PROTHYM

Phase II non-randomized study on proton radiotherapy of thymic malignancies

Version 2.2

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Phase II non-randomized study on

Proton

Radiotherapy

Of

Thymic

Malignancies

Version 2.2

Supported by SLUSG:

Swedish Lung cancer Study Group

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1.0 Synopsis

Title of study	PROTHYM Trial Proton radiotherapy of thymic malignancies The study is supported by SLUSG, Swedish Lung Cancer Study Group
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Study centres	Skandion Clinic, Uppsala, Sahlgrenska University Hospital, Gothenburg, Karolinska University Hospital, Stockholm, Akademiska Hospital, Uppsala, Norrlands University Hospital, Umeå, Örebro University Hospital, Linköping University Hospital, Skåne University Hospital, Lund
Study phase	Prospective, non-randomized phase II study
Number of patients	40 patients
Study Start	Sep 2017
Planned study period	Recruitment Start Date : Sep/2017 Target recruitment period:60 months Sep/2022) Follow up period. End date: 5 years from last treatment.
Study objectives	<u>Primary</u>: Toxicity (e.g. cardiac and pulmonary toxicity) and Local control at 5 year <u>Secondary</u>: PFS

	Overall survival Quality of life, measured by EORTC QLQ 30 + LC 14 Relapse pattern
Study design and plan	This is a multicentre non-randomized phase II study of proton beam radiotherapy in patients with thymic epithelial tumours (i.e. thymoma and thymic carcinoma) in the post-operative setting or in inoperable patients with localized disease. Patients not willing or for any reason unsuitable to undergo proton treatment will be asked to participate in a follow-up assessment after the regular photon treatment in the same manner as the included patients.
Methodology	All doses are recorded in Gy(RBE). After having checked all eligibility criteria patients will receive: • Patients with radical surgery and unfavourable histology (B2, B3, C) and/or Masaoka-Koga stage III, IVa: 2 Gy(RBE), once daily, five days a week to a total dose of 50 Gy(RBE). • Patients with non-radical surgery (R1 resection) regardless of stage and histology: 2.3 Gy(RBE), once daily, 5 days a week to a total dose of 57.5 Gy(RBE) • Inoperable patients regardless of stage and histology and patients with R2 non-radical resection: 2.5 Gy (RBE), once daily, 5 days a week to a total dose of 62.5 Gy(RBE) • Patients not willing to participate in study will receive photon therapy according to local practice (≥45 Gy) Induction or adjuvant chemotherapy may be used according to local practice. Concomitant chemotherapy is not allowed. For radiotherapy volumes see below.
Criteria for inclusion and exclusion	Inclusion Criteria:

	• Histological or cytological diagnosis of thymoma or thymic carcinoma. • With radical surgery: stage III and IVa and selected stage II with type B2, B3 and thymic carcinoma according to local routine. With non-radical surgery (R1 or R2) or inoperable patient/ patient refusing surgery: stage I - IVa, any histology • PS WHO 0 - 2. • $FEV_1 \geq 1L$ or ≥40 % of predicted and CO diffusion capacity ≥ 40% of predicted (postoperative measures) • Age ≥18 years, no upper age limit. • Written informed consent from patients. Exclusion Criteria: • Masaoka-Koga stage IVb (distant metastases). • Pregnancy. • Serious concomitant systemic disorder incompatible with the study. • Tumour motion > 0.5 cm on two repeated 4DCT
Radiotherapy planning	Treatment will be given by PBS (pencil beam scanning) technique at Skandion in Uppsala but all patients must have a photon backup plan, preferably with VMAT or IMRT technique. • Pre-treatment preparation: Fixation, wingstep • Pre-treatment imaging: 4DCT • Specification of treatment prescription o Volume specification: GTV, ITV, CTV, PTV, OAR's GTV = visible tumour growth CTV = post-operative tumour bed and/or defined margin to GTV: 0,5 cm to lung tissue and 1 cm elsewhere. Adjustment to airways, big vessels, bone will be performed. No adjuvant volumes, except for

	pleura/pericardium in between separate GTV's (stage IVa) ITV includes CTV in all breathing phases defined according to local routines PTV = ITV + 5 mm. PTV is used for dose prescription and reporting according to ICRU recommendations OAR's: heart, LADCA ,lung, spinal cord, esophagus • Registration of volumes for GTV, PTV and doses to OAR's: Lung: V_5, V_{20}, V_{40}, MLD. Esophagus: $D_{2\%}$, mean dose, Heart: $D_{2\%}$, mean dose, V_{40}. LADCA $D_{2\%}$ and mean dose. Spinal cord: $D_{2\%}$ ○ Absorbed dose prescription Group I: 2 Gy(RBE), once daily, five days a week to a total dose of 50 Gy(RBE), 5 weeks. Group 2: 2.3 Gy(RBE), once daily, 5 days a week to a total dose of 57.5 Gy(RBE), 5 weeks. Group 3: 2.5 Gy(RBE), once daily, 5 days a week to a total dose of 62.5 Gy(RBE), 5 weeks. In case of interruptions for technical or administrative reasons the total treatment time should not exceed 6 weeks. If protons could not be delivered in stipulated 6 weeks photon back-up plan should be used instead. • Relation to other therapies Up to three cycles of adjuvant/induction chemotherapy may be administered according to local routine. Radiation should start within 4-8 weeks after chemotherapy or surgery.

