

Standardized data collection (SDC) for lung cancer patients treated with curative primary or postoperative radiotherapy or chemo radiation (SDC LUNG)

Gestandaardiseerde datacollectie voor patiënten met een tumor in de long die curatieve primaire of postoperatieve radiotherapie of chemoradiatie ondergaan

Dates:

Definitive Version:

Study co-coordinator:

Prof.dr. P Lambin, Department of Radiation Oncology (MAASTRO), Maastricht University Medical Center Maastricht (MUCM+), The Netherlands.

Writing committee:

Dr. C. Oberije, Prof.dr. P Lambin Department of Radiation Oncology (MAASTRO), Maastricht University Medical Center Maastricht (MUCM+), The Netherlands.

Co-investigators:

MAASTRO Clinic:

Contact person: Esther Troost (esther.troost@maastro.nl)

Universitätsklinikum Aachen (UKA):

Contact person: Michael Eble (Meble@ukaachen.de)

Limburgs Oncologisch Centrum Hasselt (LOC):

Contact person: Paul Bulens (paul.bulens@virgajesse.be)

Centre Hospitalier de Liege (CHU):

Contact person: Philippe Coucke (pcoucke@chu.ulg.ac.be) or

Catharina Ziekenhuis Eindhoven:

Contact person: Katrien De Jaeger (katrien.d.jaeger@catharina-ziekenhuis.nl)

Table of contents

1. Summary	3
2. General introduction.....	4
2.1 Lung cancer	4
2.2 The need for individualized treatment and prediction of outcome	4
2.3 Population-based research.....	5
2.4 Measuring treatment outcomes	6
2.5 Rationale for implementation of Standardized Data Collection	6
3. Objectives of the SDC	6
3.1 General objective.....	6
3.2 Specific objectives.....	6
4. Datacollection	6
4.1 SDC general.....	6
4.2 Baseline characteristics.....	6
4.3 Treatment-related factors.....	7
4.4 Acute and late toxicity	7
4.5 Patient-rated toxicity and quality of life	7
5. Endpoints	7
6. Patient selection criteria	8
6.1 Inclusion criteria	8
6.2 Exclusion criteria.....	8
6.3 Relation with other studies	8
6.4 Therapeutic regimens	8
7. Clinical evaluation, laboratory tests and follow-up	8
7.1 Before radiotherapy.....	8
7.2 Induction chemotherapy	9
7.3 Surgery	9
7.4 During radiotherapy	9
7.5 After radiotherapy.....	9
8. Quality Assurance	10
8.1 Control of data consistency.....	10
8.2 Missing data	10
8.3 Quality control of Radiotherapy	10
9. Data considerations	10
9.1 Sample size.....	10
9.2 Statistical analysis.....	11
10. Ethical considerations	11
10.1 Privacy protection of patients	11
10.2 Study participation	12
11. Organization	12

12. Publication policy12

Appendices

A	Overview Datacollection
B	Toxicity scoring CTC version 4
C	Patient CTC questionnaire (Dutch, German and French)
D	Patient questionnaire Euro-QoL 5D-5L (Dutch, German and French)
E	Table time points patient questionnaire
F	S3 Leitlinie (German guidelines for Lungca)
G	Optional : Saliva sampling : OraGene user instructions
H	Patient information sheet
I	Patient informed consent sheet data collection
J	Patient informed consent sheet saliva collection
K	Radiomics PET-CT imaging protocol

1. Summary

Aim of the study

The primary objective of the Standardized Data Collection (SDC) for lung cancer patients is to develop and validate multi-factorial prediction models for different treatment outcomes. The long term aim is to build a Decision Support System based on validated prediction models that would facilitate individualized medicine.

Hypothesis

Our general hypothesis is that we will improve the performance of the prediction models (the Area Under the Curve (AUC) will be at least 0.05 higher) for survival and toxicity if we develop *multifactorial* models. The basic models of reference are based on demographical, clinical and treatment data. The improved multifactorial models will include additional clinical and/or imaging and/or genetic information and/or variables related to the quality of the treatment.

