decision for the individual patient, especially when his profile projects outside of guidelines. Presence of the surgeon in the discussion round is mandatory to maintain a strong position against treatment without tissue diagnosis [7]. We need to actively oppose stereotactic radiation therapy in undiagnosed lesions, which can only be tolerated in inoperable patients [105].

Accurate monitoring and improvement of quality requires an obligation to implement all individual data into a database. Improvement of quality of care with marked decrease of operative mortality over time by the simple existence of a compulsory database has been demonstrated in lung cancer patients among others [104]. Regular reports from the database are paramount to maintain motivation of participating centres at a high level.

All points of concern mentioned above should be surveyed in regular time intervals, and in particular efficiency of the screening test, and morbidity–mortality of diagnostic procedures.

The ESTS database might easily be expanded to include data of screening programs.

Appropriate education of colleagues wishing to build up a screening program is fundamental. Individual training concerning radiologists (proper use of LDCT scan, software for size and volume measurements, etc) and pathologists (interpretation of small tissue samples, aspiration cytology) are out of the scope of this article. The American College of Radiologists for instance organizes certification for radiologists interested in lung cancer screening [103]. In a team-building process, beyond individual specialist training, it appears necessary to organize interdisciplinary teaching sessions, which would be an interesting direction to complete ESTS educational offer.

Recommendation no. 10

Central registration and certification of screening centres

Accurate screening for lung cancer requires a dedicated multi-disciplinary team composed of thoracic radiologists, nuclear physicians, thoracic oncologists, radiation oncologists, thoracic surgeons and pathologists. For a screening program to be successful, a specific protocol has to be developed in every screening centre. This refers to diagnostic and therapeutic algorithms for screen-detected nodules, their follow-up, indications for further minimally invasive and invasive testing, and referral for surgical excision.

Although lung cancer screening is able to detect lung cancer at an early stage, there are inherent risks, most important being overtreatment of false-positive lesions, which may give rise to complications in asymptomatic patients [12]. For this reason, extensive quality control is required as well for radiologists, invasive pulmonary physicians, thoracic surgeons and pathologists. Every member of the team should be familiar with the screening protocol and have sufficient experience in his own specialty to reduce false-positive and false-negative results, and to minimize the risk of any additional intervention. Standardized reporting should be used for radiology, surgery and pathology reports which allow quality evaluation for these disciplines by independent auditors. National databases as the registry approved by the Centers for Medicare and Medicaid Services (CMS) in USA and maintained by the American College of Radiology, will provide accurate data on patient outcomes and clinically valid results on lung cancer screening in high-risk populations [38].

Regarding radiological examinations the American College of Radiology advocates lung cancer screening to be performed at sites providing high-quality LDCT examinations read and interpreted by qualified radiologists using a structured reporting and management system [103]. A CT accreditation program has been set up requiring use of Lung Imaging Reporting and Data System (Lung-RADS) or a similar reporting and management system. The application of Lung-RADS has been shown to increase the positive predictive value without increasing false-negative results [106]. In this way, high-quality screening is guaranteed.

On a more general basis the American College of Chest Physicians and the American Thoracic Society have defined essential components of a lung cancer screening program to provide high-quality lung cancer screening [36]. These include not only technical specifications for performing LDCT and structured reporting, but also multi-disciplinary approach and specific qualification for a lung cancer screening facility.

For thoracic surgical centres, specific criteria were developed by a common working group of the European Society of Thoracic Surgeons and European Association for Cardio-thoracic Surgery [34, 104]. Accredited centres should be able to perform a wide range of surgical interventions encompassing staging procedures, minimally invasive and open procedures. Equally, adequate postoperative care should be provided to minimize morbidity. At least requirements for general thoracic surgical units should be met [35, 72]. Thoracic surgeons should also be familiar with the new pathological classification for lung adenocarcinoma, its radiological correlation and surgical implications [45].

For pathologists a profound knowledge of noninvasive and minimally invasive lesions is required and currently, they have to deal with small biopsies, intraoperative frozen section examinations to determine the extent of resection, and be able to provide detailed information on the invasive size of the lesion together with molecular information to determine any adjuvant therapy. Specific requirements and standard operating procedures for diagnosis of non-small-cell lung cancer were recently developed by an international multi-disciplinary European Expert Group [107].

It is recommended that for a screening centre to be effective extensive experience and a multi-disciplinary approach is required, and the location should be in dedicated high-volume centres. This provides not only high-quality care but further allows centralization of data and statistical analysis of large patient populations. In this way those individuals can be identified who will benefit most from a lung cancer screening program with minimal risk involvement.

CONCLUSION

The advent of lung cancer CT screening will be a challenge to surgeons but also an opportunity to improve the outcomes for the many patients who get this disease. In all European countries preparations to support the implementation of CT screening should be considered and initiated. The ESTS hopes that this statement may provide support for these discussions and as a stimulus to getting started with the preparations.

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REPORT

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