Treatment of larger tumor volumes or >= 2 lung tumors simultaneously in lung cancer patients using SBRT in a mean-lung dose escalation study

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Primary objective: the assessment of the maximal mean lung dose that is accepted to safely treat large peripheral tumors or 2 lung metastases simultaneously using SBRT. Secondary objectives:- evaluation of local control - evaluation of regional...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Respiratory and mediastinal neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON41422

Source
ToetsingOnline

Brief title
Irradiation of large lung tumors or >= two lung tumors

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified
- Respiratory tract neoplasms

Synonym
lung cancer, Non small cell lung cancer

Research involving
Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis
Source(s) of monetary or material Support: Elekta

Intervention

Keyword: large lung tumors, lung metastases, Mean Lung Dose, Stereotactic Body Radiotherapy

Outcome measures

Primary outcome

Primary objective: The MLD that is associated with a 20% chance on dose

limiting toxicity with a confidence interval of 10%.

Secondary outcome

Secondary objectives:

- local control

- regional control

- overall survival

- quality of life

Study description

Background summary

The use of stereotactic body radiotherapy (SBRT) for small peripheral non-small cell lung cancer (NSCLC) and lung metastases is increasing due to its low complication rate and its high local control rates. However, little is known about the dose-effect relationships with respect to toxicity for larger tumors. SBRT is generally given to a highly selective patient group with small peripheral tumors up to 5 cm in diameter. Up to now, patients treated with SBRT at the NKI-AVL and worldwide did not experience excessive toxicity. It is therefore hypothesized that patients with larger tumors can be treated with SBRT as well, and thus can profit from the excellent local control rate of SBRT. However, treating larger tumors will lead to an increase of the mean lung

dose (MLD), which is correlated to the incidence of radiation pneumonitis. The effect of simultaneous treatment of 2 tumor volumes on MLD related toxicity is unknown. The aim of this study is to find the maximum MLD that can be safely delivered using SBRT in patients with tumors > 5 cm in diameter or 2 or more lung tumors simultaneously with a diameter <= 5 cm. With the results of this study more patients might profit from treatment with SBRT.

Hypothesis: It is possible to treat patients with peripheral NSCLC with a diameter larger than 5 cm with SBRT, while the chance on dose limiting toxicity remains below 20%.

Study objective

Primary objective:
the assessment of the maximal mean lung dose that is accepted to safely treat large peripheral tumors or 2 lung metastases simultaneously using SBRT.

Secondary objectives:
- evaluation of local control
- evaluation of regional control
- overall survival
- quality of life assessment

Study design

Phase I-II multicenter trial, using a time-to-event continual reassessment method (TITE-CRM), which allows continuous accrual of patients and iteratively updates the probability of dose limiting toxicity (DLT). Dose limiting toxicity is defined according to the CTCAE v4; radiation pneumonitis >= grade 3 and pulmonary bleeding >= grade 4. For the non-lung toxicity a classical phase I 3+3 design will be used with a maximum incidence of 16,7% (1/6) will be accpeted with a minumum of 2 events in order not to stop the study permanately because of small accrual. Six risk groups will be defined, increasing the MLD with 3 Gy in each step. With an MLD of 13 Gy the risk on grade 2 RP is expected to be 7%. This is considered safe and therefore the risk group with an MLD of 12-15 Gy is under evaluation and allows accrual of 2 patients. Risk groups with an MLD of <9 Gy and 9-12 Gy are open for accrual. If 90 days post treatment the estimated risk on DLT is < 20 % for both patients, the next risk group is open for accrual, while the other (lower) risk groups will be continuously reassessed on DLT. In case of DLT, the maximal MLD will be recalculated. This procedure will continue until the maximal tolerable mean lung dose is assessed.

Before, during and up to 2 years after treatment patients will be regularly seen for physical examination, CTCAE-scoring, quality of life assessment, imaging with CT-thorax, CT-PET and SPECT-CT scan.