Study Design

This is a prospective cohort study.

Endpoints

Primary endpoint 1. Two-year survival rate.

Secondary endpoints 2. Change in dyspnea (early and late toxicity);
3. Change in cough (early and late toxicity);
4. Change in dysphagia (early and late toxicity);
5. Patient-rated generic quality of life (EuroQol).

Inclusion criteria

All patients planned for curatively intended primary or postoperative radiotherapy will be included. At the first visit, patients will be informed about the standardized data collection by the treating physician. The patient's written informed consent will be obtained.

Therapeutic regimens

Patients will be treated according to the institutional protocol. It is optional to collect a saliva sample for genetic profiling. Standard follow-up appointments to assess treatment toxicity will be scheduled at two time points: 2 weeks and 3 months after radiotherapy and it's optional to schedule follow-up appointments at three more points: 6, 12 and 24 months after radiotherapy (depending on the institute this is standard clinical practice or an extra visit). In addition, patients will fill in a short questionnaire, sent by mail, at 8 time points.

Sample size

It is expected that data of 864 patients can be analyzed, while additional genetic information will be available for 606 patients. The inclusion period will be fixed at 24 months. The power calculation is based on the minimum number of patients. It is assumed that 35% of the NSCLC patients will still be alive at two year time point. A sample of 404 deceased and 202 survivors achieves 89% power to detect a difference of 0.05 between the two models using a two-sided z-test at a significance level of 0.05.

2. General introduction

2.1 Lung cancer

Lung cancer is the third most commonly occurring form of cancer in the EU (after colorectal and breast cancer and excluding non-melanoma-skin cancers), accounting for almost 260,000 newly diagnosed cases in 2004 (1). In addition, it causes most cases of cancer death in men, while it is the third cause of female cancer deaths (2). Female lung cancer mortality, although still appreciably lower than in the male population, rose by 17% from 1990-2000 in the EU. This can be explained by the increased smoking prevalence in women. In countries such as Belgium, Denmark, Sweden and the Netherlands, the smoking prevalence has fallen in recent years. Consequently, in these countries a deceleration of increasing lung cancer mortality trends for women may be expected in the future (3).

Two main variants of lung cancer can be identified: small cell and non-small cell lung cancer (SCLC and NSCLC respectively), the latter comprising approximately 80% of the lung cancer cases. Generally, NSCLC patients have a better prognosis than SCLC patients, but the survival rates remain disappointingly low: 5-year survival of 14% for NSCLC (www.IKCnet.nl). Lung cancer patients can be treated with surgery, radiotherapy, chemotherapy or a combination of these modalities. NSCLC patients with clinical stage I or II and good physical health status are treated with surgery. If patients with a clinical stage I or II tumor are inoperable for medical reasons, the tumor will be treated with radiotherapy. The introduction of stereotactic radiotherapy has made it possible to deliver high doses to the tumor while the risk of damaging the normal lung tissue is low (4). NSCLC patients with a clinical stage III tumor are usually treated with radiotherapy combined with chemotherapy. Although delivery of very high radiation doses is needed to obtain local control, due to the large tumor and nodal volume this is often impossible without causing unrepairable damage to the normal tissue of the spinal cord, esophagus and lung. If distant metastasis are present (stage IV tumor) NSCLC patients are treated palliatively with chemotherapy, targeted agents or radiotherapy, depending on the complaints of the patient. Patients with a SCLC tumor, clinical stage I-IIIIB (limited disease) are usually treated with concurrent chemoradiation. In case of distant metastasis (formerly called extensive disease) palliative chemotherapy is the treatment of choice.

