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# A Randomized Phase II Study Comparing Two Schedules of Hyperfractionated Thoracic Radiotherapy in Limited Disease Small-Cell Lung Cancer


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# 1 Background

## Small cell lung cancer

Lung cancer is one of the most common cancers malignant diseases and the most common cause of cancer-related deaths. In Norway, 2 842 new cases were diagnosed and 2 184 patients died from lung cancer in 2011.[1]

Small-cell lung cancer (SCLC) accounts for approx. 14 % of the cases. Untreated, it is usually an aggressive disease with a poor prognosis (2-3 months). SCLC metastasizes more frequently than other types of lung cancer. Up to 90 % of patients respond to therapy, but most experience relapse, and SCLC accounts for approx. 4 % of all cancer-related deaths.[2-4]

## Treatment of SCLC

Patients with localized disease can be cured through surgery, but very few (approx. 5 patients per year in Norway) are operable.[5] Thus, chemotherapy is the basic treatment for almost all patients with SCLC.[2] A previous study by the Norwegian Lung Cancer Study Group has been central in establishing cisplatin plus etoposide as the standard regimen.[3]

Concurrent chemotherapy and thoracic radiotherapy (TRT) is superior to chemotherapy alone when all lesions can be included in a radiotherapy field (limited disease, "LD SCLC").[6] Chemotherapy alone is the standard treatment for patients with more widespread disease (extended disease, "ED SCLC").[2] Prophylactic cranial irradiation (PCI) reduces the frequency of brain metastases and prolongs survival in patients who respond to the primary treatment.[7,8]

## Thoracic radiotherapy

The optimal regimen for thoracic radiotherapy (TRT) is debated. Best results have been observed in a study by Turrisi et al. comparing twice-daily hyperfractionated TRT 45 Gy in 30 fractions (two fractions per day - BID) with 45 Gy in 25 fractions – one fraction per day (OD),[4] but standard therapy in Norway and in other countries has still been 40-42 Gy in 15 fractions (OD).[3,9] A meta-analysis concluded that shorter TRT treatment time is superior to longer treatment time,[10] and in the Turrisi-study, the treatment time in the hyper-fractionated arm was 3 weeks vs. 5 weeks in the control-arm. Two fractions per day is time-consuming for patients and resource demanding. Furthermore, two fractions per day resulted in more dysphagia; and in another study, there was no benefit of hyper-fractionation.[11] An important limitation of the latter study was that a split-course regimen was used.

The NLCG has conducted a study comparing 42 Gy in 15 fractions (OD) with 45 Gy in 30 fractions (BID). The study aimed at exploring whether there were indications of a benefit of twice-daily TRT and to compare toxicity from the two TRT-regimens. Preliminary results indicate that the twice-daily regimen is superior (median overall survival: 18.8 vs. 24.7 months; 2-year survival: 41 % vs. 53 %). The patients reported slightly more dysphagia, but the difference was very small.[12] Thus, the NLCG has concluded that based on this and other studies, 45 Gy in 30 fractions (BID) is the standard TRT regimen.

Twice-daily TRT reduces the risk of local failure, but 36 % still experience local recurrence. Improved local control appears to be correlated with better survival. Despite being a chemosensitive disease, dose-intensified chemotherapy has failed to prolong survival.[2] Thus, improved TRT appears to be the best strategy for improving local control and survival rates in LD SCLC. Studies have demonstrated that 70 Gy (OD, 2 Gy per fraction) and 60 Gy (BID, 1.5 Gy per fraction) are tolerable,[13,14] but none of these regimens have been compared with 45 Gy in 30 fractions (BID) in a prospective, randomized study.

## Target volume definition

The definition of target volumes is also debated. In principle, TRT targets bulky disease, and chemotherapy micrometastases. Traditionally – and in our previous study – known lesions plus the mediastinum have been irradiated.[2,12] The challenge is that the volumes can be large, and the doses to risk organs might exceed normal tissue tolerance – especially if the dose is increased to 60 Gy.

Recent studies suggest that PET CT is superior to CT for assessment of extent of disease,[15,16] and that elective nodal irradiation can be omitted if all PET positive lymph nodes are irradiated - the incidence of isolated mediastinal nodal failure is < 3 %.[17,18] A more accurate localization of lesions will reduce the volume of irradiated normal tissue and reduce side-effects of TRT.

