

**Multimodal monitoring of
radiotherapy response in squamous
cell cancer in head & neck, lung,
oesophagus, anal canal and uterine
cervix – a basis for personalised
radiotherapy
MORRIS-study**

Sponsor

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1 Synopsis

Protocol title	Multimodal monitoring of radiotherapy response in squamous cell cancer (SCC) in head & neck, lung, oesophagus, anal canal and uterine cervix – a basis for personalised radiotherapy
Development phase	Observational study
Study population	Patients with previously untreated SCCs aimed for radiotherapy with curative intent of the oral cavity, oropharynx, uterine cervix, oesophagus, anal canal or lung.
Endpoints	<p>Primary end-point</p> <p>Loco-regional control 2 years after completion of radiotherapy</p> <p>Secondary end points</p> <ol style="list-style-type: none">1. Loco-regional tumour control (or response) 8 (-2 - +4) weeks after completion of radiotherapy2. Patterns of failure3. Progression free survival at 2 years4. Overall survival at 2 and 5 years5. Changes in imaging and metabolic data6. Site specific toxicity at 12 months after completion of radiotherapy
Study design	Non-randomised, prospective, multi centre, observational study. Patients with previously untreated SCCs aimed for radiotherapy with curative intent of the oral cavity, oropharynx, uterine cervix, oesophagus, anal canal or lung are recruited. Multimodal, functional imaging data are collected before and during the early phase of radiotherapy. In parallel to the imaging data, tumour biopsies and blood will be collected for molecular analyses that may provide explanatory information to the imaging information.
Overall aim	Prediction of short and long term outcome of treatment for squamous cell cancer (SCC) by monitoring tumour response during early treatment phases.

Specific aims

Correlate changes in imaging bio-markers to corresponding changes in tissue or blood bio-markers by repeated imaging and biopsies for better understanding of the image parameters.
To correlate data from multiparametric imaging to specific outcome
Validation of early bio-imaging predictors of tumour response and patient outcome.

Eligibility criteria**Inclusion criteria**

1. Morphologically (pathology or cytology) verified, previously untreated SCCs of the oral cavity, oropharynx, uterine cervix, oesophagus or lung.
2. The patient should be planned for treatment with radiotherapy alone or in combination with concomitant medical therapy
3. The tumour shall be radiologically and/or visually identifiable and accessible for biopsy without the need for general anaesthesia or other major interventions
4. The patient must be at least 18 years of age, able to understand the given information and, leave a written informed consent to participate

Exclusion criteria

1. The patient is unwilling to participate in the study
2. Patients with adjuvant post-operative radiotherapy (i.e. no visible remaining tumour)
3. Pregnancy or lactation
4. Contraindications to investigations with MRI, gadolinium contrast or PET-tracers
5. Patients with an estimated GFR <60 ml/min/1.73m².
6. Severe co-morbidities that are judged to significantly compromise survival in a two-years perspective.

Duration of study

The first acquisition of image data and tissue samples is performed as close as possible to start of radiotherapy. The time for the second acquisition of image data and tumour tissue will be after 1-2 weeks of treatment. The precise timing will be optimised after the separate analysis of the 20-30 first patients. The patients will then

be followed according to clinical routines for at least two years for evaluation of tumour control. In patients with remaining tumour or recurrent disease the site of the tumour will be recorded and compared with the position of the original site. Survival of patients will be followed for five years by the Swedish population registry.

Radiotherapy and possible neo-adjuvant, concomitant or adjuvant therapy

The standard treatment schedules according to clinical routines and decisions will be followed irrespective if the patient is taking part in the study or not. Specific information on all anticancer therapy (doses and timing) will be recorded for each patient. The observation will commence at start of radiotherapy irrespective when and how other supporting therapies are used.