2.2 The need for individualized treatment and prediction of outcome

The large number of patients affected by lung cancer and the disappointingly low survival rates have stimulated research in this area. Strategies to improve the treatment outcome include more aggressive therapeutic regimen (5-7). These result in better outcome, but they commonly increase severity and duration of side-effects (8). While some patients may fail to complete their treatment, others will need medication or hospitalization and sometimes these side-effects will lead to late toxicity, which will negatively influence quality of life and well-being. Therefore, new, less toxic anti-cancer therapies are being developed at the moment. Included amongst these new approaches is the use of agents, that are targeting cancer-specific pathways in the cell, thereby trying to improve the treatment outcome in terms of survival as well as toxicity (9, 10). As these new strategies and therapies are being tested, it becomes more and more apparent that certain subgroups of patients may benefit from a specific treatment, while others don't or even may have a worse outcome (11). The same is observed for the toxicity of the treatment. Some patients suffer from severe side-effects while others are relatively unaffected (12). So, there is a complex interplay of different

factors which has not yet been unraveled. These differences between individual patients are not only observed in case of treatment with medication or chemotherapy, but they also occur during radiotherapy treatment, implying that the decision to escalate the radiation dose should be individualized.

The amount of available information to explain these observations is expanding enormously due to new diagnostic tools such as genomic and proteomic profiling (e.g. based on the patient's blood or saliva), and anatomical and functional imaging techniques (e.g. CT, MRI, PET). This knowledge will enable us to predict the outcome for a certain patient in combination with a specific treatment with more accuracy. It will lead to better identification of risk groups, which results in stage migration, but it will also stimulate research focused on specific risk groups, trying to find new treatment options or other combinations of treatment options for these subgroups. It can be expected that treatment will be more personalized, which will not only save patients from unnecessary toxicity and inconvenience, but will also facilitate the choice of the most appropriate treatment. Currently, this choice is based on general guidelines, that only take into account tumor stage and physical condition of a patient (www.oncoline.nl). These guidelines are developed for groups of patients and thus lead to over-treatment in some patients and inadequate therapy in others, resulting in major expense for individuals and society.

However, prediction of outcome in order to choose the optimal treatment is complicated in view of the very complex, dynamic nature of cancer and organs at risk. In a systematic review it was concluded that physicians' prediction of survival of terminally ill cancer patients tended to be incorrect in the optimistic direction (13). This is in agreement with a study, investigating the accuracy of radiation oncologists in prediction of survival (14). Studies, investigating the performance of physicians in predicting side-effects of radiotherapy treatment, are currently lacking. However, the ability of humans, and thus physicians, to assess the risks and benefits associated with a specific combination of patient, tumor and treatment characteristics, that will ultimately include many thousands of parameters, is limited. Therefore, treatment can only become more personalized if accurate, scientifically based decision aids are developed, that can offer assistance in clinical decision-making in daily practice (see a first generation of such predictors on www.predictcancer.org)(15).

2.3 Population-based research

Less than 5% of all lung cancer patients are enrolled in clinical trials (16). Patients who meet the inclusion criteria and are willing to participate form a highly selected group, usually their general condition is better and elderly patients are underrepresented (17). Conclusions based on the results of these trials are therefore only limited applicable to the whole lung cancer population. Moreover, data of 95% of the patients is not being used. Population-based research, using data of all patients and treated in different hospitals, could avoid this selection bias and would greatly increase the amount of data, available for analysis.

Using data of many patients will facilitate model building for toxicity (18). As physicians try to avoid severe side-effects as much as possible the number of events is generally low, making it hardly possible to develop accurate models for these side-effects. In addition, models for any outcome could benefit from extra information. At the moment, models are usually based on a restricted number of variables, often limited to one kind of information. Some models use genetic information only, others are solely based on clinical factors. Different kinds of variables could offer complementary information and thus improve the performance of models (19,20).

2.4 Measuring treatment outcomes

Information about side-effects and toxicity is crucial for the development and testing of prediction models. However, patients don't always come to the outpatient clinic for follow-up and if they do, the frequency of visits is usually low. Moreover, as opposed to clinical trials, in daily practice standardized questionnaires to assess the treatment toxicity are seldomly used. Questionnaires using patient reported outcomes overcome these practical difficulties and can provide valuable information about treatment effects. It has been shown that agreement between patient and clinician is high(21) and recent projects, developing web-based applications to collect data, achieved participation rates of 60 to 90 percent (21-23).

