# Early CT and FDG-metabolic tumour volume changes show a significant correlation with survival in stage I-III small cell lung cancer: A hypothesis generating study

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# Early CT and FDG-metabolic tumour volume changes show a significant correlation with survival in stage I–III small cell lung cancer: A hypothesis generating study

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ABSTRACT

*Background:* Many patients with stage I–III small cell lung cancer (SCLC) experience disease progression short after the completion of concurrent chemoradiotherapy (CRT). The purpose of the current study was to evaluate whether CT or FDG metabolic response early after the start of chemotherapy, but before the beginning of chest RT, is predictive for survival in SCLC.

*Methods:* Fifteen stage I–III SCLC patients treated with concurrent CRT with an FDG-PET and CT scan available before the start of chemotherapy and after or during the first cycle of chemotherapy, but before the start of radiotherapy, were selected. The metabolic volume (MV) was defined both within the primary tumour and in the involved nodal stations using the 40% (MV40) and 50% (MV50) threshold of the maximum SUV. Metabolic and CT response was assessed by the relative change in MV and CT volume, respectively, between both time points. The association between response and overall survival (OS) was analysed by univariate cox regression analysis. The minimum follow-up was 18 months.

*Results:* Reductions in MV40 and MV50 were $-36 \pm 38\%$ (126.4 to 68.7 $cm^3$) and $-44 \pm 38\%$ (90.2 to 27.8 $cm^3$), respectively. The median CT volume reduction was $-40 \pm 64\%$ (190.6 to 113.8 $cm^3$). MV40 and MV50 changes showed a significant association with survival (HR = 1.02, 95% CI: 1.00–1.04 ($p = 0.042$); HR = 1.02, 95% CI: 1.00–1.04 ($p = 0.048$), respectively), indicating a 2% increase in survival probability for 1% reduction in metabolic volume. The CT volume change was also significantly correlated with survival (HR = 1.01, 95% CI: 1.00–1.03, $p = 0.007$).

*Conclusions:* This hypothesis generating study shows that both the early CT and the MV changes show a significant correlation with survival in SCLC. A prospective study is planned in a larger patient cohort to allow multivariate analysis, with the final aim to select patients early during treatment that could benefit from dose intensification or alternative treatment.



Small cell lung cancer (SCLC) represents about 15% of lung cancer cases and is characterised by a rapid growth rate, early dissemination and sensitivity to both chemo- and radiotherapy. Untreated, the outcome is poor, with a median survival of 2–3 months [1]. In the approximately 30% of patients diagnosed with stage I–III disease confined to the thorax, the addition of radiotherapy to chemotherapy has significantly increased long term survival [2,3]. The current state of the art treatment for this patient group consists of combined chemoradiotherapy [4–6], with a few studies suggesting a benefit of early administration of thoracic radiotherapy with concurrent cisplatin and etoposide chemotherapy [7–9]. Despite these recent improvements in outcome of stage I–III SCLC, the majority of patients still show disease progression shortly after the completion of treatment, with 40% having an isolated local recurrence as their first site of progression [10]. Furthermore, the treatment is associated with considerable toxicity, with up to 30% of patients experiencing grade 3 or higher esophagitis [10]. Therefore, it would be of great value to be able to select the patients that are most likely to benefit from treatment before or early during therapy. This would enable avoiding ineffective treatment with the associated side effects and costs in the patient group in which benefit is less likely. Alternatively, these patients could be offered novel experimental therapy.