### Prognostic and predictive factors

Most patients with LD SCLC (up to 90 %) respond to chemo-radiotherapy. However, many experience severe side-effects and recurrent disease. Few prognostic factors other than performance status have been identified. More knowledge about what characterizes those who respond well and long - and tolerate chemoradiotherapy is needed; in order to improve classification of patients with LD SCLC and ultimately better individualize therapy to improve efficacy and avoid severe toxicity.

## 2 Rationale for the study

The majority of patients with LD SCLC experience recurrent disease despite receiving concurrent chemoradiotherapy. New agents and dose-escalation of chemotherapy have not provided a survival benefit. Local failure accounts for high proportion of recurrences. Improved TRT might increase local control and thus reduce the recurrence rate and prolong survival. A large proportion of patients relapse and die within one and two year after therapy. Few patients survive longer than three years. Thus, two-year survival is considered a clinically highly relevant measure of efficacy.

## 3 Aims of the study

To compare two schedules of TRT with respect to local control, progression free survival, overall survival, toxicity and health-related quality of life. To characterize the patients who have the best outcomes and tolerate chemoradiotherapy (e.g. clinical characteristics, blood biomarkers, body composition).

### Primary endpoint

- 2-year survival

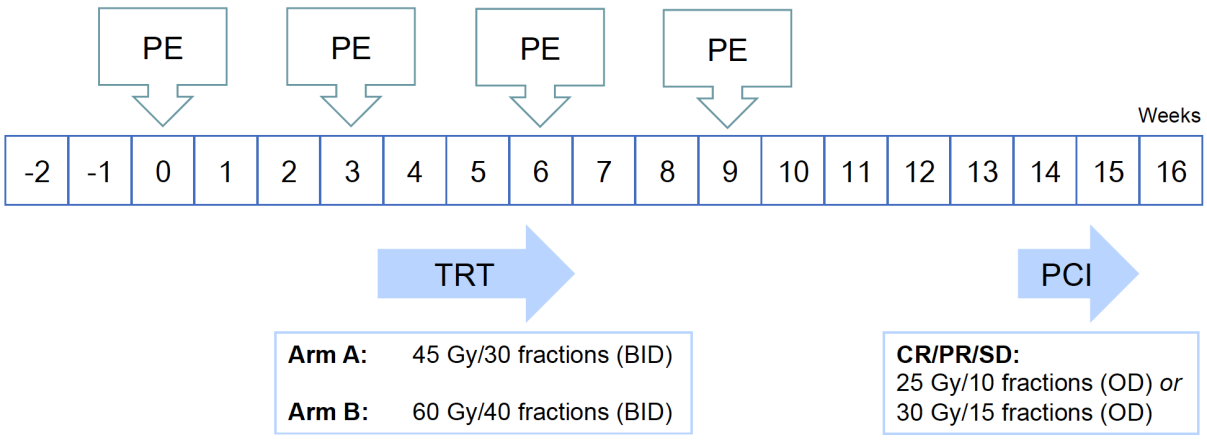
### Secondary endpoints

- Response rates
- Progression free survival
- Local control
- Overall survival
- Toxicity
- Health related quality of life

### Exploratory analyses

- Overall survival, toxicity, health related quality of life in elderly (≥ 70 years) and PS 2 patients
- Prognostic and predictive role of clinical characteristics (e.g. stage, gender, extent of disease, weight loss, PS, body muscle mass, HRQoL-scores) and blood biomarkers in relation to outcomes of therapy, course of disease, symptom development and HRQoL.
- Development of disease- and treatment related symptoms and changes in body composition

## 4 Trial design



## Trial plan – study treatment

| Week | -4/-2* - 0 | 0 | 3 | 4 | 6 | 6-8 | 9 | 12 | 15 | 16 |
|---|---|---|---|---|---|---|---|---|---|---|
| **Study treatment** | Inclusion* | PE1 | PE2 | Start TRT** | PE3 | End TRT | PE4 | Evaluation | Start PCI | End PCI |
| **Informed consent** | X | | | | | | | | | |
| **Medical history** | X | | | | | | | | | |
| **Clinical examination/ECOG PS/weight** | X | X | X | | X | X | X | X | | X |
| **Hematology,[a] creatinine[b]** | X | | X | | X | | X | X | | |
| **Pulmonary function** | X | | | | | | | X | | |
| **Biochemistry[c]** | X | | X | | | | | X | | |
| **Blood for biomarkers** | X | | | X | | | | X | | |
| **HRQoL + PGSGA + G8** | X | | | X | | X | | X | | X |
| **Timed-up-and-go and 5 meter walk test** | X | | | | | | | X | | |
| **PET CT** | X | | | | | | | | | |
| **MR caput** | X | | | | | | | | | |
| **CT thorax/abdomen** | (X) | | | | | | | X | | |