2.5 Rationale for implementation of Standardized Data Collection

Standardized Data Collection (SDC) will improve the quality of the data by defining which variables should preferably be collected and how these variables should be measured. The prospective collection of patient, tumor and treatment characteristics will facilitate the development of prediction models for survival as well as toxicity outcome based on cohorts of patients representative of the daily practice. In addition, data on survival and toxicity can be used to compare the results of new and emerging radiation delivery techniques, targeted therapies or chemotherapy regimen after they have been clinically introduced to the results obtained with the standard treatment.

3. Objectives of the SDC

3.1 General objective

The primary objective of the Standardized Data Collection (SDC) for lung cancer patients is to develop and validate multi-factorial prediction models for different treatment outcomes. The long term aim is to build a Decision Support System based on validated prediction models that would facilitate individualized medicine.

3.2 Specific objectives

- To develop, validate, and improve prediction models for overall survival;
- To develop, validate, and improve prediction models for acute and late radiation-induced side effects relevant for lung cancer patients;

4. Datacollection

4.1 SDC general

The SDC includes a prospective assessment of baseline characteristics, treatment-related factors, including dose distribution parameters, acute and late radiation-induced toxicity, and health-related quality of life. In the following paragraphs, the assessments will be described in more detail.

4.2 Baseline characteristics

The baseline patient and tumor characteristics that are considered relevant are outlined in appendix A. If an Electronic Patient Record System (EPRS) is being used in clinical practice and if the system allow to do so, the Case Report Form

(CRF) will be filled in automatically, and will not burden data managers, treating physicians or patients.

4.3 Treatment-related factors

The baseline treatment and radiotherapy characteristics that are considered relevant are also included in appendix A. Additional information on radiotherapy will be extracted in an automated way from the dose verification system (for example LANTIS or ACUITY). More detailed information regarding dosimetric parameters can be calculated using the 3D dose matrix and the imaging information of the (PET)CT-scan. This information will be retrieved from the PACS system, also in an automated way. This will not be any burden to data managers, treating physicians or patients.

4.4 Acute and late toxicity

Toxicity will be scored before, during radiation therapy and at 2 weeks, 3 and 6 months, 1 and 2 year after completion of treatment by the treating physicians or by the patient, using questionnaires (see paragraph 4.5). Follow-up will be scheduled according to the hospital's policy. If there are no follow-up appointments scheduled, toxicity will only be scored by a questionnaire, filled in by the patient. Toxicity will be scored according to CTCAE v4 (appendix B). The following scales will be scored:

- Dyspnea
- Cough
- Dysphagia

In addition, any other acute toxicity related to the treatment of the lung cancer should be reported.

4.5 Patient-rated toxicity and quality of life

Toxicity and performance status will be measured by a questionnaire based on WHO-PS and CTCAE v4.0 (appendix C). This questionnaire consists of 8 questions. Quality of life will be measured using the EuroQoL-5D-5L (appendix D). This is a small, standardized generic quality-of-life questionnaire consisting of two parts. The first part is a 5-dimensional questionnaire (5 questions), the EQ-5D. The five dimensions are mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (24). With regard to each of those dimensions, the patient is asked to indicate if he or she experiences no problems, some problems, or major problems. The resulting profile of answers (one of 243 possibilities) can be transformed to a value given by the general public: the EQ-5D index (25). The second part of the EuroQoL questionnaire is a visual analogue scale, the EQVAS, which represents the patient's judgment of his own health state. The advantage of the EuroQoL-questionnaire is its feasibility to yield utility scores expressing the health state of patients, which can be used to calculate Quality Adjusted Life Years (QALYs). QALYs combine the number of life years gained and the quality of life during these years in one single measure.

The questionnaires will be filled in by patients at the time points mentioned in Table 3 (appendix E). Filling out these questionnaires will take approximately 10 minutes every time. The questionnaires will be sent to the patient by mail.