Efficacy evaluation

1. Loco-regional tumour control (or response) 8 (-2 - +4) weeks after completion of radiotherapy
2. Patterns of failure
3. Progression free survival at 2 years
4. Overall survival at 2 and 5 years
5. Changes in imaging and metabolic data
6. Site specific toxicity at 12 months after completion of radiotherapy

Pilot study

The first 30 patients will have the study procedures at different time points after start of radiotherapy. Different sequencing of biopsy and imaging procedures will be employed. This is in order to find the shortest interval between start of therapy and imaging to be able to detect differences in functional imaging parameters. The results will be used for establishing the precise schedule for remaining patients. These patients will not be included in the final analyses.

Interim analysis

After inclusion of 100 patients for at least two months an interim analysis will be performed. The reason is to identify parameters that exhibit a rapid change between the two assessment times, in a proportion of patients. Those parameters that do not exhibit such changes will be excluded from further assessments. The protocol will subsequently be refined.

Statistical methods

To find potentially relevant patterns of response in the large amount of data for each patient, chemometric methods will be applied

To estimate the degree of agreement between predicted and observed response the Cohen's Kappa will be used.

Criteria for evaluation	Patients who have undergone per protocol imaging sessions before and during therapy
Planned sample size	412 patients
Analysis plan	The primary endpoint will be analysed when median follow up is two years.
Duration of the study	Three to four years inclusion, five year follow-up after inclusion of the last patient.

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3 Background and introduction

3.1 Background

The knowledge of factors determining treatment effect in cancer therapy is important in the treatment selection for individual patients. In some cancers impressive progress has been made over the years and has resulted in major improvements in disease control, e.g. in breast cancer. The basis for treatment selection is usually the assessment of pre-treatment characteristics of the patient and the individual tumour. Expression of certain genes, hormonal status and proliferation parameters are some examples of individual tumour properties in clinical routine use. The development in the field of molecular biology during recent decades is not reflected in a similar improvement of therapeutic results for most cancers. Particularly this is the case with most SCCs. In Sweden about 2000 SCC are diagnosed every year within lungs, head & neck, anus, cervix and esophagus.

For a large proportion of cancers the knowledge of pre-treatment parameters of predictive capacity is sparse. A number of biomarkers or combinations thereof have been identified (e.g. HPV, EGFR, ...). In the majority of cases they correlate to outcome of treatment and can therefore be described as prognostic and not specific enough for personalised therapy. In the absence of strong predictors an alternative is to explore the early changes after initiating therapy. Such changes have the potential to be relevant in the assessment of individual tumour response. It is assumed that the changes will also give leads to factors present already before treatment, which are not yet identified.

Cancer treatments; radiotherapy, chemotherapy and/or targeted therapies are frequently administered during an extended time period. The evaluation of effectiveness usually takes place a couple of months after end of therapy. Early response is commonly evaluated by agreed "*Response Evaluation Criteria in Solid Tumors*" (RECIST). Basically, measuring the diameters of tumour contours on radiological examinations makes the assessment. The results given by such end-points will not be able to discriminate between different patterns of response as for example, differential responses in subsets of the tumour. Furthermore, the time between start of therapy and evaluation often comprises the therapeutic interval in which there still exists a possibility to adapt or completely change a suboptimal treatment. Structural changes in tumours are slow compared with changes in biochemistry and other functions.

Detection of early response predictors will therefore be an important adjunct to further development of cancer therapy. Since many years, in radiotherapy, there are examples of early changes that are predictive for outcome. E.g. changes in metabolism measured by FDG-PET and labelling index by infusion of halogenated pyrimidines in vivo have both shown a strong predictive capacity as early as one week into a 6-7 weeks treatment for head and neck cancer e.g. (1,2). It is noteworthy that similar results arise from studies of completely different processes. More recent observations in cases such as cervical cancer (3,4) and head and neck cancers (5) support the hypothesis that treatment effects give rise to complex responses in different cellular processes. Such processes may be identified by a number of methods. The combination of different methods is likely to be more effective. Functional imaging techniques, as positron

emission tomography (PET) combined with magnetic resonance imaging (MRI), offer complementary information that may assess a multitude of biomarkers in patients with SCC. Diffusion, perfusion, metabolism, proliferation are examples of properties that may be studied by static and/or dynamic methods. In the present literature usually one or a few imaging biomarkers have been analysed at the time and only in small patient populations, many with encouraging results e.g. (5-9). They have rarely been further validated and thus, not established as a basis for clinical decisions (7,10).