*All imaging has to be performed within 4 weeks of the first course of chemotherapy. All other assessments should be performed within 2 weeks of the first course of chemotherapy
**Provided accordance with all study procedures and timelines, randomization can be performed until the time of start of TRT.
^Only plasma, serum and blood

## Trial plan – follow up

| Year | 1 | | | | 2 | | | | 3 | | | | 4 | | 5 | | PD |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Week** | 22 | 32 | 42 | 52 | 13 | 26 | 39 | 52 | 13 | 26 | 39 | 52 | 26 | 52 | 26 | 52 | |
| **Clinical examination** | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| **ECOG PS, weight** | | | | | | | | | | | | | | | | | |
| **HRQoL + PGSGA + G8** | | | | | | | | | | | | | | | | | |
| **CT thorax/ abdomen** | | | | | | | | | | | | | | | | | |
| **NSE, pro-GRP, CRP, albumin** | | | | | | | | | | | | | | | | | |
| **Timed-up-and-go and 5 meter walk test** | | | | | | | | | | | | | | | | | |
| **Blood for biomarkers** | | X | | X | | | | X | | | | | | | | | X |

[a]Haemoglobin, leucocytes, absolute neutrophil count, platelets on days 1 and 10 of every chemotherapy-cycle
[b]Creatinine
[b]bilirubin, ALT, LD, albumin, CRP, NSE, proGRP

# 5 Study treatment

## Chemotherapy

All patients will receive up up to four courses of cisplatin 75 mg/m$^2$ BSA IV day 1 and etoposide 100 mg/m$^2$ BSA IV day 1-3. Chemotherapy is discontinued in case of radiological progression according to RECIST 1.1, unacceptable toxicity or if a patient qualifies for a third dose reduction of chemotherapy.

**Day 1:**

- Prehydration 1000 ml 0.9 % NaCl IV over 2 hours
- Etoposide is diluted in 500 ml 0.9 % NaCl and infused over 30 minutes parallel with the last half hour of prehydration
- Cisplatin is diluted in 1000 ml 0.9 % Nacl and infused over 2 hours
- Posthydration 1000 ml 0.9 % NaCl IV over 2 hours

**Day 2-3:**

- Etoposide is diluted in 500 ml 0.9 % NaCl and infused over 30 minutes.

**Minimum antiemetic medication**

Day 1:

- 5-HT3 antagonist IV minimum 5 minutes before infusion of chemotherapy
- Dexamethason 8 mg IV (or equivalent dose of other corticosteroid)

Day 2-3:

- Metoclopramid 10 mg x 3 PO
- 5-HT3 antagonist IV minimum 5 minutes before infusion of chemotherapy if needed

Other anti-emetic therapy can be administered according to each hospital's routines (e.g. apripetant)

## Dose-adjustments, use of growth factors and replacing cisplatin with carboplatin

Recommendations before a new course of chemotherapy:

- All grade 3-4 adverse events should have resolved to grade 0-2 or to the same level as before the preceding course of chemotherapy
- ANC ≥ 1.5 x $10^9$/L and platelets ≥ 100 x $10^9$/L. Lower values might be acceptable if the nadir-phase has passed.
- Creatinine < 125 µmol/litre (if creatinine ≥ 125 µmol/litre, cisplatin should be replaced with carboplatin. See below.)

Recommendations for dose adjustments:

- In case of grade 4 neutropenia (< 0.5 x $10^9$/L), grade 4 thrombocytopenia (< 50 x $10^9$/L) or febrile neutropenia (< 1.0 x $10^9$/L, fever and treatment with antibiotics) after the preceding course the doses for the next course should be reduced to 80 % of the preceding course.
- If ANC < 1.5 x $10^9$/L or platelets < 100 x $10^9$/L on day 22 (day for the next course), the next course should be delayed until resolution of cytopenia. A dose reduction of 20% should be considered if a course is postponed more than a week.
- If a course is postponed more than three weeks, chemotherapy should be discontinued.
- Chemotherapy should be discontinued if radiological progression according to RECIST 1.1 occurs.