The anatomical extent of disease as assessed by computed tomography (CT) is an important prognostic factor in SCLC [11]. Metabolic imaging with $^{18}$F-deoxyglucose ($^{18}$FDG) positron emission tomography (PET), which is now widely applied in RT treatment planning of NSCLC [12], however, is more sensitive and

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specific for the detection of nodal and distant metastases in NSCLC [13–16], and studies indicate a potential advantage in SCLC as well [17–20]. Furthermore, PET scanning allows for the assessment of changes in glucose consumption of the tumour during chemo- and radiotherapy [21,22], providing the opportunity to determine an early response to treatment. Early metabolic changes assessed with PET have shown to be predictive of the final treatment response and outcome in multiple malignancies, including colorectal, breast and oesophageal carcinoma [23–25]. Multiple studies have shown that in advanced non small cell lung cancer (NSCLC), metabolic response after the first cycle of chemotherapy is strongly correlated with outcome [26–28]. In contrast, data on the predictive value of an early metabolic response in SCLC are scarce. Results from one study in 12 SCLC patients and one case report suggest that a metabolic response after the first cycle of chemotherapy is associated with the response directly after treatment [29,30].

Thus, the purpose of the current study was to evaluate whether response assessment on CT and/or PET early after the start of chemotherapy, but before the start of chest radiotherapy, has predictive value for survival in stage I–III SCLC as well.

## Materials and methods

### *Patients*

Patients with stage I–III SCLC treated with combination chemoradiotherapy between January 2005 and November 2008 were retrospectively evaluated. Staging consisted of a bronchoscopy and standard haematological and biochemical workup. Brain imaging was performed with either MRI or a contrast-enhanced CT. Only patients that underwent a whole body FDG-PET scan and a contrast-enhanced CT scan of the chest and upper abdomen both for staging purposes (before the start of chemotherapy) and for radiotherapy planning (after the start of chemotherapy), were evaluated.

Other inclusion criteria were: cytologically or histologically proven SCLC; limited disease, defined as UICC stage I–III, with the exclusion of T4 lesions because of malignant pleural or pericardial effusion; WHO performance status 0–2; adequate pulmonary function (FEV1 > 1 l). The minimum follow-up time after the start of RT was 18 months.

### *Treatment*

Patients received chemotherapy according to the standard protocol in the Comprehensive Cancer Centre Limburg, the Netherlands, being carboplatin on day 1 and etoposide (120 mg/m$^2$) on day 1–3. The carboplatin dose was based on the target AUC (5 mg/ml/h) $*$ (glomerular filtration rate + 25), with the glomerular filtration rate calculated according to the Cockroft–Gault formula. Chemotherapy cycles were repeated every 21 days for a total of 5 cycles. Chest radiotherapy was planned to start as early as possible after the beginning of chemotherapy. All patients were treated with a three-dimensional conformal treatment plan using 6–10 MV photons. The planning target volume (PTV) included the primary tumour and the involved nodal stations on the pre-chemotherapy PET scan, with a margin of 10 mm for the nodal stations and 15 mm for the primary tumour. No elective nodal irradiation was carried out [15]. The prescribed dose to the PTV was 45 Gy in 30 fractions in 3 weeks (1.5 Gy BID, minimum interval between two fractions of 8 h) according to the ICRU 50 guidelines [16]. After thoracic irradiation and 5 cycles of chemotherapy, re-staging was performed including a chest X-ray and contrast-enhanced CT scan of the brain. If there was no progression on chest X-ray and no brain metastases were visualised, patients were offered prophylactic cranial irradiation (PCI) to a dose of 25 Gy in 10 fractions.

### *$^{18}$FDG PET and CT imaging*

Baseline scanning consisted of either both a whole body FDG-PET scan and a contrast-enhanced CT scan of the chest, or a combined whole body FDG-PET–CT scan with contrast. A second PET and CT scan were made for RT planning, always as a combined FDG-PET–CT. Both the baseline and pre-RT scans were made in a supine position with both arms above the head to ensure optimal co-registration [17].

Concerning the PET scans, patients had to be fasting for at least 6 h before the examination. The injected total activity of FDG was calculated based on the weight of the patient: (weight $*$ 4 + 20) MBq. After a rest period of 60 min PET images were acquired. The chest CT scans were performed with intravenous contrast during free-breathing.