5. Endpoints

Primary endpoint

1. Area Under the Curve (AUC) of a model to predict two-year survival outcome.

Secondary endpoints

2. AUC of a model to predict severe treatment induced dyspnea (early and late toxicity);
3. AUC of a model to predict severe treatment induced cough (early and late toxicity);
4. AUC of a model to predict severe treatment induced dysphagia (early and late toxicity);
5. AUC of a model to predict esophageal stenosis (late toxicity);
6. Patient-rated generic quality of life evaluated with the EuroQol questionnaire.

Patient-rated toxicity will be scored using a patient questionnaire, based on the CTC v4.

6. Patient selection criteria

6.1 Inclusion criteria

All patients planned for curatively intended primary or postoperative radiotherapy will be included. At the first visit, patients will be informed about the standardized data collection by the treating physician. The patient's written informed consent will be obtained. The consent for genetic profiling based on saliva will be optional.

6.2 Exclusion criteria

All patients planned for palliative radiotherapy will not be included in the SDC.

6.3 Relation with other studies

Inclusion in clinical trials is not an exclusion criterion. It is possible to add additional assessments required for the clinical study.

6.4 Therapeutic regimens

Patients will be treated according to the institutional protocol, or the clinical trial protocol. Each centre should define its standard protocols. If the patient is treated otherwise than this standard protocol, this has to be specified.

7. Clinical evaluation, laboratory tests and follow-up

There will be three different groups of patients. Patients in group 1 are treated with radiotherapy alone, patients in group 2 will be treated with concomitant chemoradiation, and patients in group 3 will be treated with induction chemotherapy followed by radiotherapy. The assessments will be similar for all patients, except for patients in group 3 in which quality of life will be assessed prior to induction chemotherapy and after induction chemotherapy, prior to (chemo) radiation.

7.1 Before radiotherapy

Level I: standard

- The staging procedure will be carried out according to the standard procedure described in the guidelines. For the Netherlands and Belgium these guidelines can be found at www.oncoline.nl, for Germany the S3 Leitlinie applies (appendix F).

- Standardized planning (¹⁸F-FDG-PET)-CT (appendix K). This procedure will make it possible to collect and compare dosimetric and other imaging parameters, as these parameters can be influenced by the PET-CT procedure.
- Scoring of baseline toxicity by CTCAE v4.0
- Scoring of comorbidity
- Scoring of use of medication with a particular attention of angiotensin-converting-enzyme inhibitor (ACE inhibitors) and metformin
- Lung function test: not compulsory, according to common clinical practice
- Blood: not compulsory, according to common clinical practice
- Serum: not compulsory, according to common clinical practice

Level II: Optional

- Storage of saliva (appendix G)

7.2 Induction chemotherapy

Due to the variety of protocols a number of patients will be treated with induction chemotherapy [15]. In these cases, the assessments prior to treatment will be made before the start of induction chemotherapy and some assessments will be repeated prior to the start of radiotherapy.

7.3 Surgery

Postoperative radiotherapy is indicated if surgery is irradical. In these cases, the assessments prior to treatment will be made before surgery and some assessments will be repeated prior to the start of radiotherapy. In addition, it is expected that very few patients will undergo surgery after chemoradiation. In these cases assessments have to be repeated after radiotherapy but before surgery.

7.4 During radiotherapy

During radiotherapy in vivo dosimetry will be performed, if available and according to the specific department/hospital guidelines.

7.5 After radiotherapy

Level I: standard

- Scoring of acute toxicity (dyspnea, cough, dysphagia) according to CTCAE v4 by the treating physician at time point 2 weeks and 3 months after radiotherapy treatment
- Scoring of late toxicity by CTCAE v4, WHO performance status and quality of life (appendix C and D). Questionnaires will be filled in by the patient
- Recording of survival status (appendix A)

Level II: optional

- Scoring of late toxicity (dyspnea, cough, dysphagia, esophageal stenosis) according to CTCAE v4 by the treating physician at time point 6, 12 and 24 months after radiotherapy treatment

8. Quality Assurance

8.1 Control of data consistency

Data forms will be entered in the database by an automated procedure. Information will be retrieved from the Electronic Medical Files. The Data Manager will perform computerized and manual consistency checks on newly entered forms; queries will be issued in case of inconsistencies. Consistent forms will be validated by the Data Manager. Inconsistent forms will be kept "on hold" until resolution of the inconsistencies.