Use of erythropoietin for anemia is not allowed. Blood transfusions are allowed according to each hospital's routines. Hemoglobin should be > 10 g/dl during TRT.

Use of G-CSF for neutropenia is not allowed. In a study of chemoradiotherapy in LD SCLC, patients who received GM-CSF experienced more toxicity than other patients.[19]

Cisplatin should be replaced with carboplatin in case of elevation of creatinine (> 125 µmol/litre). Consider replacing cisplatin with carboplatin in case of severe non-hematological toxicity considered

related to cisplatin. The dose of carboplatin should be AUC=5-6 (Calvert's formula) at the investigators discretion, depending on the type and severity of toxicity.

## Thoracic radiotherapy

**Timing:**
Thoracic radiotherapy should start 20-28 days after the first day of the first course of PE chemotherapy – regardless of whether the second course of PE is delayed or not. Administering one course of chemotherapy before start of TRT often reduces the volume of lesions. Another advantage is that there is more time to refer to and plan TRT.

**Doses:**
Patients will be randomized to receive (Arm A) 45 Gy in 30 fractions or (Arm B) 60 Gy in 40 fractions stratifying for PS (0-1 vs. 2) and presence of pleural fluid (yes vs. no; no lower limit). All patients will receive two fractions per day, 5 days per week. Time between the fractions should be > 6 hours.

The aim is to deliver 60 Gy to all patients on Arm B. If the dose to risk organs exceeds the recommended levels, investigators should contact the protocol committee. A video-conference will be arranged within two working days. All investigators will be notified and invited to participate. If no solutions are found during the videconference, the dose should be lowered. If a dose of ≥ 54 Gy cannot be delivered, the patient goes off study.

**Arm A:**
The optimal treatment time is 19 days including week-ends. If the treatment exceeds 22 days, a compensation should be considered according to each department's routines. The treatment time will be recorded.

**Arm B:**
The optimal treatment time is 26 days (60 Gy) including week-ends. If the treatment exceeds 29 days, a compensation should be considered according to each department's routines. The treatment time will be recorded.

Compensation should be made by:

- treatment on a weekend day (preferred option)
- increased doses of the remaining fractions. Fraction-dose should not exceed 2 Gy.

All interruptions or delays will be recorded.

**CT for doseplan**
IV contrast should be administered.

**Target volume definitions:**
GTV:

- Primary lung tumor ($GTV_{primary\ tumor}$) and all lymph node metastases ($GTV_{lymph\ nodes}$) defined as all PET positive lymph nodes and lymph nodes described as possibly affected (even in case of complete response after first PE)
- Size of GTV's is defined as on CT scan just prior to TRT (after the first course of PE) using "Lung window" on CT image for tumor in lung parenchyma and "soft tissue window" for mediastinal tumor

$CTV_{primary\ tumor}$:

- $GTV_{primary\ tumor}$ + 0.5 cm in all directions – but not into bony structures, large vessels or heart provided no signs of invasion of these structures

$CTV_{lymph\ nodes}$:

- $GTV_{lymph\ nodes}$ + 0.5 cm in all directions – but not into mediastinal pleura parietale or bony structures, large vessels or heart provided no signs of invasion of these structures.
- In case of no PET positive lymph nodes, the hilum or mediastinum will not be irradiated

ITV:
If available, a 4D-CT should be used to define margins to ITV according to each department's routines. If not available, the following margins are recommended:

- $CTV_{primary\ tumor}$ + 0.8 cm laterally/anterior/posterior direction
- $CTV_{primary\ tumor}$ + 1 cm superiorly and inferiorly
- $CTV_{lymph\ nodes}$ + 0.5 cm in all directions

When using respiratory gating or IGRT, these margins will be defined according to each departments' routines.

PTV:

- Defined according to each department's routines

**Organs at risk:**

- The following organs should be contoured: Both lungs, the spinal cord (the spinal canal should be contoured as PRV), the heart and the esophagus (from just below the larynx to the gastric-esophageal junction).

- The mean lung dose (volume of both lungs together minus $GTV_{primary\ tumor}$ ) is not to exceed 20Gy. $V_{20\ Gy}$ lung should preferably not exceed 35% and $V_{5\ Gy}$ should preferably not exceed 65%.