	<u>Pre-study evaluation:</u> The treatment should start within four weeks from registration. The following are required prior to protocol entry: • CT scan thorax not older than 4 weeks, • Medical history • Weight and length • Physical examination • Performance status according to WHO • Assessment of quality of life according to QLQ 30+LC 14 • ECG • Cardiac ultrasound • Cardiac markers: NT-ProBNP and TNT • Spirometry including CO diffusion capacity • Assessment of symptoms at baseline according to NCI-CTCAE criteria version 4.0. • Pregnancy test, if applicable • Haematology: Haemoglobin; WBCC (White Blood Cells Count); Platelets count • Chemistry: CRP, serum creatinine; Serum calcium and albumin; Bilirubin, Alkaline Phosphates; LDH, ASAT and ALAT Hematology and blood chemistry need to be reassessed if older than one week before treatment start. UCG and ECG has to be performed within two weeks before start of treatment

	On treatment evaluation: • Recording of toxicity, performance status, ECG, NT-ProBNP, TNT, CRP at week 3 and end of treatment. • Weight weekly. If weight change >5%, a new CT-scan and replanning should be considered. • QLQ30 + LC14 at end of treatment • At end of treatment visit patient shall be referred to TTE/UCG which shall preferably be performed one week after completion of therapy, but at least within two weeks <u>Follow up assessment:</u> First follow-up 4 weeks after completion of therapy and three months thereafter. Then every three months during the first two years. Thereafter every six months until end of study • Recording of persistent or new toxicity • Performance status • Weight • Tumour response evaluation with CT scan at 4, 7, 13 months and every 6 months thereafter or if clinically indicated. • Spirometry including CO diffusion capacity at 6 months • ECG at each visit the first year. Thereafter annually or if clinically indicated • Cardiac markers: NT-ProBNP, TNT • Quality of life according to QLQ30+LC14 at baseline, week 3 during treatment, 1, 3, 6 and 12 months after completed radiotherapy. Thereafter at 2, 3 and 5 years after treatment.
Statistical methods:	We will perform a Kaplan-Meier analysis with the aim to compare our data with published historic data from the ITMIG international database and other datasets. Toxicity data will be analysed descriptively and there will be a comparison between the proton patients and photon control group. 40 patients will be included in the study

2.0 Abbreviations

AE	Adverse event
ALAT	Alanine aminotransferase
ASAT	Aspartate aminotransferase
CO-diff	Carbon oxide diffusion
CRP	C-reactive protein
CT	Computed tomography
4DCT	4-dimensional computed tomography
CTCAE	Common terminology criteria for adverse events
CTV	Clinical target volume
ECG	Electrocardiography
EORTC	Europena Organization for Research and Treatment of Cancer
FEV1	Forced expiratory volume, one second
Gy	Gray
Gy(RBE)	RBE-weighted absorbed dose in Gy
GCP	Good Clinical Practice
GTV	Gross tumour volume
βHCG	Human Chorionic Gonadotropin
ICRU	International Commission on Radiation Units and Measurements
IMRT	Intensity-modulated radiotherapy
ITMIG	International Thymic Malignancy Interest Group
LADCA	Left anterior descending coronary artery
LC14	Lung Cancer 14, QL-questionnaire
LDH	Lactate dehydrogenase
NCI	National Cancer Institute
NT-ProBNP	N-terminal pro b-type Natriuretic Peptide
OAR	Organ at risk
OD	Once daily
OS	Overall survival
PBS	Pencil beam scanning
PFS	Progression-free survival

PORT	Post operative radiotherapy
PS	Performance status
PTV	Planning target volume
RBE	Relative Biological Effectiveness
R1	Microscopic residual tumour directly at the resection margin
R2	Macroscopic residual tumour locally
RIHD	Radiation induced heart disease
RILD	Radiation induced lung disease
SAE	Serious adverse event
TET	Thymic epithelial tumour
TnT	Troponin T
UCG	Ultrasonic cardiography
VMAT	Volumetric modulated arc therapy
QLQ30	Quality of life questionnaire

3.0 Introduction and background

Thymic epithelial tumours (TETs or thymic malignancies) which comprise thymoma and thymic carcinoma, are rare cancers worldwide. The annual incidence is approximately 0.15/100.000 in the United States (1) and 0.32/100.000 in the Netherlands (2). According to the Swedish National Cancer Register 33 patients were diagnosed with either thymoma or thymic carcinoma in 2013 which is an approximative incidence of 0.33/100.000. TETs are heterogenous both morphologically as well as clinically. Thymomas may be associated with a spectrum of autoimmune conditions, whereas this is rare in thymic carcinomas. Thymic carcinomas are more prone to distant metastatic spread. In a Japanese retrospective analysis the survival rates differs between the groups with a median OS of patients with thymoma of 235 months compared with 32 months for those with thymic carcinomas (3) which is comparable with other reports. There is no official stage classification for thymic malignancies defined by the Union Internationale Contre le Cancer (UICC) and the American Joint Commission for Cancer (AJCC). ITMIG in collaboration with the International Association for the Study of Lung Cancer (IASLC) have published a proposal for a new staging system for the forthcoming edition of the TNM classification of Malignant Tumors (4-5).Until this system is

definitely defined ITMIG has proposed staging according to the Masaoka-Koga stage classification (6) which is generally spread and used worldwide.

Surgery remains the cornerstone in the management of TETs. Minimally invasive techniques including thoracoscopic and robotic surgery for early stage disease are gradually increasing. Chemotherapy, although often with a moderate response, has a role in downstaging as well as managing more advanced disease. There is also evolving data on targeted drugs. The role for radiotherapy is a matter of ongoing debate but the use of postoperative radiotherapy (PORT) after incomplete surgery and/or advanced stage (III/IV according to Masaoka) is more or less standard (7-9). There is considerably less evidence and weaker consensus for the efficacy of PORT of stage II patients (10) and the use of it varies worldwide. It could, however, be used in selected cases such as B3 and C patients in accordance with local routines.

