Individualized Dose Escalation for non-small cell Lung cancer (NSCLC) using volumetric modulated arc therapy (VMAT)

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i. Primary endpointTreatment toxicity in terms of acute or late grade 2-4 esophageal and pulmonary adverse events, or other grade 2-4 adverse events (RTOG Acute Radiation Morbidity Scoring Criteria and RTOG/ESTRO Late Radiation Morbidity Scoring…

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

Summary

ID

NL-OMON36216

Source
ToetsingOnline

Brief title
IDEAL-VMAT for NSCLC

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
Lung cancer

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud

Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: (Chemo)Radiation, individualized dose escalation, Stage III non-small cell lung cancer

Outcome measures

Primary outcome

Treatment toxicity in terms of acute or late grade 2-4 esophageal and pulmonary adverse events, or other grade 2-4 adverse events (RTOG Acute Radiation Morbidity Scoring Criteria and RTOG/ESTRO Late Radiation Morbidity Scoring Schema)

Secondary outcome

Local-regional failure

Progression-free survival

Overall survival

Death during or within 30 days of discontinuation of radiation treatment

Quality of life (EORTC questionnaire QLQ-C13 and QCQ-LC13, H.A.D.S. questionnaire)

Predictive value of 18F-fluoroglucose (18FDG-)PET of the primary tumor and metastatic mediastinal lymph nodes performed at three time-points: before, during (2nd week) and (3 months) after treatment; findings on 18FDG-PET-CT scans performed during treatment will not alter this.

For patients undergoing surgery after (chemo)radiation (in accordance with the

local protocol):

Rate of pathological complete responses of the primary tumor and rate of

non-viable tumor cells in

treated mediastinal lymph nodes

Correlation of immunohistochemical findings with alterations of the 18FDG-PET

signal

Study description

Background summary

In the Netherlands, approximately 10.000 new patients are diagnosed with lung cancer every year. Of these, 80% present with non-small-cell lung cancer. Between 1995 and 2008, the national incidence has risen with 16% caused by an impressive increase of 53% in women suffering from this disease. The aggressive nature of this disease leads to a one-year survival rate of 45% and a 5-year survival rate of only 14%.
It is widely accepted that surgery provides the best chance of cure in patients with resectable NSCLC (www.oncoline.nl). In practice, only 20% of patients are amenable for tumor resection with curative intent. Alternatively, stereotactic body radiation therapy (SBRT) results in excellent local control in localized early stage disease (1).
In locally advanced, irresectable disease, combined chemotherapy and external-beam radiotherapy (EBRT) are increasingly being used. Evidence suggests that concurrent schedules are more effective than sequential treatments despite increased toxicity, although the true magnitude of the additional benefit remains uncertain (2). However, a large number of patients with locally advanced NSCLC is not suitable for concurrent chemoradiotherapy due to their general condition, age, comorbidity or tumor-related factors (3). Therefore, there is a need to increase effectiveness of treatment for all patients with advanced stage NSCLC undergoing either radiotherapy alone, neoadjuvant chemotherapy followed by radiotherapy, or concurrent treatment.

Apart from the addition of chemotherapy, treatment modification by intensification of the radiotherapy schedule or by dose escalation has been proven beneficial (4). Several phase I/II trials explored altered EBRT fractionation schedules that increased the biological effective dose to the primary tumor and reduced local relapse rate (5-7). Thereby, two main principles were pursued: reduction of the dose per fraction (* 1.8 Gy), giving

two or three fractions per day (so-called hyperfractionation), aimed at sparing normal tissues while increasing the dose to the primary tumor; increase of the fraction dose (* 2 Gy), combined with a reduction in the total number of fractions (so-called hypofractionation) aimed at increasing the effective tumor dose in less radiation-sensitive primary tumors. On the one hand, hyperfractionation limits the treatment-related side-effects, on the other hypofractionation is attractive for the patient and radiation department as the number of treatment fractions can be reduced.

Intensification of the irradiation schedule by continuous, hyperfractionated radiotherapy (CHART) delivered in 12 consecutive days showed an absolute improvement in two-year survival of 9% comparing the CHART schedule with a conventional scheme in six weeks (6). Due to its heavy logistic load (i.e., 3 fractions per day with an 6-8 hour interval allowing for normal tissue repair) it is only available in a few centers. With the advent of highly conformal dose planning and delivery techniques during the last decade (i.e., 3-dimensional conformal radiation therapy, 3D-CRT; intensity-modulated radiation therapy, IMRT; volumetric-modulated arc therapy, VMAT/RapidArc; Tomotherapy), organ-sparing technology became widely available. Recently, van Baardwijk and collaborators published an individualized dose prescription study in 166 stage-III NSCLC patients (7). Using a hyperfractionated 3D-CRT technique, patients were treated to the maximally tolerable dose (MTD) by increasing the fraction number until normal tissue constraints for the healthy lung tissue and the spinal cord were met (7). One-year and two-year overall survival was 69% and 45%, respectively, with acceptable toxicity. Already in 2006, Belderbos et al. reported favorable toxicity data and an encouraging failure-free interval in 88 inoperable NSCLC patients treated with intensified, hypofractionated 3D-CRT based on the MTD to the lung (5). With a median total tumor dose of 80.1 Gy (range 49.5 Gy to 94.5 Gy), dose-limiting toxicity was only observed in 9 patients.