8.2 Missing data

In every participating hospital, there will be a Data Manager, responsible for the collection of data. In case of missing forms or variables, the Study Manager will ask the Data Manager for the information. In case the patient does not return questionnaires, the Data Manager will call the patient to remind him/her of this.

8.3 Quality control of Radiotherapy

Beam calibration should be carried out according to the protocol used in clinical practice. All clinical and radiation data, including in vivo dosimetry when available, should be stored to remain available with a short notice to a quality control panel.

9. Data considerations

9.1 Sample size

Each center will treat approximately 30 NSCLC patients per year with radiotherapy alone, 50 NSCLC patients per year will be treated with sequential chemotherapy and radiotherapy and 80 patients with concurrent chemo-radiation. Thus, a total of 640 patients per year will be eligible for this study. Assuming that 75% of the patients is willing to participate 960 patients can be included in 24 months. If the drop-out rate is 10% a total number of 864 patients will be available for the statistical analysis. If 70% of the included patients is willing to give a saliva sample (n=672) and the drop-out rate is 10%, genetic information will be available for 605 patients. The inclusion period will be fixed at 24 months. The power calculation is based on the minimum number of patients.

Power calculation:

The power calculation is based on the method described by Hanley & McNeil (26). The current MAASTRO prediction model for 2-year survival of NSCLC patients, based on clinical characteristics and basic imaging parameters (GTV and number of positive lymph node stations), yields an AUC of 0.74. We hypothesize that the AUC using new imaging and/or genetic information will increase by at least 0.05. It is assumed that 35% of the NSCLC patients will still be alive at two year time point. The correlation between the two models (initial model and extended model) is assumed to be 0.5 for the survivors and 0.5 for the deceased group. A sample of 404 deceased and 202 survivors achieves 89% power to detect a difference of 0.05 between the basic model (demographical, clinical and treatment data) and the improved model (imaging and/or genetic data added to the basic model) using a two-sided z-test at a significance level of 0.05. The size of the study group will enable us also to validate the current MAASTRO prediction models. According to simulation studies at least 100 events and 100 non-events would be needed to detect a decrease in AUC of 0.077 with 80% power (27).

9.2 Statistical analysis

Prediction models will be built using logistic or cox regression models. Missing values will be imputed using an advanced method. If the ratio events/variable is at least 10, variable selection will be performed based on the Likelihood Ratio (LR) test. To avoid deleting relevant variables a p-value of 0.3 will be used [25]. If the ratio events/variable is low, variable selection will be performed using LASSO (least absolute shrinkage and selection operator) penalized regression. The LASSO has been shown to be an excellent filter for variable selection if the number of variables is relatively large, or even exceeds the number of patients (this is for example the case in genomic data).

The performance of the models will be assessed in terms of discrimination as well as calibration. External validation cohorts will be used for this purpose. Discrimination will be assessed using the c-statistic or Area Under the Curve (AUC) of the Receiver Operating Characteristic (ROC). The c-statistic is comparable to the AUC, but can also be used for Cox regression analysis. A graphical assessment of calibration will be done by plotting the expected versus the observed probability. In addition, the Hosmer-Lemeshow test will be used. The clinical value of the models will be assessed using decision curve analysis [29,30]. This will make it possible to compare the clinical value of different models over a number of decision thresholds (or cut points for probability of outcome). Using this method, there is no necessity to choose an a priori cut point (for a clinical decision).

10. Ethical considerations

The study will be conducted according to the principles of the Declaration of Helsinki (Seoul, 2008). The local ethics committees of the participating centres must approve the trial protocol before patients are entered, according to legislation of the Netherlands.