Radiotherapy with photons for TET patients has been reported feasible and with acceptable toxicity. Treatment is generally given with IMRT-technique and doses in the literature varies between 45 and 60 Gy with 1.8 or 2 Gy/fraction.

Many of the thymoma patients will become long time survivors and thus may suffer from late toxicities such as radiation induced lung disease (RILD) (11) or radiation induced heart disease (RIHD) (12-13). For many years RIHD has been of major concern when irradiating patients with left-sided breast cancer and Hodgkin's disease. It is considered a late side effect which may become manifest 5-10 years after completion of radiotherapy, although earlier onset may occur. It includes a wide range of symptoms such as pericarditis, myocardial infarction, valvular heart disease and coronary heart disease (14-15). Lately this has become a greater concern when treating thoracic malignancies such as lung and esophageal cancer (16). Depending on the good prognosis, there is a strong rationale as to try to limit the cardiac dose to the thymoma patients. Comparing treatment plans for protons vs photons has shown that it is possible to reduce the cardiac dose with protons (personal communication Nyman & Bäck).

How to detect and follow-up on RIHD is an ongoing subject for discussion. Different imaging techniques have been suggested (17-18) and there is also some data on biomarkers predicting cardiac toxicity after chemotherapy and radiation therapy (19). There is, however, no golden standard regarding screening for RIHD.

Radiotherapy with protons have emerged as a potential possibility to achieve local control and eventually reduce the risk for late toxicity and secondary tumors. From early on, thymic malignancies was recognized as a group who would eventually benefit from proton therapy (20-21). Treating thoracic malignancies with protons is cumbersome because of many reasons; tumor and organs at risk motion may result in interplay effects which compromise dose distribution being one of them. Movement of mediastinal structures occurs but seems to

be minor compared to the movement in the lung parenchyma and patients with Hodgkins' disease has been successfully treated with protons. TETs are generally located in close proximity to the mediastinum. Recent years more and more data have been published showing superior dose distribution and feasibility regarding toxicity while treating thymomas with protons (22-24). The majority of previous thoracic proton therapies have been given with passively-scattered technique. At the Skandion Clinic all patients will be treated with pencil beam scanning (PBS) with proton energies ranging from 60 to 230 MeV. This technique may further optimize dose distribution although planning, quality assurance and motion management is even more crucial (25-26).

4.0 Rationale and Objective of the study

4.1 Objective

To explore whether proton radiotherapy is feasible and results in an acceptable local control

4.1.1 Primary Objective

Toxicity (eg cardiac and pulmonary toxicity).

Local control at 5 years. Local control is defined as freedom of locally progressive disease; ie CR (complete remission) or SD (stable disease) based on CT or PET/CT evaluation

4.1.2 Secondary Objective

Overall survival, progression-free survival, relapse pattern, quality of life measured with QLQ 30 + LC 14.

5.0 Study Design

5.1 Description

This is an open, non-randomized multicentre, phase II trial, to investigate the efficacy and toxicity in PBS proton therapy of thymic malignancies

5.2 Time Schedule

The trial is expected to start after Ethics Committee has approved the protocol.

Target recruitment period is estimated to be 60 months.

End date is estimated to be five years from last treatment.

5.3 Treatment Schedule

The study population will consist of three patient categories;

A patients who have undergone radical surgery

B patients who have undergone non-radical surgery

C patients who are considered inoperable.

Radiotherapy doses will differ between the groups. We have assumed that RBE for protons is1.1 and the prescribed dose is the corresponding dose for photons (Gy(RBE). Within brackets is the physical dose.

Patients who have undergone radical surgery but has an unfavorable histology (B2, B3, C) and/or Masaoka stage III or IVa (selected stage II-patients can be considered according to local practice) will receive 2 Gy(RBE) once daily, five days a week to a total dose of 50 Gy(RBE) (1.82 Gy OD, total dose 45.5 Gy)

Patients who have undergone non radical surgery (R1), regardless of stage and histology, will receive 2.3 Gy(RBE) once daily, five days a week, to a total dose of 57.5 Gy(RBE) (2.09 Gy OD, total dose 52.25 Gy)

Patients who are considered medically inoperable, or refuses surgery, regardless of stage and histology, and patients who have undergone R2 non-radical resection will receive 2.5 Gy(RBE) once daily, five days a week, to a total dose of 62.5 Gy(RBE) (2.27 Gy OD, total dose 56.75 Gy)

Patients not willing to participate in study, but willing to be included in follow-up according to study protocol will receive photon therapy according to local practice. The total dose must be ≥45 Gy.

Up to three cycles of chemotherapy may be administered prior to start of radiation according to local practice. Radiation therapy shall then start within 4-6 weeks after completion of the third cycle. Use of concomitant chemotherapy is not allowed.

If surgery has been performed, radiation therapy shall start 4-8 weeks thereafter

5.4 Treatment duration

The radiotherapy overall treatment time in all of the patient categories should preferably be five weeks. In case of interruptions for either technical or administrative reasons the treatment time should not exceed six weeks. If protons cannot be delivered in stipulated six weeks, photon backup plan shall be used instead.

5.5 Reason for discontinuation of treatment

- Progressive disease under any time of treatment is reason for stopping the treatment
- Adverse reaction that is severe or life threatening that precludes further treatment.
- Major protocol violations such as unjustified substantial modifications of the radiotherapy treatment.
- Missing essential data as for safety and/or efficacy assessment that cannot be recovered are missing
- Patient refusal, or withdrawal of informed consent.

5.6 Follow-up

First follow-up 4 weeks after completion of therapy, then at four months and every three months thereafter for the first year, then every six months for a maximal five years in total.

Recording of persistent or new toxicity, performance status and weight will be done at all visits.