- The maximum dose to the spinal cord is 54Gy (see appendix)

- The mean heart dose should preferably not exceed 35Gy and is not to exceed 46Gy. $V_{40\ Gy}$ should preferably not exceed 80%, $V_{45\ Gy}$ should preferably not exceed 60% and $V_{60\ Gy}$ should preferably not exceed 30%.

- A maximum dose of 60Gy to the esophagus is acceptable, but should preferably be lower if a certain field arrangement can accomplish that. The mean esophageal dose should preferably not exceed 34Gy.

- A maximum dose of 60Gy to the brachial plexus is acceptable, but should preferably be lower if a certain field arrangement can accomplish that.

If these conditions cannot be met, the dose-plan should be discussed with the protocol committee. A videoconference will be arranged within two working days. If these conditions still cannot be met – or a videconference cannot be arranged within this time-frame, the total dose on arm B can be lowered to ≥ 54 Gy. If the conditions are still not met, the patient will be off study and treated according to the department's routines.

**Central review:**
A complete treatment radiotherapy plan should be sent to the central study office for review.

**Assessment of toxicity:**

- To be performed before start of TRT, then every week and by the end of TRT (within 2 days before or after the last day of TRT).
- In case of grade 3-4 toxicity, the patients should be followed at least once per week until toxicity has resolved to the same level as before TRT – or to grade 2 or less

### Prophylactic cranial irradiation

2-3 weeks after the last course of PE, response should be evaluated on a CT scan according to RECIST 1.1. Patients with CR/PR/SD should receive PCI 2.5 Gy x 10 to the whole brain, 5 fractions per week. PCI should start within 6 weeks of the last course of PE.

## 6 Statistical considerations

### Sample size calculation

In our previous study of LD SCLC, 2-year OS for those who received 45 Gy/30 fractions was 53 %. The aim of the study is to provide an estimate of a potential survival benefit of high-dose hyperfractionated TRT. We consider a 25 % improvement in 2-year survival to be of clinical relevance.

To show an improvement in 2-year OS of 25 % (from 53 % to 66 %) with a one-tailed α=.10 and β=.20, 73 patients are required on each arm. We expect a drop-out rate and enrolment of ineligible patients of maximum 5 %, and aim to enrol a total of 154 patients.

### Enrolment plan

Based on experience from our previous study, we expect to enrol 35-40 patients a year. The first patient will be enrolled in Q4 2013, and according to our schedule, the last patient should be randomized by the end of Q4 2019. All patients will be followed for 24 months, and we aim at completing follow-up in Q4 2021.

# 7 Eligibility criteria

1. Histologically or cytologically confirmed small-cell lung cancer
2. No prior systemic therapy for SCLC
3. Previous radiotherapy to the thorax is not allowed
4. Limited disease (stage II-III)
5. Stage I if ineligible for surgery
6. Age ≥ 18 years
7. ECOG Performance 0-2
8. Measureable disease according to the RECIST 1.1
9. Adequate organ function defined as:
    a. Serum serum alanine transaminase (ALT) ≤ 3 x upper limit of normal (ULN)
    b. Total serum bilirubin ≤ 1.5 x ULN
    c. Absolute neutrophil count (ANC) ≥ 1.5 x $10^9$/L
    d. Platelets ≥ 100 x $10^9$/L
    e. Creatinine < 100 µmol/L and calculated creatinine-clearance > 50 ml/min. If calculated creatinine-clearance is < 50 ml/min, an EDTA clearance should be performed.
10. No malignant cells in pericardial or pleural fluid (at least one sample should be analysed if pleural fluid is present)
11. Pulmonary function: FEV1 > 1 l or > 30 % of predicted value and DLCO > 30 % of predicted value
12. No serious concomitant systemic disorders (for example active infection, unstable cardiovascular disease) that in the opinion of the investigator would compromise the patient's ability to complete the study or interfere with the evaluation of the efficacy and safety of the study treatment
13. No conditions – medical, social, psychological – which could prevent adequate information and follow-up
14. No clinically active cancer other than SCLC. Hormonal therapy for prostate cancer or breast cancer and basocellular carcinoma of the skin is allowed.
15. No pregnancy or lactating women
16. All fertile patients should use safe contraception
17. Written informed consent

# 8 Assessments

All imaging should be performed within 4 weeks before the first course of chemotherapy. All other assessments should be performed within 2 weeks of the first course of chemotherapy.