The imaging biomarkers under study correspond to a number of molecular events in the tumour. It is therefore natural to investigate an array of molecular changes in parallel. The parallel investigations may also spread light over the influence of tumour heterogeneity. The infrastructure of the Department of Oncology in Umeå has access to clinical, dedicated MR-PET equipment for research and development. A core facility with metabolomics and molecular pathology is also a part in the project. At the radiotherapy department in Lund there is presently a MR system available and also availability to PET-CT equipment at the hospital for investigation of study patients. Furthermore another PET-CT equipment will be installed at the radiotherapy department in Lund in near future.

The concept of metabolomics is the systematic study of the unique chemical fingerprints caused by specific cellular processes, where the analysis is expanded to hundreds to thousands of metabolites (< 1kDa). This can be compared to traditional metabolic studies where only a limited set of molecules is studied. Metabolomics has attracted large interest in recent years, since it has the power and scope to resolve fundamental biological issues that cannot be readily addressed using other approaches. Metabolomics information represents a more complete description of the organism closest to the function or phenotype, but also more complex than explanations based on, e.g. functional genomics, proteomics and transcriptomics. To model the systems biology from genome to function or phenotype (tumour) based on these pieces of information, using parametric methods is not realistic today. However, to analyse the systems biology by non-parametric methods as applied in metabolomics research is fully feasible. Current studies of metabolomics are, however, limited to samples representing the whole system or by invasive methods obtained samples and cannot detect heterogeneities in tumours or even locate the signalling tissue. In order to move the metabolomics from isolated research studies to diagnostic predictive and monitoring systems, there is a need for more powerful data collection and data processing tools. Both PET and MRI have the capability to measure metabolic activity and system vascularity in volume elements of approximately 1-10 mm³. The molar sensitivity of a PET system is very high, in the order of 10⁻¹⁵ molar. The combination of the high spatial resolution of the MRI technique and the high sensitivity of the PET system will enable detection of, e.g. therapy-resistant tumour sub-volumes. Sampling of repeated functional images will be an integrated part of the large-scale data sampling. The initial aim of the project will be to determine metabolic fingerprints over time from samples and images, and correlate these to disease, therapy and outcome. Chemometrics and projection-based methods such as Principal Component Analysis (PCA), Partial Least Squares (PLS) and Orthogonal PLS (OPLS) are well-established methods in metabolomics for predictive modelling, powerful data visualization and model interpretation (Holmes & Antti 2002, Trygg, Holmes et al. 2007). However, time trends of a biological system are

not generally considered in metabolomic studies. In the current projects the time aspect will be implemented as part of a holistic-system biology approach. This approach is, in general, assumed to give more comprehensive information of the metabolic mechanism associated with biological functions and disease (Madsen et al. 2010).

4 Aims of the trial

4.1.1 Overall aim

Prediction of short and long term outcome of treatment for squamous cell cancer (SCC) by monitoring tumour response during early treatment phases.

4.1.2 Specific aims

- Correlate changes in imaging bio-markers to corresponding changes in tissue or blood bio-markers by repeated imaging and biopsies for better understanding of the image parameters.
- To correlate data from multiparametric imaging to specific outcome
- Validation of early bio-imaging predictors of tumour response and patient outcome.

4.2 End points

4.2.1 Primary end point

- Loco-regional control 2 years after completion of radiotherapy

4.2.2 Secondary end points

- Loco-regional tumour control 8 (-2 - +4) weeks after completion of radiotherapy
- Patterns of failure
- Progression free survival at 2 years
- Overall survival at 2 and 5 years
- Changes in imaging and metabolic data
- Site specific toxicity at 12 months after completion of radiotherapy