Tumour response evaluation with CT scan will be done at 4, 7, 10 and 13 months after therapy and every 6 months thereafter or if clinically indicated.

Quality of life according to QLQ30 + LC 14 will be measured at baseline, week 3 during treatment, and of treatment, 1, 3, 6 and 12 months after completion of radiotherapy. Thereafter at 2, 3 and 5 years after treatment. The administration of the questionnaires will be handled centrally by the Clinical Trial Unit at the Oncology Departent, Sahlgrenska University Hospital.

Spirometry including CO diffusion capacity will be repeated at 6 months after therapy and at end of study

UCG will be performed within two weeks after completion of therapy and at end of study, i e 5 years after treatment

ECG will be recorded at each visit

5.7 Stopping Rules

The trial will stop prematurely for the following considerations:

- If emerging toxicities are of such a serious nature that continuation of the trial becomes unacceptable.

- If the recruitment is too low to expect completion of the study in its present form within an acceptable period of time (inclusion estimated to be 60 months)

- If the number of dropouts as described above (5.5) is too high and this situation cannot be acceptable for a period of time.

5.8 Ending and completion of the study

The study is finished when an estimated number of 40 evaluable patients have completed the treatment according to the protocol and are followed for 60 months.

5.9 Patient registration

Before patients agree to participate in this trial all patients will be given oral and written information. A “Patient information sheet” and a consent form, prepared in the local language will be handed out to the patients. The formal consent form must be signed and dated by the patients and investigator before they are submitted to any study-specific procedure.

Patients that fulfil the eligibility criteria and have signed and dated the formal consent will be registered by phone to the Clinical Trial Unit, Sahlgrenska University Hospital, Göteborg at phone number +46 700 90 60 97. Treatment should start within four weeks from registration.

5.10 Quality control/monitoring

The study will be monitored according to ICH/GCP by visits and calls to the investigator. During site visits, the monitor shall review original patient records and document retention. Additionally, the monitor shall observe study procedure and will discuss any problem with the

investigator. The investigator will provide direct access to source data/documents for trial related monitoring audits, EC review and regulatory inspections.

Monitoring will be provided by Clinical trial Unit at the Oncology Department at Sahlgrenska University Hospital.

5.11 Records retention/subject identification

It is the investigator's responsibility to retain sufficient information regarding the identity of the patients, so that any Health Authorities may access this information, if needed. Copies of all pertinent information, including patient identity and allocation number and individual patient data records, will be retained in a confidential manner by the investigator for a minimum period of 15 years from study completion.

5.12 Data management

Data collection during the study will be performed by the monitor and data management will be performed at Study coordinating center.

5.13 Ethics

The study will start after approval from authority and Ethical committee and it is the responsibility of the Investigator-Sponsor to supply the co-investigators with a copy of the final assessment. This study will be conducted in compliance with the protocol and in accordance with the ethical principles put forward in the Declaration of Helsinki and in accordance with GCP rules.

The rights, safety and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

Study personnel involved in conducting this trial will be qualified by education, training and experience to perform their respective tasks.

6.0 Study Population

6.1 Source

Patients with histologically confirmed thymoma or thymic carcinoma

6.2 Inclusion Criteria

- Histological or cytological diagnosis of thymoma or thymic carcinoma
- With radical surgery stage III, IVa and selected stage II with type B2, B3 or thymic carcinoma according to local routine
- With non-radical surgery (R1 or R2), stage I - IVa, any histology
- Medically inoperable, or patient refusing surgery, stage I - IVa, any histology
- PS WHO 0 - 2.
- $FEV_1 \geq 1L$ or $\geq 40\%$ of predicted and CO diffusion capacity > 40% of predicted (post-operative measures).
- Age $\geq$18 years, no upper age limit.
- Written informed consent from patients.

6.3 Exclusion Criteria

- Masaoka-Koga stage IVb (distant metastases)
- Pregnancy.
- Serious concomitant systemic disorder incompatible with the study.
- Tumour motion > 0.5 cm on two repeated 4DCT

7.0 Evaluations

7.1 Pre-study evaluations

- CT scan thorax and upper abdomen including adrenals, not older than 4 week, documentation of measurable and unmeasurable disease sites.
- Medical history
- Physical examination
- Performance status according to WHO
- Assessment of quality of life according to QLQ 30+LC14

- Pre-treatment weight loss registration
- Electrocardiogram (ECG)
- Transthoracic echocardiogram (TTE)/UCG
- Spirometry with CO diffusion capacity
- Body weight and length
- Assessment of symptoms at baseline according to NCI-CTCAE criteria, version 4.0
- Pregnancy Test

All women of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L of β-HCG) within 72 hours prior to the start of study.

- Haematology: Haemoglobin, WBCC, Neutrophils and Platelets count.
- Chemistry: Serum creatinine, calcium and albumin, Bilirubin, Alkaline Phosphates, LDH, ASAT, ALAT,CRP, TNT, NT-proBNP

7.2 On Treatment evaluation

- Recording of toxicity and performance status, at week 1, 3 and 5 during treatment
- Weight every week
- Registration of volumes for GTV, PTV, constraints doses to normal tissues: Lung: V_5, V_{20}, V_{40}, MLD. Esophagus: $D_{2\%,}$mean dose. Heart: mean dose, V_{40}. LADCA: $D_{2\%,}$ mean dose Spinal cord: $D_{2\%}$

7.3 Post Treatment evaluation/Follow up

First follow-up 4 weeks after completion of therapy, then at four months and every three months thereafter during the first year. After that follow-up every six months until end of study

- Recording of persistent or new toxicity
- Performance status
- Weight
- Tumour response evaluation with CT scan at 4, 7 and 13 months after therapy and every 6 months thereafter or if clinically indicated. Chest x-ray is sufficient at other follow-up visits.