- Weight, height, weight loss last 3 and 6 months, pain
- Medical history, medication, smoking history
- Clinical examination, ECOG performance status
- Extent of disease
- Pulmonary function
- CT scan (thorax and upper abdomen including L2 of the column)
- MRI of the brain
- Whole body PET CT
- Blood samples: Haemoglobin, leucocytes, absolute neutrophils count, platelets, bilirubin, ALT, LD, albumin, creatinine, CRP, NSE and proGRP
- Blood samples for biomarker analyses
- HRQoL reported on the EORTC QLQ-C30 + LC-30, PG-SGA for assessment of nutritional status and G8 for assessment of geriatric functional status
- Pregnancy test (fertile women only)

# 9 Evaluation and follow-up

### Survival

**OS (Overall survival)** is measured from the date of the first day of the first course of chemotherapy until the date of death from any cause (or last contact/observation if lost to follow-up – or the follow-up is completed before all patients die).

**PFS (Progression free survival)** is measured from the date of the first day of the first course of PE to the first date of objective progression (according to RECIST 1.1) of disease or of death from any cause.
For each patient who has not died or has non-progression at the cut-off date for the analysis, PFS will be censored at the date of the patient's last tumor assessment prior to the cut-off date. Statistical survival analyses will be done with Kaplan Meier. Log rank test will be used for comparing groups.

### Patients reported outcomes (health related quality of life, nutritional status and geriatric functional status)

HRQoL will be assessed using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) C30 and the lung cancer specific module LC13. The QLQ-C30 measures fundamental aspects of HRQoL and symptoms commonly reported by cancer patients in general, the LC13 measures symptoms commonly associated with lung cancer and its treatment.

The Patient-Generated Subjective Global Assessment (PG-SGA) has been validated for assessment of nutritionalt status in general – and in cancer patients.

The G8 is used to identify patients who would benefit from a comprehensive geriatric assessment and is correlated with geriatric functional status.

Aquestionnaire for assessment of PG SGA and G8 has been developed.

The patients will report HRQoL, PG SGA and G8 status:

- at inclusion
- within 1 week before start of and within 1 week after end of TRT
- at evaluation 3 weeks after the fourth course of PE
- within 1 week after end of PCI
- at follow-up every 3 months until 36 months after start of chemotherapy. Then every 6 months until 5 year after start of therapy.

All HRQoL scores will be transformed to a scale from 0 to 100 according to the EORTC scoring manual. A difference in mean scores of >10 is considered clinically relevant. For group comparisons of baseline scores during and after chemotherapy, and changes in scores from baseline, the Mann–Whitney test will be used. Primary HRQoL-endpoints are dysphagia and dyspnea. Other exploratory HRQoL-analyses will be conducted.

### Toxicity

Toxicity will be assessed from reported blood values and adverse event. Toxicity will be classified and graded according to CTCAE 4.0. Toxicity will be compared using Pearson's Chi-square and Fischer's exact tests.

### Radiological evaluation of response

All CT scans should include the level of the 3$^{rd}$ lumbar vertebra. At this level, the whole body contour should be included.

Response will be assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.

**Measurable disease:**

- Presence of al least one measurable lesion.

**Measurable lesions:**

- Lesions that can be measured in at least one dimension with longest diameter ≥10 mm (by CT scan). Lymph nodes must have a short axis ≥15mm.

**Non-measurable lesions:**

- All other lesions including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 mm to <15 mm short axis.
- Lesions considered truly not measurable: bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphatic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by CT/MRI.
- Previously irradiated lesions
- Skin lesions assessed by clinical examination
- Brain metastases

The same method of assessment and the same technique should be used to characterize each lesion at baseline and during follow-up.

**Target lesions:**

- A maximum of 5 measurable lesions (maximum 2 per organ), representative of all involved organs and suitable for accurate repetitive measurements should be identified and measured as target lesions (TL) at baseline.

**Non-target lesions:**

- All other lesions (or sites of disease) should be identified as non-target lesions and recorded at baseline. Measurment are not required and these lesions should be followed as “present” or “absent”.

**Sum of the longest diameter (SoD):**

- A sum of all target lesions (maximum 5) will be calculated and reported as the baseline SoD. The baseline SoD will be used for further assessments of objective tumor response.
- If a lesion has completely disappeared, the longest diameter should be recorded as 0 mm.
- If a lesion is considered too small to measure but present, a default value of 5 mm should be applied. (If measurable the accurate value should be recorded even if <5mm).

