OSPEDALE SANTA CROCE E CARLE - CUNEO

‘SOS2’ Trial

SOS^2 - A monocenter prospective no-profit interventional study for lung cancer early diagnosis with tomosynthesis: re-evaluation of lung nodule detection rate at 5 years

Diagnosi precoce del tumore polmonare con tomosintesi: studio interventistico, con dispositivo medico, prospettico, monocentrico, no-profit

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Contents

Abbreviations

DTS	Digital Tomosynthesis
CT	Computer Tomography
REID	Risk of Exposure-Induced Death
BEIR	Biologic Effects of Ionizing Radiation
QoL	Quality of Life
OS	Overall Survival
LLE	Loss of Life Expectancy
ROC	Receiver Operating Characteristic
NELSON	The Dutch-Belgian Randomized Lung Cancer Screening Trial (Dutch acronym)
ICH	International Conference On Harmonisation
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
CRF	Case Record Forms

Synopsis

Sponsor	Santa Croce e Carle Hospital founded by the Fondazione CRC di Cuneo
Project Title	A monocenter prospective no-profit interventional study for lung cancer early diagnosis with tomosynthesis: re-evaluation of lung nodule detection rate at 5 years
Version	July 15th, 2017
Study Phases	Phase 3
Coordinators	Maurizio Grosso (study chairman), Stéphane Chauvie (study coordinator)
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Population	Subjects enrolled in previously closed SOS trial (high risk subjects for lung cancer) without confirmed lung cancer.
Study Objectives	To evaluate the lung cancer detection rate in the population of high risks subjects previously enrolled in lung cancer screening trial with chest digital tomosynthesis (SOS trial).
Participating centers	Single center, Santa Croce e Carle Hospital
Overall Study design	The study aims to evaluate the lung cancer detection rate. Patients that previously were enrolled in SOS study will be called by project assistants and booked for DTS examination. In case the subject refuses to perform examination a phone interview for follow-up will be carried out acquiring information on the status of the subject, on the variation of quality of life, on smoke habits and on attitude toward lung cancer screening. For the subject accepting the DTS examination the same questionnaire will be filled onsite just before examination. DTS will be then performed and blindly evaluated by two radiologists. DTS findings will be classified based on their dimension (large axis measurement), radiological characteristics (calcific, pleural, solid, partially solid and ground glass opacity) and position (in the 5 lobes). Findings will be then classified using LUNG-RADS [1]. The results of the DTS,in case of negative report, will be communicated with a letter to the patient. The subjects with one or more nodules larger than 5 mm, not clearly benign, will undergo diagnostic contrast enhanced CT and will be followed according to Fleischner society [2] criteria.

	Discordant and positive cases will be discussed in a consensus session among radiologists and thoracic surgeons. The consensus results will be used in the following analysis.
Endpoints	*Primary* Lung cancer detection rate. *Secondary* • Percentage of lung cancer addressed to radical surgery treatment; • Sensitivity of DTS evaluating the number of lung cancer occurred in the population of SOS study in the last 5 years; • Mortality • Overall survival (OS) • Quality of Life (QoL) • Cost-effectiveness
Eligibility criteria	*Inclusion criteria:* • current or former smoker status; • for former smokers, the maximum time since quitting smoking must be below 10 years. • smoking history of at least 20 pack-years; • age 45-80 years; • no previous history of cancer in the 10 years before the beginning of the study; • be able to stand and hold the breath for 11 seconds during image acquisition • previous participation to SOS trial *Exclusion criteria:* • pregnancy
DTS	*Acquisition* DTS is performed with Discovery XR650 (GE Healthcare, Milwaukee, WI). Images are acquired with a source-to-image distance of 180 cm. The tube voltage is set to 120 kVp with 3 mm Al inherent and 0.2 mm additional Cu filtration. The DTS acquisition consists of 60 projection images along a vertical source path spanning 30° of total tube angular motion. The set of 60 images is acquired in 10 s in breath hold condition. Images are reconstructed at 3 mm plane spacing in the coronal plane. Image reconstruction is done using a filtered back-projection algorithm and a sliding average of seven adjacent planes is taken to reduce noise and low-contrast tomosynthesis artifacts. *Dose* The mean effective dose expected for DTS is 0.09±0.04 mSv. Based on organ doses the loss of life expectancy (LLE) and the risk of exposure-induced death (REID) are calculated for lung cancer for man and women and for breast cancer for women using BEIRVII[3] model. REID for lung cancer for men and women are 10/100.000 and 3/100.000 respectively. REID for breast cancer for women are 10/100.000. LLE were 0.2 h for men and 0.6 h for women. These values are small respect to the baseline mortality in the normal population that are 7700/100.000 and 4.600/100.000 for lung cancer for men and women and 3.000/100.000 for breast cancer [3]. *Referral*