- Quality of life according to QLQ30+LC14 at baseline, week 3 during treatment, end of treatment, 1, 3, 6 and 12 months after completion of radiotherapy. Thereafter at 2, 3 and 5 years after treatment.
- Spirometry with CO diffusion capacity at 6 months after therapy and at end of study

7.4 Transthoracic echocardiogram (TTE)/UCG

A comprehensive TTE examination will be performed at three times: within two weeks prior to radiation therapy, within two weeks from completion of radiation therapy and at the end of the study. The TTE examinations are performed using the existing equipment at the local hospital. Age, gender, length and weight of the patient are recorded before start. During examination heart rate and presence of arrhythmias are documented. Image sampling follows a standardised protocol (Appendix) and is performed by a biomedical scientist or cardiologist at the local hospital. The examination is thereafter transferred (by CD/DVD) for central evaluation by study responsible cardiologist. All values are related to the age, gender and body size of the patient.

7.5 Schedule of assessments

Table 1

	Prior to RT	During RT	End of RT	Within 2 weeks from RT	4 weeks
Medical history	X				
Physical examination	X	X	X		X
Weight & PS	X	X	X		X
NT-Pro-BNP, TNT, CRP	X	X	X		X
Hematology	X		X		X
Creatinine, calcium, albumin, bilirubin, ALP, ASAT, ALAT, LDH	X		X		X
Electrocardiogram	X	X	X	X	X
PET-CT-scan	optional				
Tumor assessment by CT[1]	X				
TTE/UCG	X			X	

Spirometry[3]	X				
Assessment symptoms and toxicity	X	X	X		X
QLQ[2]	X		X		

	4 months from RT	6 months from RT	Follow up	End of study	
Medical history					
Physical examination	X		X	X	
Weight & PS	X		X	X	
NT-Pro-BNP, TNT, CRP	X		X	X	
Hematology	X		optional		
Creatinine, calcium, albumin, bilirubin, ALP, ASAT, ALAT, LDH	X		optional		
Electrocardiogram	X		X	X	
PET-CT-scan	optional				
Tumor assessment by CT[1]	X		X	X	
TTE/UCG	X			X	
Spirometry[3]		X		X	
Assessment symptoms and toxicity	X		X	X	
QLQ[2]	X	X	X	X	

1. CT scan will be performed before inclusion (not older than 4 weeks), at 4, 7, 10 and 13 months after therapy and every 6 months thereafter during follow up or until progressive disease.
2. Quality of life will be measured by using QLQ C30 and LC14 module at baseline, week 3 of treatment, end of treatment ,1, 3, 6 and 12 months after completion of therapy. Thereafter at 2, 3 and 5 years after treatment.
3. Spirometry including CO diffusion capacity will be performed before inclusion, after 6 months and at end of study

8.0 Radiotherapy

All patients included in the study must be able to receive prescribed dose to the target volume without exceeding absorbed doses to the organs at risk. Dose planning shall be performed with a CT-based system. A 4DCT for the planning is mandatory and has to be repeated before start of treatment. If tumour motion exceeds 0.5 cm proton therapy will not be given. All patients needs to have a photon backup plan, preferably with IMRT/VMAT technique although 3DCRT is allowed. Treatment planning can be performed on either average CT from the 4D-CT or a regular CT. Slice thickness is to be maximally 3 mm. If the photon plan is superior to the proton plan, the photon plan is to be used and the patient will be excluded from the study and followed up according to the photon cohort protocol.

8.1 Fractionation and duration

Proton therapy will be given with pencil beam scanning (PBS) with proton energies in the range of 60 – 230 MeV at reference point according to ICRU 78.

For details on fractionation and treatment se section 5.3

Patients with a photon plan superior to the proton plan will receive fractionation and total dose according to local routine

8.2 Planning Target Volume

The different volumes of interest shall be defined in agreement with ICRU 78.

OAR's: heart, LADCA ,lung, spinal cord, esophagus

Gross Tumour Volume (**GTV**):

Visible tumour growth

Clinical Target Volume (**CTV**):

Post-operative tumour bed and/or defined margin to GTV: 0,5 cm to lung tissue and 1 cm elsewhere. Adjustment to airways, big vessels, bone will be performed. No adjuvant volumes, except for pleura/pericardium in between separate GTV's (stage IVa)

Internal Target Volume (**ITV**)

The ITV volume includes CTV in all breathing phases defined according to local routines

Planning Target Volume (**PTV**):

Includes ITV + 5 mm margin. PTV is used for dose prescription and reporting according to ICRU recommendations

The volumes of GTV, CTV, ITV and PTV shall be recorded in the CRF.

8.3 Doses to organs at risk

- Spinal cord

The maximum dose to the spinal cord is 48 Gy EQD2. The spinal cord shall be defined as the content of the spinal canal.

- Lung

Normal lung tissue is to be spared as much as possible. The volume of the lung (minus GTV) that should not receive doses above 20 Gy should be ≤ 35 % (V_{20} < 35 %). Dose-volumes histograms should be performed and the percentage of the lung volume minus GTV receiving a dose >5, >20 and >40 Gy as well as mean lung dose shall be recorded (V_5, V_{20}, V_{40}, MLD)

- Esophagus

The esophagus shall be delineated from the esophageal entrance to cardia. The mean dose should be < 45 Gy EQD2. The mean dose as well as the volume of the esophagus receiving > 50 Gy EQD2 (V_{50}) shall be recorded.