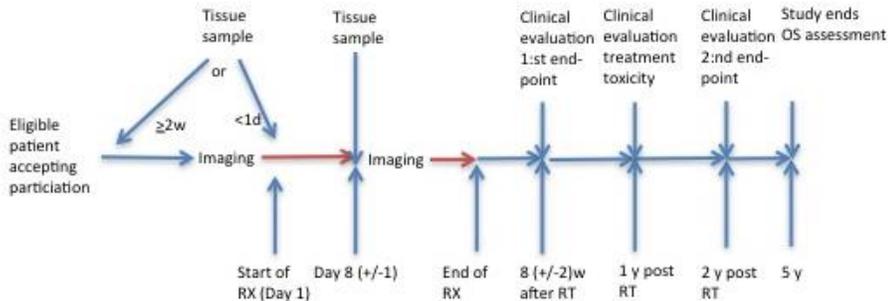
5 Study design

The study is prospective, multi-centre, non-randomised observational study for investigation and validation of imaging biomarkers for early treatment response. Patients are recruited with previously untreated SCCs aimed for radiotherapy with curative intent of the oral cavity, oropharynx, uterine cervix, oesophagus, anal canal or lung. Multimodal, functional imaging data are collected before and during the early phase of radiotherapy. In parallel to the imaging data, tumour biopsies and blood will be collected for molecular analyses that may provide explanatory information to the imaging information.

5.1 Study period

The inclusion period is calculated to be three to four years. The study ends five years after inclusion of the last patient.

6 Study flow chart



7 Overview of study assessments

Patients will be investigated by MR, PET and biopsy/FNAC (fine needle aspiration cytology) twice during the study period.

The first session of imaging will be performed within two weeks from planned start of radiotherapy (without reference to any other possible anticancer treatment (e.g. chemotherapy). In cases where MR and PET are not performed simultaneously they should be performed not more than one week apart. Tissue specimens should be obtained as soon as possible before imaging.

The tissue specimen for metabolomics analyses should be immediately frozen (within minutes from procedure!). Matching specimen for histological verification and future molecular biology studies should also be obtained and handled according to addendum.

The second assessment will be performed on Day 8 (+/-1) after start of radiotherapy (date of first radiation fraction is defined as Day 1). Adjustments of the timing for the second assessment will be determined by using pre-planned variable times for the first 20-30 patients in the pre-study. Thus, optimising the time interval for different sub-sites. In departments where MRI and PET can not be performed simultaneously, the MRI should be performed according to protocol. The PET assessment should be performed in close connection but not more than 24 h apart from MRI. The biopsy/FNAC should preferably be performed after imaging in order to avoid bleeding or edema blunting the imaging. It is recommended that the images produced are used as guidance for directing the biopsies at volumes assumed to contain active tumour tissue. If this is not practically

possible the biopsy/FNAC may be performed before imaging under the condition that the surgeon provides detailed description of the location of the biopsy in order to allow for correcting the results for possible artefacts in the vicinity of the biopsy.

For imaging sessions the patients shall be in therapy position wearing regular fixation devices for therapy. E.g. in the head and neck region this means that head coils etc may not be used and other coil arrangements with flexible coils will be predominant. In order for the patients to avoid higher degrees of discomfort the total time for the imaging procedure shall be planned to last not more than 30 minutes. This means that the number of protocols used for each imaging session must be carefully optimised. The first 20-30 patients will be the part of a pre-study where the usefulness of different protocols will be evaluated and the procedure optimised.

8 Patient selection criteria

8.1 Inclusion criteria

1. Morphologically (pathology or cytology) verified, previously untreated SCCs of the oral cavity, oropharynx, uterine cervix, esophagus, anal canal or lung.
2. The patient should be planned for treatment with radiotherapy alone or in combination with concomitant medical therapy
3. The tumour shall be radiologically and/or visually identifiable and accessible for biopsy without the need for general anaesthesia or other major interventions
4. The patient must be at least 18 years of age, able to understand the given information and, leave a written informed consent to participate

8.2 Exclusion criteria

1. The patient is unwilling to participate in the study
2. Patients with adjuvant post-operative radiotherapy (i.e. no visible remaining tumour)
3. Pregnancy or lactation
4. Contraindications to investigations with MRI, gadolinium contrast or PET-tracers
5. Patients with an estimated GFR <60 ml/min/1.73m².
6. Severe co-morbidities that are judged to significantly compromise survival in a two-years perspective.