	Two independent radiologists carry out blinded independent central reviewing for DTS. Discordant and positve cases are discussed in consensus.
Treatment	Subjects are managed in line with Fleishchner Society criteria for the management of small pulmonary nodules and treated using physicians' choiche (no indication is given to treatment of patient from this trial).
Radiotherapy	Radiotherapy is performed based on physician's choice (no indication is given to treatment of patient from this trial).
Sample size	The primary objective of this study is to calculate the detection rate on lung cancer at 5 years distance from the previous DTS. In the SOS study 1843 subjects were enrolled and lung cancer was found in 18 (0.8%) of them at baseline. 1703 subjects performed the first round DTS at one-year distance and lung cancer was found in 5 (0.3%) of them. The number of patients needed to be confident that the disease will be detected if present at or above the specified prevalence of 0.3% with a confidence of 5% (i.e. assuming that the true prevalence is at least 0.3%, then a sample consisting only of subjects without lung cancer would occur 5% of the time or less given a sample with the calculated size) is 998. Allowing for a drop out of no more than 50%, a minimum number of 1496 subjects is required.
Timelines	Expected accrual time: September 2017 / August 2018 Patients with positive TC will be subjected to diagnostic investigations to identify the pathology according to Fleischner Society. Length of Follow-up: no follow-up is foreseen for these patients
Background and rationale	Lung cancer is the leading cause of cancer-related death around the world. In 2008 there were nearly 1.6 million new cases worldwide, accounting for the 12.7% of all new cancer diagnoses[4]. Despite decreasing trends in smoking and resulting decrease in lung cancer mortality, the population at risk for lung cancer continues to be large[5]. In the past years several programs have been developed to screen for lung cancer using low-dose chest computed radiography (CT). However, only recently different studies demonstrated a clear reduction in mortality[5,6]. In particular,NLST low dose CT screening trial demonstrated a 6.7% reduction in the death rate compared to chest X-ray with a positive screening test rate for lung cancer detection of 24.2%, compared to 6.9% for conventional X-ray[7]. The use of CT as a screening test has nonetheless recently prevailed over the concern for the cost and the radiation burden[8]. Digital tomosynthesis (DTS) is a limited angle tomography that allows reconstruction of multiple image planes from a set of projection data acquired over a relatively small angle of X-ray tube movement[9]. Santa Croce and Carle Hospital has this technology from March 2010, thanks to a donation of Fondazione CRC. Although it does not have the spatial depth resolution of computed tomography, it provides high-resolution images in the sagittal planes at a lower dose and cost than CT[10]. Several studies have shown that DTS offers advantages over conventional chest X-ray and comparable of those of CT[11–13]. The Studio OSservazionale (SOS) was a clinical trial conducted within Santa Croce e Carle Hospital sponsored by Fondazione CRC analysing smokers and former smokers aged 45-80 with no cancer diagnosis. All the subjects in whom a suspicious nodule was detected by DTS underwent diagnostic CT. The SOS study demonstrated that baseline DTS detected pulmonary abnormalities in 14.5% and lung cancer in 1.0% of the subjects[14], comparable to results obtained in CT screening programs. A second DTS, within the same study, executed one year later reported pulmonary abnormalities in 0.7% and lung cancer in 0.3% of the subjects[15].