- Heart

The whole heart shall be delineated including the atriums and chambers but not the great vessels. No constraint is used, but the aim is to keep the dose as low as possible. Mean dose and volume receiving > 10 Gy EQD2 ,> 20 Gy EQD2 and > 40 Gy EQD2 (MHD, V_{10}, V_{20}, V_{40}) shall be recorded.

- LADCA

LADCA (Left Anterior Descending Coronary Artery) shall be delineated. No constraint will be used but $D_{2\%}$ and D_{mean} shall be recorded

8.4 OAR priority

Table 2 Prioritized dose volume objectives and constraints in EQD2

Priority	Volume	Objectives and constraints in biological dose Gy(RBE)	Objectives and constraints in physical dose Gy
1	Spinal cord	48	43.64
2	Lung (total)	V_{20} < 35 %	$V_{18.2}$ < 35 %
3	Esophagus	Mean dose < 45	Mean dose < 40.1
4	GTV	$D_{100\% >}$ 100 %	$D_{100\% >}$ 100 %
5	CTV / ITV	$D_{98\% >}$ 95 %	$D_{98\% >}$ 95 %
6	PTV*	$D_{2\% <}$ 105 % $D_{98\% >}$ 95 %	$D_{2\% <}$ 105 % $D_{98\% >}$ 95 %
7	Heart	As low as possible	
8	LADCA	As low as possible	

*****Dose volume objectives for PTV may be disregarded if other strategies like robust optimization are used to ensure CTV coverage

8.5 Treatment planning

<u>Treatment technique</u>

The radiation treatment can be given with protons or photons (3DCRT/IMRT/VMAT).

Dose computation and optimization

Dose calculation	Reference dosimetry is carried out according to the IAEA report TRS 398 (2000). The absorbed dose in the patient geometry shall be calculated by using validated algorithms. The calculation grid shall be at maximum 3 mm.

In order to facilitate the optimization procedure, help structures and volumes may be defined.

For proton treatments, see treatment planning and optimization guidelines in the Skandion Clinic treatment planning instruction manual (Delprocess 5 / Gör dosplanering och QA-plan och godkänn dosplan / Dosplaneringsmanual)

Treatment plan evaluation

A robustness test should be performed for each proton treatment in 12 test cases according to the recommendations in the Skandion Clinic treatment planning instruction manual (Delprocess 5 / Gör dosplanering och QA-plan och godkänn dosplan / Dosplaneringsmanual). Tolerance levels that should be fulfilled in the robustness test for treatments with the prescribed doses are described in table 2

Table 3. Tolerance levels that should be fulfilled in the robustness test. RBE value/model 1.10 is used.

	Tolerance levels
CTV: all test cases	$D_{98\%} \geq 90\%$
CTV: for at least 10 of 12 robustness test cases	$D_{98\%} \geq 95\%$
GTV: all test cases	$D_{95\%} \geq 100\%$
GTV: for at least 10 of 12 robustness test cases	$D_{98\%} \geq 100\%$
Spinal cord: all test cases	$V_{48\ Gy\ (RBE)} \leq 100\%$

DVH parameters of OARs used for definition of objectives and constraints (table 2)	According to clinical judgement

8.6 Patient monitoring before and during treatment

Before treatment starts patients will undergo a control 4D-CT at Skandion Clinic. If tumour motion exceeds 0.5 cm proton treatment will not be given and patient will receive the photon backup plan instead.

Image guided and adaptive treatment delivery

The position of the patient shall be verified based on MV imaging, CBCT, kV imaging and/or surface imaging.

For photons, the position of the patient shall be verified daily, or at least the first 3 days and then weekly during the treatment. A statistical analysis shall be performed after the first 3 treatments. Based on the analysis, the treatment delivery shall be adapted according to protocol for corrective action.

For protons daily imaging is required. Patient weight will be controlled once a week. If weight loss/gain > 5% a control CT will be performed at Skandion Clinic, otherwise control CT will be performed weekly with the possibility to re-plan if the difference between the dose distribution of the original treatment plan and the dose distribution based on this new CT is not in accordance with the tolerance levels specified for the robustness test (see table 3).

8.7 Interruption of radiotherapy

After radiotherapy starts, efforts should be made to avoid interruptions in the planned schedule. If an interruption must be made due to technical or administrative reasons the following policy will be applied. At least four fractions a week must be given. If this is not possible with protons the photon backup plan must be used. Try to maintain the total treatment time as close to 5 weeks as possible.

8.8 Quality assurance

The absorbed dose to the patient shall be estimated based on in vivo measurements according to clinical routine procedures. If in-vivo dosimetry is not applicable, pre-treatment patient specific quality assurance (QA) must be performed.

Treatment plan parameters should be recorded for quality assurance purposes. The volume of GTV and PTV should be registered as well as dose/volume-parameters to organs at risk: Lung: V5, V20, V40, MLD. Esophagus: V60, V80, mean dose. Heart: V10, V20, V40, mean dose, Spinal cord: Dmax.

9 Adverse events

9.1 Definition

Adverse events (or adverse experience) (AE):

An AE is any untoward medical occurrence in a subject or clinical investigation subject treated within a study protocol and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the radiation treatment, whether or not considered related to the radiotherapy

Due to regulatory requirements, events occurring during pre- and post-treatment periods should also be designated as AEs. Therefore, safety surveillance - reporting of (S)AEs - commences at the time when the subject is enrolled into the study (date of signature of the informed consent) until the End of Study Visit has been performed.

Serious adverse event or reaction/experience (SAE):

- A serious AE (experience) or reaction is any untoward medical occurrence that at any dose:
- Results in death
- Is life-threatening
- **NOTE:** The term ”life-threatening” in the definition of ”serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity

- Is a congenital anomaly/birth defect or
- Is an important medical event

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in cases of important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

Examples of such events are intensive treatment in an emergency room, or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse, or malignant tumors when they are histologically different from the primary tumor.