9 Study procedure

9.1 Study entry

9.1.1 Mandatory investigations

1. Adequate clinical assessment with a TNM classification and histology/FNAC (showing squamous cell carcinoma).
2. Body weight and height
3. ECOG Performance status
4. P-Creatinine

5. Tumour biopsy and blood sampling in patients participating in the exploratory part of the study.
6. Registration form including informed consent
7. The disease specific module of the EORTC QLQ-C30 for reporting late RT effects should be offered for the patient to fill out and forward to the data centre in a pre-stamped envelope. With the exception of sites where no such module is available.

Investigations number 1-4 are clinical routine investigations, and are thus not regarded as study specific procedures.

9.1.2 Instructions regarding women of childbearing potential

Pregnancy must be excluded before a fertile woman can be included in the study.

9.2 Evaluation during treatment

Concomitant anticancer medication should be recorded with substance, dose and time for administration in the CRF.

9.3 Evaluation after completion of treatment

At two months after completion of therapy an assessment of tumour control and morbidity must be made. Tumour control is assessed by clinical examination together with endoscopy, palpation, control biopsies and appropriate imaging as judged indicated by the responsible physician.

9.4 Surgery

If surgery is performed, this must be recorded.

9.5 Follow-up

- Patients should be seen every three months for two years after completion of radiotherapy and a full clinical assessment should be made.
- One year after end of radiotherapy, the patient will be asked to fill out the disease specific module of the EORTC QLQ-C30 for reporting late RT effects. The questionnaire will be distributed to the patient at the time of inclusion in the study and posted to living patients after one year. One year after completion of radiotherapy the questionnaire will be posted to living patients for self-assessment of late radiotherapy side effects. If not answered, one reminder will be distributed.
- After two years, evaluation of locoregional control should be made every 6 months up to 5 years. At five years, a last follow-up is recommended at the treatment centre with the aim at evaluating late side effects. Any additional follow-up beyond 5 years is not included in the study protocol, each physician decides on further follow-up.

Patients should be monitored for local recurrence and if symptoms arise that are suspicious of distant metastases appropriate investigations must be carried out to confirm or exclude their presence. Also, **if a locoregional recurrence is found, a CT/MR for documentation is mandatory and screening for distant metastases should be performed.** If distant metastases develop but there is no evidence of local recurrence within the irradiated volume, effort should be made to continue to monitor the primary site. **In all cases histological confirmation should be performed.**

9.6 End of treatment or follow-up

Follow-up by the protocol ends when any of the events below occurs:

- If 5 years of follow-up is reached
- If residual tumour or a locoregional recurrence is diagnosed that cannot be treated with curative intent. Survival will then be followed by the Swedish population registry
- In cases of other serious medical conditions, follow-up ends as judged by the investigator. Survival will then be followed by the Swedish population registry
- If the patient dies before 5 years' follow up
- Withdrawal of consent

10 Radiotherapy

Radiotherapy will be performed according to clinical routines of each participating centre. The patients may be treated with X-rays, electrons or protons.

10.1 Patient position and fixation

The patient should be treated in supine position, adequately positioned and fixated according to the routines at each treatment centre.

10.2 Patient radiotherapy data acquisition

Full 3-D treatment plans together with data from the oncology information system will be stored in the local research database at each treatment centre. The use of the nationally agreed research database for radiotherapy (MIQA) is recommended. The collection of data that will be sent to the coordinator of RT-data will be anonymised and assigned the patient's number in the study when the selection of relevant data is analysed. A treatment planning imaging (slice thickness $\leq 3\text{mm}$) should be performed with the patient in treatment position, adequately fixated. Optionally, a co-registered MRI- or PET-scan should also be performed as aid for tumour delineation.

11 Biobank

As primary biobank, Biobank Norr in Umeå, will be used. Until analysis samples will be kept in the local bio-banks at each hospital.