1. Background and introduction

Lung cancer is the leading cause of cancer-related death around the world, it represents 13% of all new cancer diagnoses [4]. The lung cancer incidence is gradually increasing, especially among women and young people, but the fraction of cured patient remains low. In 80% of cases lung cancer, in early phase, is treatable only with surgery without chemotherapy or adjuvant radiotherapy and the survival perspective at five years exceeds 70% [4] . Recently several studies [5,16] showed a relative reduction in lung cancer mortality of 20% in high-risk subjects enrolled in screening trials performed with low-dose Chest CT [7]. As a consequence, several of scientific guidelines recommended chest Computed Tomomgraphy (CT) in lung cancer screening. CT examination allows detection of small nodules and a good quality of the image but its disadvantages includes high cost and high radiation dose [8]. Digital tomosynthesis (DTS) is a limited angle tomography that allows reconstruction of coronal images from a set of projection acquired over a small angle of X-ray tube movement [9]. This technique is available in the AO Santa Croce e Carle since 2010 and more than 5000 have been executed with it. Several studies demonstrates that DTS is a reasonable alternative to the CT and allows a better evaluation of suspects nodules compared to conventional chest RX [11–13].

2. Objectives of the trial

2.1. General objectives

To evaluate the lung cancer detection rate in the population of high risks subjects previously enrolled in lung cancer screening trial with chest digital tomosynthesis (SOS trial).

Repeating the DTS at 5 years from the baseline exam will permit to pursue three different tasks:

1) find subjects with lung cancer to be addressed to radical surgery treatment;
2) calculate the sensitivity of DTS evaluating the number of lung cancer occurred in the population of SOS study in the last 5 years;
3) establish the correct timing for DTS screening.

2.2. End-points

- Mortality
- Overall survival (OS)
- Quality of Life (QoL)
- Cost-effectiveness

3. Patient selection criteria

3.1. Patients inclusion criteria

Inclusion criteria:

- current or former smoker status;
- for former smokers, the maximum time since quitting smoking below 10 years.
- smoking history of at least 20 pack-years;
- age 45-75 years;

- no previous history of cancer in the 10 years before the start of the study;
- be able to stand and hold the breath for 11 seconds during image acquisition
- previous participation to SOS trial

3.2. Exclusion criteria

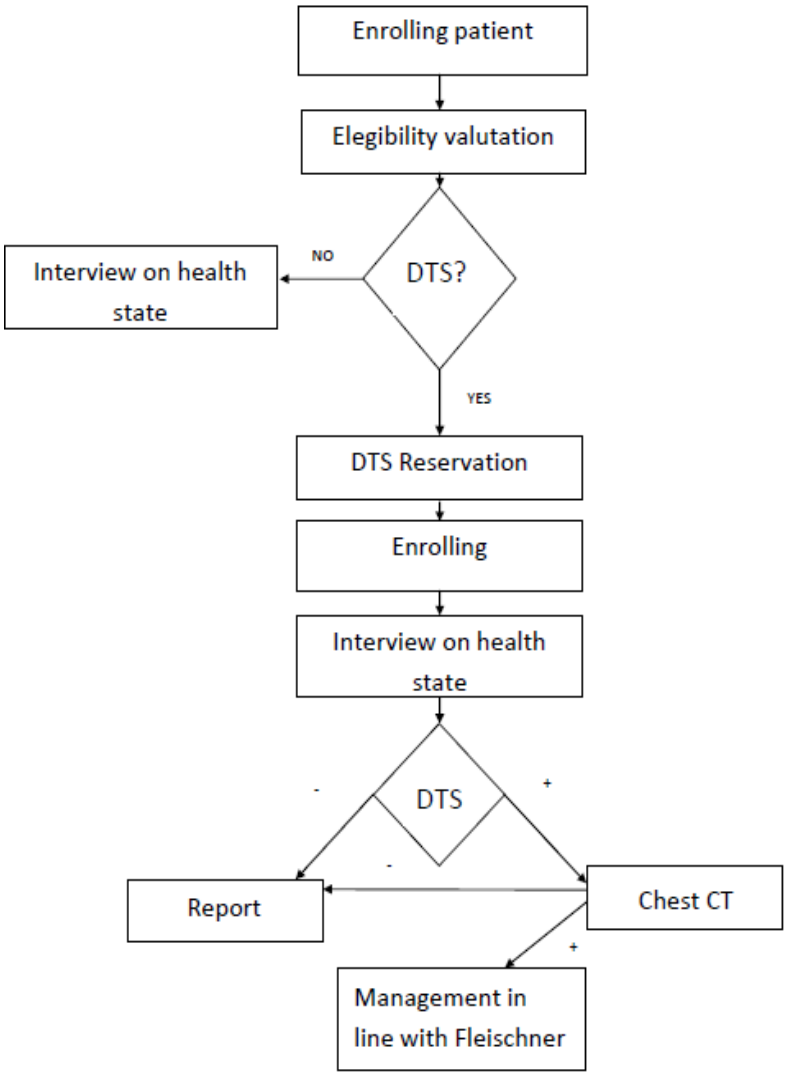
Exclusion criteria:

- pregnancy

4. Trial Design

During this study, about 1700 subjects, who have been enrolled in SOS Observational Study will undergo a DTS. The study will be presented as an observational clinical trial and registered on clinicaltrials.gov. Initially, all the subjects that participated in the SOS study, will be contacted by phone and invited to perform a DTS in Carle Hospital. When accessing the hospital the subjects will be asked to fill-in a form to confirm that the inclusion criteria of the SOS study are still met. DTS will be then performed and blindly evaluated by two radiologists. DTS findings will be classified based on their dimension (large axis measurement), radiological characteristics (calcific, pleural, solid, partially solid and ground glass opacity) and position (in the 5 lobes). Findings will be then classified using LUNG-RADS[1] schema and ROC analysis will be applied. Inter-observer variability will be analyzed with Krippendorff's Alpha[17].

Discordant and positive cases will be discussed in a consensus session among radiologists and thoracic surgeons. The consensus results will be used in the following analysis. The subjects with one or more nodules larger than 5 mm, not clearly benign, will undergo diagnostic contrast enhanced CT and will be followed in line with Fleischner Society[2].



5. Evaluation criteria

Lung cancer will be histologically proven, following the procedure of Pathology Division that use a double blinded analysis of biological material.

5.1. Overall survival

Overall survival (OS) defined as the time from randomization until death as a result of any cause (with at least five years of follow-up).

5.2. Quality of life

Related end-points are termed in the chapter on "Quality of life" (chapter 9).

5.3. Cost-effectiveness
Related end-points are defined in the Chapter on "Economic evaluation" (chapter 10).

6. Statistical considerations

6.1. Statistical design

6.1.1. Sample size

The primary objective of this study is to calculate the detection rate on lung cancer at 5 years distance from the previous DTS. In the SOS study 1843 subjects were enrolled and lung cancer was found in 18 (0.8%) of them at baseline. 1703 subjects performed the first round DTS at one-year distance and lung cancer was found in 5 (0.3%) of them.

Assuming a binomial model for the occurrence of the disease (Flanders WD and Kleinbaum DG. Basic Models for Disease Occurrence in Epidemiology, International Journal of Epidemiology, Volume 24, Issue 1, 1 February 1995, Pages 1–7) the number of patients needed to be confident that the disease will be detected if present at or above the specified annual incidence of 0.3% with a confidence of 5% (i.e. that assuming the true incidence is at least 0.3%, then a sample consisting only of subjects without lung cancer would occur 5% of the time or less given a sample with the calculated size) is 998. Allowing for a drop out of no more than 50%, a minimum number of 1496 subjects is required.

6.2. Analysis
Findings will be then classified using LUNG-RADS[1] schema and ROC analysis will be applied. Inter-observer variability will be analysed with Krippendorff's Alpha.

