Determination of the predictive value of FDG-PET-CT scans, blood proteins and blood cells for the prognosis for patients with lung cancer receiving concurrent chemo-radiation

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The objective of this study is to investigate the evolution of the 18F-deoxyglucose (FDG) uptake and the tumour characteristics determined in the plasma of patients with lung cancer during and after concurrent radiotherapy and chemotherapy.

Ethical review	Approved WMO
Status	Pending
Health condition type	Respiratory tract neoplasms
Study type	Observational invasive

Summary

ID

NL-OMON31446

Source
ToetsingOnline

Brief title
FDG-PET-LUNG / TACIR

Condition

- Respiratory tract neoplasms

Synonym
lungcancer

Research involving
Human

Sponsors and support

Primary sponsor: MAASTRO clinic
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: blood proteins, FDG-PET-CT, lungcancer, prognosis

Outcome measures

Primary outcome

Tumour response, measured with FDG-PET-CT scans 3 months post-radiation, as a

function of delta FDG uptafe the first week during radiotherapy

Secondary outcome

- Incidence of acute radiation-induced oesophagitis

- Incidence of radiation-induced pulmonary toxicity 3 and 9 months

post-radiotherapy

Study description

Background summary

Until the 1980*s, the "standard of care" for the dose, volume and beam arrangements for the treatment of non-small cell lung cancer (NSCLC) were established by the Radiation Therapy Oncology Group (RTOG) dose-escalation trial 7301 (1). In this study, 375 patients were randomly assigned to receive either 40 Gy in 4 weeks with a 2-week break (split-course), 40 Gy in 4 weeks, 50 Gy in 5 weeks, or 60 Gy in 6 weeks. The complete and partial response rates (as assessed clinically and radiographically) were 48% in patients treated with 40 Gy, 53% in those treated with 50 Gy, and 56% in those receiving 60 Gy. The incidence of local failure (also evaluated clinically) was lower in patients treated with 60 Gy (33%) than in those receiving 50 Gy (39%) or 40 Gy (44%-49%). Despite a modest improvement at three years, by five years the overall survival was approximately 5%.

In the early 1990*s, the results of several large randomised trials reported increased survival with the addition of cisplatin-based chemotherapy (2-5).

Each of these trials utilized conventional radiation therapy and delivered 40-50 Gy to the elective nodal regions and 60-65 Gy to the gross disease. Despite the modest improvement demonstrated in these trials, there remains much room for improvement. Long-term survival was still only 8-14%. LeChevalier and co-workers (3,4) reported a decreased incidence of distant metastases, but both arms had a local control rate of only 15-17% when evaluated by bronchoscopy and biopsy at 3 months and 10% at 2 years after completion of therapy. These results are considerably lower than the local control rates of 40-60% reported by soft clinical evaluation (1).

In addition, lung cancers are usually quite large at presentation. It is the norm to have bulky tumours measuring greater than 2-5 cm. It is thought that doses up to 100 Gy may be necessary to sterilize the size of tumours frequently treated in bronchogenic carcinoma (6).

Further attempts at dose escalation were carried out in the RTOG prospective hyperfractionation trial 8301 (5). A total dose of 60 Gy, delivered in 2 Gy per day fractions in 6 weeks, was compared with 69.6 Gy BID and with chemotherapy followed by 60 Gy in 458 patients, the overwhelming majority of them suffering from stage III NSCLC. The 5-year survival was respectively 5 %, 6 % and 8 %.

The overall treatment time, in which radiotherapy is delivered, is of utmost importance for survival. In general, both anti-tumour effects and the acute side- effects increase when shortening the overall treatment time, but late side effects are less sensitive to a change in overall treatment time. Prolongation of the radiation treatment by a few days or a treatment interruption by several weeks such as the rest period introduced in a split course schedule led to a decrease in tumour control or in survival. In the RTOG trial evaluating different hyperfractionated schedules, the 2-year survival rate dropped from 33% to 14% if the treatment had been delayed for more than 5 days (7). However, the proof of principle came from the CHART (continuous hyperfractionated accelerated radiation therapy) trial in which 563 patients of whom the majority had stage III NSCLC were randomised between the classical 60 Gy in 30 fractions in 6 weeks and 54 Gy in 12 days (three fractions per day) in order to overcome the accelerated tumour proliferation in standard daily radiotherapy (8). The absolute 2-year survival was 20 % in the 60 Gy in 6 weeks group, compared to 29 % in the CHART arm ($p=0.008$). Moreover, the relative risk of local progression was reduced by 21 % ($p=0.033$). However, ultimately, only 13 % of the patients in the CHART group and 9 % in the standard arm were free of local cancer.