Events not to be treated as SAEs

Progression of disease is not to be regarded as a SAE.

Due to the seriousness of the disease in this study, certain conditions defined as SAEs will be excluded from expedited reporting on a SAE report form:

- Elective hospitalization and surgery for treatment of disease
- Elective hospitalization to simplify treatment or study procedures

9.2 Recording of Adverse Events

All AEs must be documented in the appropriate section of the CRF. For SAEs, a SAE report form (initial or follow up) must be completed in addition.

The following aspects must be recorded for each event in the CRF:

- A description of the AE in medical terms, not as reported by the subject;
- The date of onset (start date)
- The date of recovery (stop date)

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately on the Adverse Event module of the CRFs using the CTCAE Version 4.0

A written version will be available at each study site, see also. CTCAEv4.0. Version 4.0 http://ctep.cancer.gov/reporting/ctc.html

Serious adverse events should be noted on the Serious Adverse Event Report form.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilisation or until it has been determined that study treatment or participation is not the cause. Serious adverse events, which are still ongoing at the end of the study period, must be followed up to determine the final outcome.

Any serious adverse event, which occurs after the study period and is considered to be possibly related to study treatment or study participation should be recorded and reported immediately.

The grade as assessed by the investigator according to the definitions in CTCAE v4.0.

Grade 1 = mild

Grade 2 = moderate

Grade 3 = severe

Grade 4 = life-threatening or disabling

Grade 5 = death related to AE

- The causal relationship to therapy as assessed by the investigator; the decisive factor in the documentation is the temporal relation between the AE and the study drug. The following judgments of the causality to study procedures are to be used:

  Not Related; There is not a temporal relationship to study treatment.

  Not Likely; There is a temporal relationship to study treatment, but there is not a reasonable causal relationship between the treatment and the AE.

  Possible; there is a reasonable causal relationship between the study treatment and the AE.

  Probable; there is a reasonable causal relationship between the study treatment and the AE.

  Certain/Definite; there is a reasonable causal relationship between the study treatment and the AE. Action taken (none, treatment discontinued, dose reduction, treatment delayed, concomitant medication given, new or prolonged hospitalization, procedural surgery).

- The outcome according to the following definitions:

- Recovered with sequelae.
- Recovered without sequelae.
- Ongoing, no therapy.
- Ongoing, therapy.
- Died.
- Change in toxicity grade/severity.

- Seriousness: yes or no
- In case of SAEs it must be indicated whether the SAE is the leading event, i.e. the primary medical reason for SAE reporting.

9.3 Reporting of Serious Adverse Events

In the event of the occurrence of any clinical AE or abnormal laboratory test value that is serious or medically important during the course of the study or the post-treatment period, irrespective of the treatment received by the subject, the co-investigator is obliged to immediately inform the Investigator-Sponsor.

The immediate report by the co-investigator to the Investigator shall be followed by detailed, written reports using the SAE report form (for an “initial” SAE or for “follow-up” information on a previous SAE). The immediate and follow up reports shall identify subjects by unique code numbers assigned to the latter.

For names, addresses, telephone and fax numbers, see below.

If the adverse event is life-threatening or results in death it should be recorded and reported as soon as possible or within 7 days and for all other suspected serious unexpected adverse reaction shall be recorded and reported as soon as possible but within a maximum of fifteen days of the first knowledge. The Investigator shall ensure that for a reported death of a subject, the investigator shall supply the Ethics Committee with any additional information as requested.

A copy of the reports to the Regulatory Authorities and Ethics committees should be sent to the Investigator (principal investigator), Hillevi Rylander fax no: 0046 31 823931.

Annually throughout the clinical trial, the Investigator shall provide the local Regulatory Authority, Ethics committee, with a listing of all suspected serious adverse reactions which have occurred over this period and a report of the subject´s safety.

The finally listing and report will be 60 days after data-lock point.

9.4 Monitoring of subjects with adverse events

Any AE that occurs in the course of a clinical study must be monitored and followed up until the End of Study Visit. In addition SAEs must be reported via a SAE report form (see section 9.3 Reporting of serious adverse events).

It is the responsibility of the investigator that any necessary additional therapeutic measures and follow-up procedures are performed.

9.5 Patient Removal from Study Therapy due to Adverse Events

Any subject who experiences an adverse event may be withdrawn at any time from the study at the discretion of the investigator.

If a subject is withdrawn wholly or in part because of an adverse event, this should be noted on the Study treatment form in addition to the Adverse Event section. The monitor should be informed without delay of all subjects who are withdrawn for this reason.

9.6 Death on Study

Any death occurring between the study inclusion and 30 days following the last radiotherapy treatment must be reported as a SAE within 7 days, regardless of the relation to the radiotherapy. Death occurring during the study follow-up period (i.e. later than 30 days after the last infusion) need only to be reported as serious adverse event if it is thought that there is a possible relation to the radiotherapy (possible, probable). All deaths should be reported on the death report form section on the CRF regardless of cause.

10.1 RECIST 1.1 criteria for response

Complete response (CR): Disappearance of all clinical evidence of tumor (target and non-target lesions), determined by two observations not less than four weeks apart.

Partial response (PR): 30% or greater decrease in the sum of the longest diameter of target lesions, determined by two observations not less than 4 weeks apart. No unequivocal increase in the size of non-target lesions or the appearance of new lesions may occur.

Stable disease (SD): Steady state of response (i.e. not PR and not PD) of at least 9 weeks duration. There may be no appearance of new lesions for this category.