6.3. End of study
End of study befalls when all of the next criteria have been satisfied:
1. One year after start-up
2. At least 80% of the subjects enrolled in SOS trial have been contacted
3. The database has been fully cleaned and frozen for the analysis

6.4. Study duration
The start of the study is planned for September 2017. All patients defined by inclusion criteria will be included in the study. The enrollment is done by email. Patients are advised to contact the administrative staff to book an appointment to perform the exam. If the study is completed prematurely, the reasons must be documented. The last patient is expected to enter the study at the end of August 2018.

7. DTS evaluation and revision
Blinded independent central reviewing for DTS.

8. Independent data monitoring committee
This trial will NOT be monitored and scrutinized by an Independent Data Monitoring Committee (IDMC) because no toxicity is expected due to the DTS examination.

9. Quality of life evaluation

Although reducing mortality and morbidity still represent the crucial issue in clinical research, efforts to reduce adverse effects and control symptoms have reached a prominent role in devising therapeutic strategies.
Cancer treatments may produce adverse effects and diminish the QoL even when survival is extended. Progress in the acceptance of new cancer therapies is sometimes critically dependent on their QoL consequences.
Health-related QoL is a multidimensional concept which represents the physiological, psychological and social influences of the disease and the therapeutic process from the patient's perspective. It comprises four principal components: physical, emotional and social well-being, and daily-life functioning.

9.1. Rationale

In 'SOS trial', QoL is a secondary endpoint. Since no difference in QoL is expected due to physical events only emotional, social, and cognitive events will be analyzed.

9.2. QoL instrument

In order to understand the impact of long-term psychosocial outcomes of lung cancer screening a QoL questionnaire will be adopted to measures the effectiveness of a screening program of the smoking habits of the subjects, anxiety and decision satisfaction. The reliability and validity of the questionnaire are highly consistent across different language-cultural groups.

10. Cost-effectiveness analysis

During the study the costs associated with the DTS procedure are evaluated, comparing them to those incurred for the execution of the CT in the subjects positive to the DTS.

10.1. Methods

10.1.1. Type of Economic Evaluation.

Since a predictable variance in effectiveness, a cost-effectiveness analysis is justified.

10.1.2. Choice of Comparator.

The results are compared to the data obtained from the NELSON study and the National Screen Screening Trial for the evaluation of the effectiveness of screening in the control of 10-year mortality due to lung cancer.

10.1.3. Patient population

The patient population for the economic evaluation is the same as defined by the inclusion/exclusion criteria of the clinical trial.

11. Pharmacokinetics

No pharmacokinetics evaluation will be performed in this study.

12. Translational research

Does not apply.

13. Publication policy
The final publication of the study results will be elaborated by the Study Chairman on the basis of the analyses completed at the Data Center.

14. Enrollment and randomization procedures
Patients will be registered in the study via the study website at the time of exam.

15. Forms and procedures for collecting data
Data will be collecting in anonymous form in a database accessible only to the study group.

16. Reporting and evaluation of adverse events

Does not apply.

17. Quality assurance

17.1. Control of data consistency
Data forms will be entered in the database by the study assistants.

18. Ethical considerations

18.1. Patient Protection
The responsible investigator will guarantee that this study is led according with either the Declaration of Helsinki and its amendments, and the national, regional and local laws and rules, so to provide adequate protection of the patient.
The protocol has been written, and the trial will be steered according to the ICH Harmonized Guideline for Good Clinical Practice (http://www.ifpma.org/pdfifpma/e6.pdf).
The protocol was approved by the Local Ethics Committees

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Codice Protocollo:SOS2

18.2. Subject identification
The name of the patient will not be asked for, nor detailed and recorded in the cloud database. A serial identification number will be ascribed to each patient enrolled into the trial. This number will recognize the patient and must be contained within all the study fans.

18.3. Informed consent
All patients will be learned of the goals of the study, the absence of potential adverse events, the procedures and impending hazards to which he/she will be exposed, and the procedures and algorythm of treatment allocation.