Intervention

A treatment plan is generated with a prescription dose of 3x18 Gy. The MLD will be calculated in Normalized Total Dose (NTD) using the Linear Quadratic(LQ)-model. If the calculated MLD falls in a risk group that is open for accrual and the predicted toxicity is lower than 20%, the patient will receive the prescribed dose. Otherwise the MLD is stepwise decreased by de-escalating the fraction size to a minimum of 3 x 14Gy, which is a conservative estimation of a similar biologically equivalent dose to 24 x 2.75 Gy using the Linear Quadratic Linear (LQL)-model. In case a fractionation of 3 x 14 Gy is not feasible, the patient will be excluded from the study and receives the standard treatment.

Study burden and risks

It is expected that the patients included in the study will benefit from a higher local control rate compared to conventional fractionation; however there is an unknown risk that the patients will experience excessive lung toxicity. Patients included in the study have the benefit of a short and curative irradiation with 3 fractions in 7-10 days compared to conventional irradiation (24 fractions in 32 days).
Before and after treatment, 3 extra SPECT/CT scans will be made; at 1-2 weeks pre-SBRT and at 4 months and 18 months post SBRT. The extra dose delivered through these extra images equals about 1% of the treatment dose and is thus considered to be neglegible.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Inclusion criteria for riskgroup A and B
- Weight loss < 10% in the last three months
- WHO-performance status <= 2 (see Appendix II)
- Medical inoperable patients or patients refusing surgery
- Chemotherapy is allowed in neoadjuvant and adjuvant setting, with exclusion of the period 4 weeks pre-SBRT and 6 weeks post-SBRT.
- Before patient registration, written informed consent must be given according to ICH/GCP, national and local regulations (see section 11.3).
- Check of inclusion by PI (h.peulen@nki.nl and j.belderbos@nki.nl*) by sending
oScreenshot of CT-thorax with tumor location
oCase summary
oTreatment plan
Risk group A specification (large lung tumors):
- NSCLC (Cytological or histological proven) patients with one peripheral tumor >5 cm with tumor staging cT2bN0M0 or cT3N0M0 (chest wall infiltration is no exclusion criteria, as long as the tumor diameter is > 5 cm).
- In patients without cytological or histological confirmation of NSCLC, a growing FDG-PET positive lesion (SUV >5) is accepted if a contra-indication for invasive diagnostic examination (or refusal) is present
- Or a single peripheral lung metastasis in inoperable patients with a diameter of > 5 cm. In case of first presentation of metastatic disease, cytological or histological proof is obligated.
Risk group B specification (lung metastases):
- Patients with 2 peripheral lprimary NSCLC <= 5 with tumor staging cT1-2aN0M0 (cytological/histological proven or growing and PET positive as described in section 5.2.2)
- Patients having two or more peripheral lung tumors without unacceptable dose overlap
- Or patients with >= 2 peripheral lung metastases <= 5 cm of any origin at any location in the lung. In case of first presentation of metastatic disease, cytological or histological proof is obligated. This is not necessary in case of a history of an already proven disseminated disease.

Exclusion criteria

- patients with more lung tumors/metastases who will very likely be retreated within 6 months
- Patients with central tumors
- Pancoast tumors
- Prior radiotherapy treatment to the thorax.
- Patients previously treated with adriamycin agents in case of heart involvement within the treatment field
- FEV1 and DLCO less than 40 % of the age-adjusted normal value
- patients receiving any systemic treatment
- pregnancy
- patients receiving Bevacizumab within 3 months prior to SBRT or within 1 month post SBRT.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	28-10-2011
Enrollment:	35
Type:	Actual

Ethics review

Approved WMO

Date:	12-09-2011
Application type:	First submission

Review commission:	METC NedMec
Approved WMO Date:	06-05-2013
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-01-2014
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-07-2014
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-02-2015
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-11-2015
Application type:	Amendment
Review commission:	METC NedMec

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL35442.031.11