Progressive disease (PD): 20% or greater increase in the sum of the longest diameter of target lesions or unequivocal progression of non-target lesions. Appearance of new lesions will also constitute progressive disease.

The duration of response will be measured from the time measurement criteria are met for CR/PR until the first date the recurrent or progressive disease is objectively documented.

10.2 Safety analysis

A safety analysis regarding toxicity will be performed by the principal investigator after inclusion of 15 subjects. The analysis will be focused on the frequency of unwanted side effects and their severity.

10.3 Quality of life analysis

Quality of life will be measured by using QLQ C30 and LC14 module at baseline, week 3 of treatment, end of treatment ,1, 3, 6 and 12 months after completion of therapy. Thereafter at 2, 3 and 5 years after treatment.

11.0 Statistics

We will perform a Kaplan-Meier analysis with the aim to compare our data with published historic data from the ITMIG international database and other datasets. Since there is a limited amount of published thymoma data concerning heart we will also try to relate heart toxicity with published data from Hodgkin and breast cancer studies. Toxicity data will be analysed descriptively and there will be a comparison between the proton patients and photon control group. 40 patients will be included in the study

12.0 Publication

The aim is that the study will be published in international journals**.** A separate publication will include result of the cardiological data

The Vancouver declaration (Br Med J:296, 401-405, 1988) should be followed in all publications based on this study.

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14.0 Appendix

Appendix 14.1

PROTHYM - TRANSTHORACIC ECHOCARDIOGRAM (TTE) PROTOCOL

Image sampling is performed by a biomedical scientist or cardiologist at the local hospital. The examination is thereafter transferred (by CD/DVD) for evaluation by study responsible cardiologist**.**

To be noticed and listed:

Age

Gender

Length (cm) and weight (kg) of the patient

Heart rate (per minute)

Arrhythmias (all kind of arrhythmias should be documented)

Long axis:

1. Left ventricle end-diastolic diameter (LVEDD)
2. Left ventricle outflow tract diameter (zoom LVOT)
3. Aortic valve color
4. Mitral valve color
5. Ascending aorta (diameter)

Short axis:

1. Left ventricle mid-section view
2. Left ventricle M-MODE (just below the mitral valve)
3. Aorta mid-section view (valve morphology)
4. Pulmonary valve: color and doppler CW+PW

4CH:

1. 4 Chamber view (motion)
2. Left ventricle zoom (motion/volume)
3. Atrium size (Right atrium / Left atrium)
4. Pulmonary vein: doppler PW (for S/D measure)
5. Mitral valve: color and doppler CW+PW (for E/A measure)
6. Aortic valve: color and doppler CW+PW (for VTI measure)
7. Tricuspidal valve: color and doppler CW (gradient)
8. Tissue doppler (1. Lateral RV, 2. Septum, 3. Lateral LV)

2CH:

1. 2 Chamber view (motion)
2. Left ventricle zoom (motion/volume)

3CH:

1. 3 Chamber view (motion)

Subcostal view:

1. 4 Chamber view
2. Vena Cava diameter and variation during sniffing (central vein pressure)

Appendix 14.2

Performance Status: WHO = Zubrod = ECOG

Activity Status	Description
0	Asymptomatic, fully active, and able to carry on all predisease performance without restrictions.
1	Symptomatic, fully ambulatory but restricted in physically strenuous activity and able to carry out performance of a light or sedentary nature, eg, light housework, office work.
2	Symptomatic, ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours: in bed less than 50% of day.
3	Symptomatic, capable of only limited self-care, confined to bed or chair more than 50% of waking hours, but not bedridden.
4	Completely disabled. Cannot carry on any self-care. Totally bedridden.
5	Dead

Appendix 14.3

CTC version 4.0

Adverse event	1	2	3	4	5
Dysphagia	Symptomatic, able to eat regular diet	Symptomatic and altered eating/swallowing	Severely altered eating/ swallowing, tube feeding or TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	death
Esophagitis	Asymptomatic, clinical or diagnostic observations only; interventions not indicated	Symptomatic, altered eating/swallowing; oral supplements indicated	Severely altered eating/ swallowing, tube feeding or TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	death
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN or hospitalization indicated	-	-
Fatigue	Fatigue relieved by rest	Fatigue not relieved by rest, limiting instrumental ADL	Fatigue not relieved by rest, limiting sel care ADL	-	-
Cough	Mild symptoms; non-prescription intervention indicated	Moderate symptoms, medical intervention indicated; limiting instrumental ADL	Severe symptoms, limiting self care ADL	-	-
Dyspnea	Shortness of breath with moderate exertion	Shortness of breath with minimal exertion; limiting instrumental ADL	Shortness of breath at rest; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	death
Pneumonitis	Asymptomatic, clinical or diagnostic observations only; interventions not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms, limiting self care ADL; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (e.g.tracheotomy or intubation)	death

Febrile neutropenia	-	-	present	Life-threatening consequences; urgent intervention indicated	death

Appendix 14.4

Masaoka-Koga Staging System

Stage	Definition
I	Grossly and microscopically completely encapsulated tumour
IIa	Macroscopic transcapsular invasion
IIb	Macroscopic invasion into thymic or surrounding fatty tissue, or grossly adherent to but not breaking through mediastinal pleura or pericardium
III	Macroscopic invasion into neighboring organ (ie pericardium, great vessel, or lung)
IVa	Pleural or pericardial metastases
IVb	Lymphogenous or hematogenous metastasis

Adapted from *Pathol Int* 1994;44:359-367

Appendix 14.5

World Health Organization Classification of Thymoma

Type	Histological Description
A	Medullary thymoma
AB	Mixed thymoma
B1	Predominantly cortical thymoma
B2	Cortical thymoma
B3	Well-differentiated thymic carcinoma