They will be informed as to the strict privacy of their patient data, but that their medical records may be revised for trial purposes by authorized individuals other than their treating physician. A patient informed consent statement is given (in Italian) as an appendix to this protocol (See 22.3.2.). Within the informed consent, it is highlighted that the participation is voluntary and that the patient is permitted to refuse further participation in the protocol whenever he/she wants. This will not prejudice the patient's care in any setting. It is the responsibility of the individual investigator to explain the enclosed informed consent document.
The 'informed consent' form is an essential constituent of the documents and modules needed for protocol submission to the ethics committee for approval.
Documented informed consent must be obtained for all patients included in the study before they are registered or randomized at the Data Center. This must be done in agreement with the national and local regulatory requirements.
The informed consent procedure obeys the ICH guidelines on Good Clinical Practice. This implies that "the written informed consent form should be signed and personally dated by the patient or by the patient's legally acceptable representative".

19. Administrative responsibilities

19.1. The study coordinator

The Study Chairman(in cooperation with the Data Center) will be responsible for writing the protocol, revising all case report forms and documenting his/her review on evaluation forms, discussing the contents of the reports with the Data Manager and the Statistician, and for publishing the study results. He will also, as a rule, be responsible for replying all clinical queries about eligibility, treatment, and the assessment of the patients.

20. Trial sponsorship and financing.

Santa Croce e Carle Hospital, thanks to a donation of Fondazione CRC, will cover costs of DTS examination, data organization, supervision and project assistance.

21. Trial insurance

Covered by Santa Croce e Carle Hospital

22. Appendix

22.1. Definitions

22.1.1. WHO performance status scale

Eastern Cooperative Oncology Group (ECOG, Zubrod, World Health Organization) performance scale

22.1.2. Fleischner's society criteria

Lung-RADS Version 1.0 Assessment Categories Release date: April 28, 2014

Category	Category Descriptor	Category	Findings	Management	Probability of Malignancy	Estimated Population Prevalence
Incomplete	-	0	prior chest CT examination(s) being located for comparison part or all of lungs cannot be evaluated	Additional lung cancer screening CT images and/or comparison to prior chest CT examinations is needed	n/a	1%
Negative	No nodules and definitely benign nodules	1	no lung nodules nodule(s) with specific calcifications: complete, central, popcorn, concentric rings and fat containing nodules	Continue annual screening with LDCT in 12 months	< 1%	90%
Benign Appearance or Behavior	Nodules with a very low likelihood of becoming a clinically active cancer due to size or lack of growth	2	solid nodule(s): < 6 mm new < 4 mm part solid nodule(s): < 6 mm total diameter on baseline screening non solid nodule(s) (GGN): < 20 mm OR ≥ 20 mm and unchanged or slowly growing category 3 or 4 nodules unchanged for ≥ 3 months			
Probably Benign	Probably benign finding(s) - short term follow up suggested; includes nodules with a low likelihood of becoming a clinically active cancer	3	solid nodule(s): ≥ 6 to < 8 mm at baseline OR new 4 mm to < 6 mm part solid nodule(s) ≥ 6 mm total diameter with solid component < 6 mm OR new < 6 mm total diameter non solid nodule(s) (GGN) ≥ 20 mm on baseline CT or new	6 month LDCT	1-2%	5%
Suspicious	Findings for which additional diagnostic testing and/or tissue sampling is recommended	4A	solid nodule(s): ≥ 8 to < 15 mm at baseline OR growing < 8 mm OR new 6 to < 8 mm part solid nodule(s: ≥ 6 mm with solid component ≥ 6 mm to < 8 mm OR with a new or growing < 4 mm solid component endobronchial nodule	3 month LDCT; PET/CT may be used when there is a ≥ 8 mm solid component	5-15%	2%
		4B	solid nodule(s) ≥ 15 mm OR new or growing, and ≥ 8 mm part solid nodule(s) with: a solid component ≥ 8 mm OR a new or growing ≥ 4 mm solid component	chest CT with or without contrast, PET/CT and/or tissue sampling depending on the *probability of malignancy and comorbidities. PET/CT may be used when there is a ≥ 8 mm solid component.	> 15%	2%
		4X	Category 3 or 4 nodules with additional features or imaging findings that increases the suspicion of malignancy			
Other	Clinically Significant or Potentially Clinically Significant Findings (non lung cancer)	S	modifier - may add on to category 0-4 coding	As appropriate to the specific finding	n/a	10%
Prior Lung Cancer	Modifier for patients with a prior diagnosis of lung cancer who return to screening	C	modifier - may add on to category 0-4 coding	-	-	-