12 Statistical plan

12.1 Sample size determination

From the expected number of eligible patients with each diagnose, three separate study groups are identified

1. Lung cancer
2. Head and neck cancer
3. Cervix, esofagus and anal carcinoma

The first two subgroups will be analysed separately as well as aggregated with all other groups. In group no 3 the number of patients with each diagnosis is expected to be too low to make valid statements for each entity. This group will therefore mainly be analysed together with all cases.

The overall aim of the study is to identify and validate parameters predictive to outcome of treatment. To estimate the degree of agreement, the Cohen's Kappa is commonly used. It is defined as the proportion on the main diagonal that exceeds the expected number if a random classification is performed. It is normalised to fit the interval (0,1) where 0 is a random classification and 1 is a 100% correct classification.

For personalised therapy purposes a correct classification in 90 % of cases is desired. We assume that the proportions of responding patients are either distributed similarly (50 %/50 %) or that only 20 % are responders. $H_0: k = k_0$, $H_1: k = k_1$, $k_1 > k_0$. Assuming $k_0 = 0.4$ (which is considered to indicate a poor agreement) and $k_1 = 0.7$ (which is considered to indicate a good agreement) and if the probability of correct rejection of H_0 is set to 90 % the number of patients needed is 63 or 80 depending on response rates (50 % or 20 %). Thus, a number of patients of about 70 for each study group should be optimal to answer the study questions. In addition to the 70 patients of each group, the data from 30 patients from the head and neck cancers and lung cancers will be used for hypothesis generation. Their data will not be re-used for validation. From previous experience, a proportion of patients will for medical or other reasons not contribute with the second set of data. It is assumed that 20% of patients will have incomplete data sets. Thus, the number of included patients in each group will be aimed at 100. Additionally, the 30 first patients will be part of a pilot study and not analysed further for the study end-points. The total number of patients needed for the study is estimated to 412 during the three years of accrual. However, each group will be closed earlier for further inclusion if 100 evaluable patients are reached. Image and bio-marker analyses will be performed only on those with complete data sets from imaging sessions.

12.2 Statistical methods

Changes in imaging parameters and metabolomics patterns will be used for statistical inference. We also intend to apply multivariate data reduction and texture analyses techniques on multi-dimensional parametric images from the study population. In this part of the project a close collaboration is planned with the project of T Nyholm. All data will be stored in communicating databases for future re-analyses when long-term follow-up data is available and new methods for multiparametric analyses become available. Contrary to many studies that result in "promising results" we aim to bring preliminary findings to a higher level of validation and thus prepare for large scale clinical studies. In

the clinical data sampling procedures a pre-determined fraction of the patients will be randomised and stored separately for hypothesis validation.

Survival endpoints will be compared by Cox regression stratified for tumor site and corrected for all other covariates used in the minimization algorithm – i.e. a multivariate Cox regression will be applied with tumour sites as strata as covariates

The primary analysis will be based on the intention-to-treat analysis set. Every effort will be made to collect survival data on subjects, including subjects withdrawn from treatment for any reason, who are eligible to participate in the study and who have not withdrawn consent for survival data collection. OS is defined for each patient as the time between radiotherapy start date and death. If a patient has not expired, the patient will be censored at the time of last contact (last known alive date).

12.3 Subject Population(s) for Analysis

Intention to treat population: Any subject included in the study, regardless of whether they received planned treatment.

Protocol-compliant population: Any subject who was randomized and received the planned treatment.

12.4 Pilot study

The first 20-30 patients will be part of a pre-study where the timing and protocols for investigation are optimised. These patients will not be included in the analysis of the main study. One of four patients will be randomly chosen for belonging to the “hypothesis generation group” (HGG). Their data will be analysed in the search of a number of predictive parameters for outcome. The remaining patients’ data will be used for validation of hypotheses. The HGG will not be used in this validation process. The first analyses will be performed when the number of study patients is reached. The second analysis will be performed two years after including the last patient. The third analysis will be performed when five years have passed since the last inclusion of a patient.

13 Quality assurance

13.1 Control of data consistency

All patients included in the study are identified by the patient identification number. Identification code lists that links patients’ names to the patients’ identification number must be stored in the Investigator File.