The patients will be recruited from the patients that are referred to the participating centres and fulfil the inclusion criteria. During their first visit to the radiation oncology department patients will receive the patient information sheet and the informed consent sheet. The treating radiation oncologist or the research physician assistant will explain the study to the patient. Patients will have at least three days to decide whether they will participate in this cohort study. All radiation oncologists that treat those patients can inform them. The extra burden for the patients, including the saliva sample and questionnaires will be mentioned by the physician. Written informed consent will be obtained from each patient according to local practice. The patient information files and the informed consent are available in the appendices of this protocol. After receiving the signed informed consent sheet, the data manager of the centre will register the patient and send the first questionnaire. If a patient agrees to give a saliva sample, this will be done during the simulation appointment (preparation for radiotherapy).

10.1 Privacy protection of patients

To ensure the privacy of individual patients data will be coded. Within each institute a person will be responsible for coding the patient data. A sequential identification number will be automatically attributed to each patient registered in the study. This number will identify the patient and will also be used to link clinical data to imaging and genetic data. Only the dedicated people of the Data Centre have access to this code. The DNA samples will be stored either in a local biobank or in the Maastricht biobank. An identification number will be attributed to each sample. Accessing the table that contains the link between the DNA sample and the clinical and/or imaging data will be restricted to people of the Data

Centre. Moreover, results from genomic analysis will not be available to the treating cancer specialist or insurance companies neither will patients themselves or their physician receive these results.

10.2 Study participation

Patients may decide to stop their contribution to this trial without giving any reason. They will thereafter be treated and followed according to the standard procedures. If any new information that may affect the management of the included patients will become available during this study, patients will be informed immediately.

The extra burden for the patients is relatively small. Participation in the biobank study is optional. For this study patients are asked to give 2 mL of saliva (ORAgene DNA Kit). The questionnaires have to be filled in before the start of any treatment, during treatment and afterwards at specified time points. They will be sent to the patients by mail if patients do not have an appointment (either for treatment or for follow-up) at that time point. Filling in the questionnaire will take less than 10 minutes.

Patients can always contact an independent physician. This information is included in the patient information files.

As this is a cohort study with no new treatment and no additional risk insurance is not needed.

11. Organization

The investigator will be responsible for inclusion of patients and day-to-day management of the trial. The investigator will monitor the progress of the study on ethical and scientific grounds. Web based Electronic CRF will be used. In each participating centre a data manager will be responsible for the data collection. Patients will be included in the study by the treating physician.

12. Publication policy

All information resulting from this study is considered to be confidential. Study coordinators and a statistician will complete a data check before data can be analyzed.

Any publication, abstract or presentation comprising results from the study must be submitted for examination and approval to study coordinators. Publication policy is in accordance with CCMO regulations.

The first and the last author of the publication will be the coordinating investigators. The other co-authors will be:

- Investigators of the main recruiting centres listed in order of decreasing number of included patients;
- Only investigators having entered 20 % or more of the patients;
- The statistician of the trial.

Publication of the sub-studies (biological and medico-economic studies) will be addressed in the same way.