IMPORTANT NOTES FOR USE:

1) Negative screen: does not mean that an individual does not have lung cancer
2) Size: nodules should be measured on lung windows and reported as the average diameter rounded to the nearest whole number; for round nodules only a single diameter measurement is necessary
3) Size Thresholds: apply to nodules at first detection, and that grow and reach a higher size category
4) Growth: an increase in size of > 1.5 mm
5) Exam Category: each exam should be coded 0-4 based on the nodule(s) with the highest degree of suspicion
6) Exam Modifiers: S and C modifiers may be added to the 0-4 category
7) Lung Cancer Diagnosis: Once a patient is diagnosed with lung cancer, further management (including additional imaging such as PET/CT) may be performed for purposes of lung cancer staging; this is no longer screening
8) Practice audit definitions: a negative screen is defined as categories 1 and 2; a positive screen is defined as categories 3 and 4
9) Category 4B Management: this is predicated on the probability of malignancy based on patient evaluation, patient preference and risk of malignancy; radiologists are encouraged to use the McWilliams et al assessment tool when making recommendations
10) Category 4X: nodules with additional imaging findings that increase the suspicion of lung cancer, such as spiculation, GGN that doubles in size in 1 year, enlarged lymph nodes etc
11) Nodules with features of an intrapulmonary lymph node should be managed by mean diameter and the 0-4 numerical category classification
12) Category 3 and 4A nodules that are unchanged on interval CT should be coded as category 2, and individuals returned to screening in 12 months
13) LDCT: low dose chest CT

Link to McWilliams Lung Cancer Risk Calculator

Upon request from the authors at: http://www.brocku.ca/lung-cancer-risk-calculator
At UptoDate http://www.uptodate.com/contents/calculator-solitary-pulmonary-nodule-malignancy-risk-brock-university-cancer-prediction-equation

22.2. Technical Procedures

22.2.1. Procedure for the pathological review of diagnosis

The diagnosis made in blinded indipendent review by the local pathologists will be accepted for the Registration. Disagreement will be resolved by consensus.

22.2.2. Procedures for DTS examination

Patient Preparation and **Acquisition Protocol.**

DTS is performed with Discovery XR650 (GE Healthcare, Milwaukee, WI). Images are acquired with a source-to-image distance of 180 cm. The tube voltage is set to 120 kVp with 3 mm Al inherent and 0.2 mm additional Cu filtration. The DTS acquisition consists of 60 projection images along a vertical source path spanning 30° of total tube angular motion. The set of 60 images is acquired in 10 s in breath hold condition.

Technical Requirements for DTS scanners including image reconstruction

Images are reconstructed at 3 mm plane spacing in the coronal plane. Image reconstruction is done using a filtered back-projection algorithm and a sliding average of seven adjacent planes is taken to reduce noise and low-contrast tomosynthesis artifacts.

DTS analysis
Two independent radiologists carry out blinded independent central reviewing for DTS. Discordant and positve cases are discussed in consensus.

22.2.3. Quality of Life evaluation

Guidelines for administration of questionnaires

EORTC Quality of Life evaluation: guidelines for administration of questionnaires (revised January 2001)
The instructions given below are intended to provide some general guidelines for collecting quality of life (QoL) data in EORTC studies. These instructions apply to all types of questionnaires.