Apart from these reported studies, there are three hypofractionation trials being conducted elsewhere. In the UK, two 3D-CRT based phase I/II trials have been approved investigating individualized dose escalation based on normal tissue dose constraints in patients with stage II or stage III NSCLC. In the IDEAL-CRT trial (ISRCTN12155469), concurrent chemotherapy is combined with a total radiation dose of 63*73 Gy given in 30 fractions over 6 weeks. The dose is prescribed such that each patient has the same risk of grade *2 radiation pneumonitis, but it may be limited by the tolerance dose of the spinal cord or esophagus. Based on this, patients are allocated to one of seven total dose levels ranging from 63 Gy to 73 Gy in 30 fractions. The second trial, IsoToxic Accelerated RadioTherapy (I-START; CRUK/10/005), has recently been approved for patients with locally advanced NSCLC to be treated with radiation only. According to this protocol, the dose to an individual patient is prescribed as the maximum achievable dose within the range of 58*65 Gy in 20 fractions over 4 weeks, by observing established dose constraints to organs at risk. The primary endpoint of both trials is to establish the maximally tolerable dose to the

esophagus and lung during and shortly after treatment. In the US, the University of Wisconsin is conducting a helical tomotherapy-based hypofractionation study (NCT00214123) with pulmonary toxicity (pneumonitis grade 3 lasting for more than 2 weeks) as primary endpoint. The purpose of this trial is to pilot reducing the duration of radiation treatment for lung cancer patients from 6 to 5 weeks using tomotherapy.

The reported hypo- and hyperfractionation studies have a *trial-and-error* approach for dose-level estimation in common. In a recent in silico trial in 26 stage III NSCLC patients, we have investigated the use of a dedicated software tool for individual dose escalation by hypofractionation (8). Based on an existing, clinical IMRT treatment plan (66 Gy in 33 fractions), radiation dose was escalated by scaling the radiation dose until the maximum tolerated dose constraints for the healthy lung, the esophagus, spinal cord, brachial plexus or heart was met. By doing so, the physical total tumor dose could be escalated by 2.3 to 21.1 % (range 67.5 Gy to 79.9 Gy). Further dose escalation was hampered by the maximally tolerated esophageal dose in 58% of the patients, and by the mean pulmonary dose in 23% of the patients.

The aim of this present study is to test the feasilibity and toxicity of individualized hypofractionated radiotherapy, and to report outcome data. In case this phase II trial has favorable results, a phase II/III trial on maximally tolerable, individualized, hypofractionated radiotherapy within a shorter overall-treatment time is aimed for.

Study objective

i. Primary endpoint
Treatment toxicity in terms of acute or late grade 2-4 esophageal and pulmonary adverse events, or other grade 2-4 adverse events (RTOG Acute Radiation Morbidity Scoring Criteria and RTOG/ESTRO Late Radiation Morbidity Scoring Schema); (maximum) expected increase in normal tissue complication probability of the lung (NTCPlung) is 18.5% [see 3.c.].

ii. Secondary endpoint
Detection of increase in tumor control probability (TCP) of (expected) 20% [see 3.c.]
Local-regional failure
Progression-free survival
Overall survival
Death during or within 30 days of discontinuation of radiation treatment
Quality of life (EORTC questionnaire QLQ-C13 and QCQ-LC13, H.A.D.S. questionnaire)

Predictive value of 18F-fluoroglucose (18FDG-)PET of the primary tumor and metastatic mediastinal lymph nodes performed at three time-points: before, during (2nd week) and (3 months) after treatment; findings on 18FDG-PET will

not influence the treatment.

For patients undergoing surgery after (chemo)radiation (in accordance with the local protocol):
Rate of pathological complete responses of the primary tumor and rate of non-viable tumor cells in
treated mediastinal lymph nodes
Correlation of immunohistochemical findings with alterations of the 18FDG-PET signal

iii. Final aim:
Ultimately, this phase II and the possible consecutive phase III trial aim at improving treatment outcome for patients with stage IIIA/B NSCLC without increasing toxicity to unacceptable limits.