**Evaluation of target lesions**

| | |
|---|---|
| Complete Response (CR) | Disappearance of all target lesions. All pathological lymph nodes selected as TL must have a reduction in short axis to <10 mm. |
| Partial Response (PR) | At least a 30% decrease in the SoD of target lesions taken as reference the baseline SD. |
| Progressive disease (PD) | At least a 20% increase in the SoD of target lesions, taking as reference the smallest sum on study.<br>The sum must also demonstrate an absolute increase of at least 5 mm.<br>The appearance of one or more new lesions. |
| Stable Disease (SD) | Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters on study. |

**Evaluation of non-target lesions**

| | |
|---|---|
| Complete Response (CR) | Disappearance of all non-target lesions and normalization of tumor marker level.<br>All lymph nodes must be non-pathological in size (<10 mm short axis). |
| Non-CR/ Non-PD | Persistence of one or more non-target lesions and/or maintenance of tumor marker level above the normal limits. |
| Progressive disease (PD) | Unequivocal progression of existing non-target lesions (one or several).<br>The progression must be clinically significant for the physician to consider changing or stopping therapy.<br>The appearance of one or more new lesions. |

**Evaluation of overall best response**

The best overall response is the best response recorded from the start of the study treatment until the end of treatment (disease progression). The patient’s best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance

of new lesions. (In case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks.)

**Algorithm for evaluation of overall best response:**

| Target lesions | Non-target lesions | New lesions | Overall response |
|---|---|---|---|
| CR | CR | No | CR |
| CR | Non-CR/Non-PD | No | PR |
| CR | Not evaluated | No | PR |
| PR | Non-PD or not evaluated | No | PR |
| SD | Non-PD or not evaluated | No | SD |
| Not evaluated | Non-PD | No | Not evaluable |
| PD | Any | Yes or No | PD |
| Any | PD | Yes or No | PD |
| Any | Any | Yes | PD |

# 11 Discontinuation

The criteria for enrolment must be followed explicitly. If a patient who does not meet enrolment criteria is enrolled, that patient should be discontinued from the study and the patient will be excluded from the analyses. Other reasons for discontinuation:

- The local investigator decides that the patient should be withdrawn from the study (i.e. due to adverse events)
- The patient decides to discontinue
- The patient requires other treatment than the study therapy
- Non-compliance with study procedures
- Pregnancy or failure to use adequate contraception (fertile patients)
- Progressive disease according to RECIST 1.1 during study therapy

All patients will be followed according to the Trial Plan (unless the consent is withdrawn).

# 12 Serious adverse events

Serious adverse events (SAE) occurring at any time after study enrolment or within 30 days of discontinuation should be reported to the Principal Investigator within 24 hours after the investigator is notified about the event. SAE is defined as an event leading to:

- death
- hospitalization – or prolonged hospital stay (unless hospitalization is unrelated to study therapy or study procedures)
- a life-threatening experience
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above

Events unrelated to study therapy or study procedures - or due to progression of the SCLC - should not be reported as an SAE. SAEs will be reported to the Norwegian Medicines Agency according to current regulations.

# 13 Post-study therapy

Progressive disease should be assessed on imaging (CT or MRI) along with other assessments listed in section 4 – “Trial plan – follow up”. Any post-study therapy should be at the treating physician’s discretion. All post-study therapy will be recorded.

# 14 Organization of the study

The study will be conducted by the Norwegian Lung Cancer Study Group – which is a collaborative group of physicians from all disciplines involved in diagnosis, staging and treatment of lung cancer in Norway. The group develop national guidelines for treatment of lung cancer, as well as conducting basic and clinical research on lung cancer. Due to an extensive network of physicians at all hospitals in Norway where lung cancer patients are treated, the study group has been able to conduct several large phase III trials on both NSCLC and SCLC. The NLCG has discussed and agreed to conduct this study, and is capable of doing so within the planned timeframe.

The principal investigator will be Bjørn Henning Grønberg, MD, PhD. Dr. Grønberg is a specialist in oncology, and is responsible for treatment of lung cancer patients at the Cancer Clinic at St. Olavs Hospital. Furthermore, he holds a research position at the European Palliative Care Research Centre (PRC) at the Department of Cancer Research and Molecular Medicine at the Norwegian University of Science and Technology. His research experience is mainly from clinical studies of lung cancer.