Study data will be recorded via using Case Report Forms (CRF). Study data may be recorded directly into the CRF, ie the CRF may be the source data. Prior to study start, the Investigator and the Monitor must identify and document the expected source location of every CRF data. Expected source locations are for example the subject’s medical record, laboratory reports and the CRF itself.

Accurate and reliable data collection will be assured by verification of the CRF against the investigator’s records and medical records by the study monitor, as well as study integrity, compliance with the protocol and applicable regulations.

13.2 Site Monitoring

In consistency with the principles of GCP, the sponsor takes responsibility for monitoring of the study. As an external monitor for the study a research nurse or equivalent, not involved in any aspects of the study, will be appointed. The external monitor is experienced in clinical trials and monitoring, and acting under responsibility of CTU, Norrlands universitetssjukhus.

During the study, the monitor will have regular contacts with the study sites, including onsite visits in order to ensure that the study is conducted and documented properly in compliance with the protocol, GCP and applicable regulatory requirements.

The trial will be monitored consistent with the demands of the trial and site activity to verify that the:

- Data are authentic, accurate, and complete
- Safety and rights of subjects are being protected
- Trial is conducted in accordance with the currently approved protocol and any other trial agreements, GCP and all applicable regulatory requirements.

13.3 Direct access to source data/documents

The sponsor has the responsibility to maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. Investigators files and subjects clinical source documents must be kept for at least 10 years after completion or discontinuation of the study.

14 Data management

14.1 Patient registration procedure

Subject eligibility will be established before inclusion. Subjects will be given a identification number consecutively, as subjects are eligible for enrolment.

If a subject discontinues from the study, the subject number will not be reused, and the subject will not be allowed to re-enter the study.

The Data Centre (CTU, Norrlands universitetssjukhus) is responsible for the registration procedure. When a patient is found to be eligible and has signed a written informed consent, registration will be performed via the study coordinating person.

A registration form should be filled out before inclusion of each patient. This form will contain all relevant data on the patient

14.2 Case Report Forms

Study data will be recorded via the CRF. During study treatment the CRF should be filled in weekly, and after completion of treatment the CRF should be filled in at each time point for follow-up.

The investigator at the enrolling site is responsible for collection of source data if patient visits are decentralized to other clinics.

14.3 Patient's questionnaires

Each patient will be asked to fill out the disease specific module of the EORTC QLQ-C30 for reporting late RT effects. This procedure will be performed before treatment starts and one year after end of radiotherapy. The questionnaire will be distributed to the patient at the time of inclusion in the study and posted to living patients after one year. One year after completion of radiotherapy the questionnaire will be posted to living patients for self-assessment of late radiotherapy side effects. If not answered, one reminder will be distributed. The Data Centre will register the completed forms in the study database.

15 Ethical considerations

15.1 Patient protection

The study is to be performed in accordance with the ethical recommendations of the Helsinki declaration and the ICH-GCP guidelines, or the laws and regulations of the country, whichever provides the greatest protection of the patient.

15.2 Patient integrity

The investigator must assure that the patient's anonymity will be maintained and that their identities are protected from unauthorized parties. On CRFs or other documents submitted to the Data Center patients should only be identified by their identification code, year and date of birth and initials.

15.3 Informed consent

All subjects will receive written and oral information about the aims of the study, discomfort inflicted and possible hazards. They will be informed about the strict confidentiality of their patient data, but that their medical records may be reviewed for trial purposes by authorized individuals other than their treating physician.

It will be emphasized that the participation is voluntary and that the patient is allowed to decline further participation whenever he/she wants. If the patient wishes to withdraw from the study, he or she will be offered the standard treatment at the clinic.

A signed, informed consent must be obtained from the patient before study entry. In the cases where the patient declines to participate in the study the conventional procedures according to local practice should be offered.

If new safety information results in significant changes in the risk/benefit assessment, the consent form should be reviewed and updated if necessary. All patients (including those already being investigated) should be informed of the new information, given a copy of the revised form and give their consent to continue in the study.