Study design

This is a non-randomized single-centre open label study.
a. Patients with stage IIIA/B NSCLC scheduled to undergo radiation treatment (with sequential or concurrent chemotherapy) with curative intent (33 fractions in 6 * weeks) are asked to participate in this study.
b. Before initiation of treatment, all patients undergo a routine 18FDG-PET-CT scan at the Department of Nuclear Medicine for tumor delineation and treatment planning purposes.
c. For all patients participating in this study, an individualized, hypofractionated treatment plan is generated on the basis of an original, clinically acceptable plan. No randomization is performed.
d. Based on the radiation doses to the organs at risk (lung, esophagus, spinal cord, brachial plexus and heart), individual dose escalation in keeping with the maximally tolerable constraints is performed. This is achieved by scaling the prescribed dose of the existing treatment plan using a dedicated software routine.
e. During the treatment, the treating physician weekly scores the patients* toxicity (RTOG Acute Radiation Morbidity Scoring Criteria).
f. At three-weekly intervals (during radiotherapy or sequential/concurrent chemoradiation), the patients are asked to complete a quality of life questionnaires (EORTC questionnaire QLQ-C13 and QCQ-LC13, H.A.D.S. questionnaire). This is repeated when patients are seen for routine follow-up.
g. After completion of treatment, patients will regularly be followed at the Department for Radiation Oncology/Pneumology to assess late toxicity (RTOG/ESTRO Late Radiation Morbidity Scoring Schema).

Intervention

i. Patients included in this study will be subjected to the following procedures:

Standard 18FDG-PET-CT-scan with intravenous contrast agent for radiotherapy planning purposes prior to treatment
18FDG-PET-CT-scan with intravenous contrast agent in the end of the 2nd week of treatment
18FDG-PET-CT-scan with intravenous contrast agent 3 months after the end of treatment
Completion of quality of life questionnaires (QLQ-C13, QCQ-LC13, and H.A.D.S.) three-weekly during treatment and at regular follow-up visits thereafter.

ii. Procedures not affecting the patient
A clinically acceptable radiation treatment plan will be generated using the institute*s standard treatment planning system (Pinnacle3). Subsequently, the radiation dose of the standard treatment plans is rescaled using special-purpose MATLAB routines.
The treating physician will assess acute radiation related morbidity on a weekly basis using the RTOG/ESTRO Acute Radiation Morbidity Scoring Schema.

Study burden and risks

i. Patients included in this study will be subjected to the following procedures:
Standard 18FDG-PET-CT-scan with intravenous contrast agent for radiotherapy planning purposes prior to treatment
18FDG-PET-CT-scan with intravenous contrast agent at the end of the 2nd week of treatment
18FDG-PET-CT-scan with intravenous contrast agent 3 months after the end of treatment
Completion of quality of life questionnaires (QLQ-C13, QCQ-LC13, and H.A.D.S.) three-weekly during treatment and at regular follow-up visits thereafter.

ii. Regular follow-up visits after the end of treatment
After the end of treatment, regular follow-up appointments are scheduled at the Department of Radiation Oncology/Pneumology:
first 6 months: monthly;
until end of 2nd year: every 3 months;
3rd year: every 6 months;
annually until death thereafter.

At these appointments, the relevant medical history will be taken and a general physical examination performed. Furthermore, late radiation induced toxicity is scored by the treating physician using the RTOG/ESTRO Late Radiation Morbidity Scoring Schema.

The potential risks include increased treatment-related toxicity, e.g., pulmonal complaints and dysphagia on the basis of esophagitis. The additional radiation exposure caused by two additional 18FDG-PET-CT scans is in the light

of the external-beam radiation dose negligible.

Contacts

Public
Universitair Medisch Centrum Sint Radboud

Postbus 9101
6500 HB Nijmegen
NL
Scientific
Universitair Medisch Centrum Sint Radboud

Postbus 9101
6500 HB Nijmegen
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Histologically or cytologically confirmed stage IIIA/B NSCLC (excluding pleural effusion or mixed pathology)
2. Irresectable disease (as assessed by multidisciplinary team) or patient refusing surgery
3. Disease which can be encompassed within a radical radiotherapy treatment plan in keeping with standard practice at the participating center
4. Proposed treatment consists of radiotherapy alone, induction chemotherapy followed by radiotherapy, or concurrent chemoradiation
5. WHO performance status 0 or 1
6. Adequate respiratory function: FEV1 * 1.5 L and DLCO > 40%, predicted on baseline

pulmonary function tests
7. Age * 18 years, no upper age limit
8. Estimated life expectancy of more than 6 months
9. Patient is available for follow-up
10. Written informed consent obtained

Exclusion criteria

1. Clinically diagnosed NSCLC
2. Previous or current malignant disease likely to interfere with the protocol treatment or comparisons
3. Prior thoracic radiotherapy
4. Prior lobectomy / pneumonectomy
5. Prior chemotherapy using gemcitabine or bleomycine
6. Superior sulcus tumors if the brachial plexus is within the high-dose volume
7. Medically unstable (e.g., ischaemic heart disease, esophageal disorders)
8. Pregnancy
9. Connective tissue disorders
10. Inability to comply with protocol or trial procedures

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	31-07-2012
Enrollment:	60
Type:	Actual

Ethics review

Approved WMO Date:	27-02-2012
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	NL35536.091.11