1. Who is the responsible person (RP) for Qol data collection?
The overall-responsible person for QoL data collection is the study-co-ordinator of the trial.
However, for practical reasons, it is strongly recommended that one person is responsible for the organization of QoL data collection in each Institution. This can be a physician, data manager, (research) nurse or a psychologist. Such a person should have the full protocol at his/her disposal as well as the questionnaire. This person would also be the intermediate contact point in case of any necessary clarification asked by the Data Center.

2. Who should fill out the questionnaire?
In principle, it is the patient him/herself who has to fill out QoL forms and preferably without help from others. If a patient is too sick to complete the questionnaire or if the patient is not able to fill out the questionnaire for reasons such as forgetting his/her glasses, another person could read the questions without making any comments and report the answers on the forms. If a patient received this type of help, please note this on the form.

3. What instructions should be given to the patient?
At entry into a study, the RP should give the patient an explanation of the objective of the study and instructions for filling out questionnaires. The patient should be informed that participation in the QoL protocol is voluntary and that the information provided is confidential (identification is only for administrative purposes and includes patient's initials, date of birth and today's date).
The following issues should be explained to the patient:

- ¬ The schedule of assessments.
- ¬ The questionnaire is a self-administered questionnaire that should be filled out preferably by the patient him (her) self.
- ¬ The patient should *circle* the choice that best corresponds to his/her situation.
- ¬ There is no right or wrong answer to any of these questions.
- ¬ All questions should be answered.

The RP should make sure that the patient understands the instructions.
At each subsequent assessment as defined by the protocol, the patient should receive the questionnaire from the RP or by other appropriate staff if the RP is not available.

4. Where should the patient fill out the questionnaire?

The patient should complete the questionnaire in the clinic, ideally in a quiet, private room. If this is not possible, the waiting room is an acceptable alternative. In general, it does not take more than 5 to 10 minutes to fill out a questionnaire, but patients should be given the time they need to answer all questions.

5. When should the patient fill out the questionnaire?

When a QoL assessment is planned, the questionnaire should be given to the patient preferably before the meeting with the physician, ensuring that the patient has enough time to complete the questionnaire. If the patient receives therapy, the questionnaire should be filled out before administration of the treatment. The questionnaire should not be taken home and/or mailed.

6. Review of the completed questionnaire.

After the patient has filled out the questionnaire, the person handling the questionnaire should:

- Check the answers for omissions, for incorrectly completed questions and for inconsistent answers; *If this is the case:*
  - Please ask the patient for the reason for omissions or incorrect answers. If the patient prefers not to answer a question, this should be noted on the form;
  - Additional explanation may be provided, but the questions should not be rephrased;
  - Any additional comments could be added by the person handling the questionnaire (if possible in English) followed by their name and signature.

7. Missing forms

If for some reason the patient is unable or does not wish to complete a quality of life questionnaire the reason, and date of the visit should be documented on the questionnaire and returned to the person responsible for completing the CRF's (case record forms).

8. Mailing to the Data Center

The questionnaire should be sent to the Data Center with the CRF's. As it is not possible to retrospectively collect missing quality of life data, please make sure the patient completes the questionnaire at the time-point when he/she is supposed to fill it out.
Thank you very much for your cooperation. If you have any remarks on this leaflet or if you need further information, please contact:

EORTC Quality of Life evaluation: instructions for Monitors

- Check if all QL questionnaires have been filled out on schedule
- If not, the Monitor should inform the person in charge of data collection and explain again the schedule of the QL questionnaires.
- Make sure the QL questionnaires are correctly completed
- If not, tell the responsible person to explain again to the patient how to fill out the QL questionnaires at the next visit.

22.2.4. Checklists

Logistics checklist

- ☐ Inform the patient according to the patient briefing record and hand out the Information for Patients and Declaration of Consent to him/her.
- ☐ Inform the patient before start of treatment about the quality of life survey and hand out the QoL form to him/her.
- ☐ Check the inclusion and exclusion criteria and document the results on the I/E form.
- ☐ Fill DTS review form after DTS is performed
- ☐ Fill CT review form after CT if needed
- ☐ Confirmation of the diagnosis: the primary histology report must be available
- ☐ F-up eCRF

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