15.4 Independent ethics committees

This protocol and any accompanying material provided to the patient, such as written patient information used to obtain informed consent, will be submitted by the investigator to the independent Regional Ethical Review Board in Umeå. Approval from the committee must be obtained before starting the study, and should be documented in a

letter to the investigator specifying the date on which the committee met and granted the approval.

15.5 Risk-benefit analysis

Since the treatment of each patient's disease will not be affected by the assessment procedure or the results of it, the risks are limited to the imaging and biopsy procedures.

15.5.1 Imaging procedures

For the imaging procedure in the cases of simultaneous MRI and PET or a combination of PET- CT and MRI the risks are equivalent to those encountered with routine examination with each modality alone. They can be divided into three categories

1. **Discomfort.** Patients may experience discomfort due to restriction of movements etc due to the confined space in the MRI equipment. In severe cases claustrophobia may prevent the patient from participating in the study. Patients experiencing severe discomfort will be encouraged to refrain from participating or to stop the participation.
2. **Reactions towards contrast agents.** The routines for Gd-contrast precautions at each participating centre will be followed. Gadolinium contrasts with known low risk for severe side effects should be used. Patients with an estimated GFR <60 ml/min/1.73m² should not participate.
3. **Radiological hazards.** The amount of injected ¹⁸F-FDG will be optimised and the exposure to a standard dose of FDG (4 MBq/kg) will result in an exposition of 10 mSv (20 mSv for two examinations). In comparison the exposition in the environment in Sweden gives about 3 mSv/year. In the situation of the patients of the study, adults subjected to radiotherapy, the risk for long term effects from the radiation from the PET tracer, administered twice, may be considered as very small. In cases when the combination of PET and CT is used "low-dose CT" will be used. The CT examinations adds approximately 1 mSv each.

15.5.2 Surgical procedures

The biopsy/FNAC procedure is well known. It may inflict pain and discomfort for the patient. The risk for severe complications is low and with proper routines the risk for the patient may be considered minimal. Patients will not be subject to general anaesthesia for the cause of this investigation but every other method to reduce pain and discomfort will be taken. If general anaesthesia is required for this investigation alone, the patient will be withdrawn from this part of the study.

15.5.3 Potential benefits

The potential benefit of finding predictive markers for therapy response is vast but will not benefit the individual patient in the study. The potential to improve therapy in the future, however, is significant.

The patients in the study are covered by the Swedish Patient Insurance and the Swedish Pharmaceutical Insurance.

16 Participating centres

All Swedish hospitals with resources to perform the study will be invited to take part in the study.

Each centre must expect to include a minimum of 5 patients per year. If a centre includes less than 2 patients during one year, that centre shall be closed. Previously included patients will then be followed according to the protocol but no further inclusion is accepted from that centre.

Centres from other European countries may be accepted as participants in the study as decided by the study group.

17 Ownership of the data

The Study Group consisting of the investigators at the participating centres owns the data. The patient material of the individual centre cannot be extracted for publications to answer the questions of this study. The Study Group must approve future research projects utilizing data from the present study. In case the Study Group is not active the sponsor may make the decisions of the use of data.

17.1 Meetings

Regular meetings with representatives from all participating centres (Study Group) will be held twice per year or when considered necessary. The Study Steering Committee will also have separate regular meetings. In the time between Study Group meetings, the members of the Study Steering Committee shall act as contact persons and will have an executive role. Decisions taken shall be discussed at the meetings of the Study Group. The Study Steering Committee shall prepare and arrange the meetings of the Study Group.

17.2 Reporting and Publication

All presentations of data from the study should only be made after agreement within the Study Group. The results of the study will be submitted to an internationally recognized medical journal. Apart from the Study Group, each participating centre with at least 20 patients included will be guaranteed co-authorship for 1 person and if more than 30 patients, co-authorship for 2 persons is guaranteed when the study is reported. In addition to this, persons with special responsibilities within the study may become co-authors. The Vancouver declaration will be followed in all publications based on this study.

18 Flow chart study procedures

19 References

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Addendum 1; Handling of biobank samples (Swedish)

Addendum 2; Procedures for MRI investigations an data collection

Addendum 3; Procedures for PET imaging and data collection