The other members of the protocol-committee are Odd Terje Brustugun, Nina Helbekkmo and Rene van Helvoirt – all specialists in oncology with extensive experience with treatment and research on lung cancer, particularly radiotherapy. Dr. Brustugun is responsible for treatment of lung cancer patients at the Department of Oncology at Oslo University Hospital. Furthermore, he holds a research position at the Department of Cancer Research at the Norwegian Radium Hospital. His research experience is mainly from translational and clinical studies of lung cancer. Dr. Helbekkmo works at the Pulmonology Department at the University Hospital of North Norway. Her research has mainly focused on clinical studies of lung cancer. Dr. Helvoirt works at Sørlandet Hospital in Kristiansand and chairs the national committee which develops and updates Norwegian guidelines for radiotherapy of lung cancer.

The PRC is a part of the European Association of Palliative Care Research Network (EAPCRN) and was established in 2009. It is located at St. Olavs Hospital – Trondheim University Hospital in Trondheim, Norway. The PRC is funded by St. Olavs Hospital, the NTNU and the Norwegian Cancer Society. The study management will consist of personnel at the PRC. The NTNU - represented by IKM/PRC - will be the responsible research institution for the study.

# 15 Ethical aspects

Despite encouraging results of hyperfractionated TRT, a large proportion of patients still experience local recurrence within the radiotherapy fields and there is a need for improved therapy. Higher doses of TRT might improve local control, but can also cause more toxicity. Thus, we have designed this study to investigate whether there are indications of a survival benefit of high-dose TRT – and to compare tolerability. The patients will be followed closely with respect to acute and long term radiation side effects.

The study is approved by a Regional Committee for Medical Research Ethics in Central Norway. All patients will receive oral and written information about the study and provide a written informed consent before enrolment.

# 16 Publication

The results will be submitted for publication in international peer-reviewed medical journals, and abstracts presenting preliminary results will be submitted for presentation at international meetings. Authorship will be defined according to the Vancouver Rules.

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# 17 Appendix

**Calculation of maximum radiotherapy dose to the spinal cord**
The following calculations are based on data from the QUANTEC-project (1). It is worth noticing that the $\alpha/\beta$ ratio for myelopathy (≥ grade 2) is now estimated to be 0.87 – implicating that the dose per fraction is considered more important than before.

The risk for the following total doses are now estimated to be (2 Gy/fraction):

- 50 Gy approx. 0.2 %
- **54 Gy** **< 1 %**
- 60 Gy 6 %
- 69 Gy approx. 50%

| Dose/ fraction | No. of fractions | Total dose | $BED_{10}$ | $BED_{0.87}$ | |
|---|---|---|---|---|---|
| **2.0** | **27** | **54** | **65** | **178** | |
| 2.8 | 15 | 42 | 54 | 177 | |
| 1.5 x 2 | 30 | 45 | 52 | 123 | |
| 1.5 x 2 | 30 | 45 | 52* | 127* | *Adjusted for incomplete repair, $t_{1/2}$ = 1.5 hs |
| 1.5 x 2 | 30 | 45 | 52* | 150** | **Adjusted for incomplete repair, $t_{1/2}$ = 4 hs |
| 1.5 x 2 | 36 | 54 | 62 | 147 | |
| 1.5 x 2 | 36 | 54 | 63* | 153* | *Adjusted for incomplete repair, $t_{1/2}$ = 1.5 hs |
| 1.5 x 2 | 36 | 54 | 63* | 180** | **Adjusted for incomplete repair, $t_{1/2}$ = 4 hs |

*mono-exponential repair – half-time for repair 1.5 hours
** mono-exponential repair – half-time for repair 4 hours

$BED_{10}$ ($\alpha/\beta$ = 10): biological effect in early responding normal tissue and tumor
$BED_{0.87}$ ($\alpha/\beta$ =0.87): biological effect in the spinal cord

* and ** indicates that the BED-values are adjusted for incomplete repair within the 6 hours between the two daily fracions. This leads to an increased biological effect. There are indications (e.g. from the CHART-study) that the spinal cord has a longer half-time for repair than other organs. Here, the BED has been adjusted for two different half-times (1.5 and 4 hours). The real half-time is probably between these values.

Conclusion: The risk for myelopathy is < 1 % at a dose of 1.5 Gy x 2 x 18. Concurrent chemotherapy might increase this risk.

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## EORTC QLQ C30 + LC 30


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## PG-SGA + G8


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