Two phase III trials demonstrated superior survival, but at the cost of higher toxicity, by delivering chemotherapy and radiotherapy concomitantly, compared to the delivery of chemotherapy followed by radiation (9,10). In a 220 patient trial, Furuse et al could demonstrate a 5-year survival of 15.8 % when chemotherapy was given together with radiation, which compares favourably with a survival rate of

8.9 % by sequential chemotherapy and radiotherapy (9). Similarly, Curran and co-workers found a median survival of 17.0 months in the concurrent QD arm and 14.6 months in the sequential arm with corresponding 4-year survival rates of respectively 21 % and 12 % (p=0.046) in a trial with 597 evaluable patients (10). The better survival was due to a better local control by delivering radiation and chemotherapy at the same time (9). The drawback was, however, a higher incidence of toxicity.
In patients suffering from stage III B NSCLC, even sequential treatment with vindesin, ifosfamide and cisplatin, followed by cisplatin sensitised radiotherapy to a dose of 52 Gy in 20 fractions resulted in a local failure rate of 70 % (11).

It is thus clear that even with the best classical radiation and chemotherapy schedule, results remain disappointing.

However, the fact that increasing the local control rate by delivering radiotherapy either in a short period of time like in the CHART trial, or concomitantly with chemotherapy improves survival supports the idea that radiation dose escalation could lead to further improvements of prognosis.

Radiation dose escalation is however limited by radiation-induced lung and oesophageal damage (8, 9, 12-26). The dose-volume parameters for lung injuries are known to some extend (for review, see 27). In general, with a mean lung dose (MLD) of 10 Gy, < 5 % of the patients will develop a reversible grade 2 (i.e. corticosteroid dependent) radiation pneumonitis. When the MLD increases to 15 Gy, about 10 % of the patients will develop grade 2 radiopneumonitis, and with a MLD of 20 Gy, 15 % will have a grade 2 or more pneumonitis, with about 1% of toxic deaths. The MLD also gives a hint for the post-treatment lung function, with a decrease of approximately 1 % per Gy, but the variability is large. It has also been suggested that pneumonitis is more frequent in patients with lower versus upper lobe tumours. This may be due to the inclusion of the proximal conducting airways within the CT-defined superior part of the lung, thus over-estimating the volume of *functional* lung.
For radiation-induced oesophageal damage, the relation between dose-volume parameters and the incidence of injury is less clear, and no firm conclusions could be drawn (28).

Study objective

The objective of this study is to investigate the evolution of the 18F-deoxyglucose (FDG) uptake and the tumour characteristics determined in the plasma of patients with lung cancer during and after concurrent radiotherapy and chemotherapy.

Study design

Prospective study.

Study burden and risks

One extra FDG-PET-CT scan and five extra blood collections.

Contacts

Public
MAASTRO clinic

Dr. Tanslaan 12
6229 ET Maastricht
Nederland
Scientific
MAASTRO clinic

Dr. Tanslaan 12
6229 ET Maastricht
Nederland

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Histological or cytological proven non-small cell or small cell lung cancer. Mixed histologies (NSCLC and SCLC) are allowed;
UICC stage I-III (in case of small cell lung cancer: limited stage);
WHO performance status 0-2;

Less than 10 % weight loss the last 6 months;
In case of previous chemotherapy, concurrent chemo-radiotherapy can start after a minimum of 21 days after the last chemotherapy course;
No recent (< 3 months) severe cardiac disease (arrhythmia, congestive heart failure, infarction);
No active peptic oesophagitis;
Life expectancy more than 6 months;
Measurable cancer;
Willing and able to comply with the study prescriptions;
18 years or older;
Not pregnant and willing to take adequate contraceptive measures during the study;
Have given written informed consent before patient registration ;
No previous radiotherapy to the chest.

Exclusion criteria

Not non-small cell or small cell histology, e.g. mesothelioma, lymphoma
Malignant pleural or pericardial effusion
History of prior chest radiotherapy
Recent (< 3 months) myocardial infarction
Uncontrolled infectious disease
Distant metastases (stage IV)
Patients with active peptic oesophagitis in the last year
Less than 18 years old
Pregnant or not willing to take adequate contraceptive measures during the study

Study design

Design

Study phase:	3
Study type:	Observational invasive
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL
Recruitment status: Pending

Start date (anticipated):	01-05-2006
Enrollment:	60
Type:	Anticipated

Ethics review

Approved WMO Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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
EudraCT	EUCTR2006-002229-22-NL
ClinicalTrials.gov	NCT00522639
CCMO	NL12007.026.06