13. References

1. Boyle P, Ferlay J. Cancer incidence and mortality in Europe, 2004. *Ann. Oncol.* 2005;16:481–488.
2. Ferlay J, Parkin DM, Steliarova-Foucher E. Estimates of cancer incidence and mortality in Europe in 2008. *Eur. J. Cancer.* 2010;46:765–781.
3. Levi F, Lucchini F, Negri E, *et al.* Trends in mortality from major cancers in the European Union, including acceding countries, in 2004. *Cancer.* 2004;101:2843–2850.
4. Timmerman RD, Kavanagh BD, Cho LC, *et al.* Stereotactic body radiation therapy in multiple organ sites. *Journal of Clinical Oncology.* 2007;25:947–952.
5. Aupérin A, Le Péchoux C, Rolland E, *et al.* Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. *Journal of Clinical Oncology.* 2010;28:2181–2190.
6. Bradley J. A review of radiation dose escalation trials for non-small cell lung cancer within the Radiation Therapy Oncology Group. *Seminars in Oncology.* 2005;32:S111–3.
7. van Baardwijk A, Wanders S, Boersma L, *et al.* Mature Results of an Individualized Radiation Dose Prescription Study Based on Normal Tissue Constraints in Stages I to III Non-Small-Cell Lung Cancer. *Journal of Clinical Oncology.* 2010;28:1380–1386.
8. Bentzen SM, Trotti A. Evaluation of early and late toxicities in chemoradiation trials. *Journal of Clinical Oncology.* 2007;25:4096–4103.
9. Bentzen SM, Harari PM, Bernier J. Exploitable mechanisms for combining drugs with radiation: concepts, achievements and future directions. *Nat Clin Pract Oncol.* 2007;4:172–180.
10. Provencio M, Sánchez A, Garrido P, *et al.* New molecular targeted therapies integrated with radiation therapy in lung cancer. *Clin Lung Cancer.* 2010;11:91–97.
11. Mok TS, Wu Y-L, Thongprasert S, *et al.* Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N. Engl. J. Med.* 2009;361:947–957.
12. Bentzen SM, Hendry JH. Variability in the radiosensitivity of normal cells and tissues. Report from a workshop organised by the European Society for Therapeutic Radiology and Oncology in Edinburgh, UK, 19 September 1998. In: Vol 75. 1999:513–517.
13. Chow E, Harth T, Hruby G, *et al.* How accurate are physicians' clinical predictions of survival and the available prognostic tools in estimating survival times in terminally ill cancer patients? A systematic review. *Clin Oncol (R Coll Radiol).* 2001;13:209–218.
14. Chow E, Davis L, Panzarella T, *et al.* Accuracy of survival prediction by palliative radiation oncologists. *International Journal of Radiation Oncology*Biophysics*Physics.* 2005;61:870–873.

15. Lambin P, van Stiphout R. Predicting outcomes in radiation oncology—multifactorial decision support systems. *Clinical Oncology*. 2012.
16. Sateren WB, Trimble EL, Abrams J, *et al*. How sociodemographics, presence of oncology specialists, and hospital cancer programs affect accrual to cancer treatment trials. *J. Clin. Oncol.* 2002;20:2109–2117.
17. Ruysscher DD, Botterweck A, Dirx M, *et al*. Eligibility for concurrent chemotherapy and radiotherapy of locally advanced lung cancer patients: a prospective, population-based study. *Annals of Oncology*. 2008;20:98–102.
18. Deasy JO, Bentzen SM, Jackson A, *et al*. Improving normal tissue complication probability models: the need to adopt a “data-pooling” culture. *Int. J. Radiat. Oncol. Biol. Phys.* 2010;76:S151–4.
19. Acharya CR, Hsu DS, Anders CK, *et al*. Gene expression signatures, clinicopathological features, and individualized therapy in breast cancer. *JAMA*. 2008;299:1574–1587.
20. Nevins JR, Huang ES, Dressman H, *et al*. Towards integrated clinico-genomic models for personalized medicine: combining gene expression signatures and clinical factors in breast cancer outcomes prediction. *Hum. Mol. Genet.* 2003;12 Spec No 2:R153–7.
21. Basch E, Iasonos A, McDonough T, *et al*. Patient versus clinician symptom reporting using the National Cancer Institute Common Terminology Criteria for Adverse Events: results of a questionnaire-based study. *Lancet Oncology*. 2006;7:903–909.
22. Ashley L, Jones H, Thomas J, *et al*. Integrating cancer survivors' experiences into UK cancer registries: design and development of the ePOCS system (electronic Patient-reported Outcomes from Cancer Survivors). *Br J Cancer*. 2011;105 Suppl 1:S74–81.
23. van de Poll-Franse LV, Horevoorts N, van Eenbergen M, *et al*. The Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship registry: scope, rationale and design of an infrastructure for the study of physical and psychosocial outcomes in cancer survivorship cohorts. *Eur. J. Cancer*. 2011;47:2188–2194.
24. Brooks R, Rabin R, de Charro F. *The Measurement and Valuation of Health Status Using EQ-5D: A European Perspective*. Kluwer Academic Pub; 2003.
25. Dolan P. Modeling valuations for EuroQol health states. *Med Care*. 1997;35:1095–1108.
26. Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. *Radiology*. 1983.
27. Steyerberg EW. *Clinical Prediction Models*. Springer; 2009.