### *Early response assessment*

The "CT volume" was calculated for both time points by the sum of the volume of the primary tumour and involved lymph nodes delineated on CT. For the primary tumour, the GTV was delineated based on CT only using the lung window settings (width = 1700, level = −300). The involved lymph nodes were delineated in mediastinal window setting ($W$ = 600, $L$ = 40). The metabolic volume (MV) of FDG-uptake areas was quantified both within the primary tumour and in the involved nodal stations using the 40% (MV40) and 50% (MV50) threshold of the maximum standardised uptake value ($SUV_{max}$). Metabolic and CT response was assessed by the relative (%) change in MV and CT volume, respectively, between both time points.

### *Statistical analysis*

Overall survival (OS) was calculated with the Kaplan–Meier method starting from the first day of chemotherapy. Both metabolic and CT response were analysed for their association with OS by univariate cox regression analysis.

## Results

Patient and treatment characteristics are described in Table 1. The median follow-up of all patients was 89 weeks (range 39–200 weeks). Patients' age ranged from 48 to 85 years and 14/15 patients had stage III SCLC. All patients received a RT dose of 45 Gy in twice daily fractions of 1.5 Gy. The median time interval between the two scans was 28 ± 11 days for CT and 20 ± 8 days for PET. Table 2 provides an overview of the CT and metabolic volumes before and after chemotherapy, as well as the absolute and relative change in volume between the two time points. The relative change of the MV40 and MV50 was −36 ± 38% (126.4 to 68.7 cm$^3$) and −44 ± 38% (90.2 to 27.8 cm$^3$), respectively. The CT volume change was −40 ± 64% (190.6 to 113.8 cm$^3$). The change in metabolic and CT volumes per patient is graphically shown in Fig. 1, where the MV40 is chosen to illustrate the change in metabolic volume. Both the change in MV40 and MV50 were significantly correlated with the CT-volume change (Pearson correlation coefficient: 0.55, $p$ = 0.032 and 0.70, $p$ = 0.004, respectively).

The median OS was 20 months (95% CI: 14.7–25.3 months), with a 1 and 2 year OS rate of 87% and 40%, respectively. Both the change in MV40 and MV50 showed a significant association with survival (HR = 1.02, 95% CI: 1.00–1.04 ($p$ = 0.042) and HR = 1.02, 95% CI: 1.00–1.04 ($p$ = 0.048), respectively), indicating a 2% increase in survival probability for each 1% reduction in metabolic volume. The CT volume change was also significantly correlated with survival (HR = 1.01, 95% CI: 1.00–1.03, $p$ = 0.007). On basis of the imaging reports and other correspondence during

**Table 1**
Patient and treatment characteristics.

| | *N* ± SD (%) |
|---|---|
| Median age | 64.0 ± 10.5<br>Range 48–85 |
| Gender | |
| Male | 9 (60.0) |
| Female | 6 (40.0) |
| Stage | |
| IIA | 1 (6.7) |
| IIIA | 6 (40.0) |
| IIIB | 8 (53.3) |
| PCI | |
| Yes | 13 (86.7) |
| No | 2 (13.3) |
| Median interval between start of chemotherapy and RT (days) | 21 ± 8.4<br>Range 7–35 |
| Dose | |
| 45 Gy | 60 (100.0) |
| Median OTT of RT | 21 ± 1.5<br>Range 18–23 |
| Median SER | 42 ± 8.9<br>Range 27–56 |

SER: Time between the start of any treatment and the end of RT; PCI: prophylactic cranial irradiation.

**Table 2**
CT- and metabolic volume changes.

| | Median (±SD)<br>range |
|---|---|
| Interval pre-post CT scan (days) | 28 (±11.3)<br>8–60 |
| Interval pre-post PET scan (days) | 20 (±8.4)<br>13–39 |
| MV40 preCTx ($cm^3$) | 126.4 (±94.6)<br>9.8–368.5 |
| MV40 postCTx ($cm^3$) | 68.7 (±93.7)<br>6.7–366.6 |
| Absolute change MV40 ($cm^3$) | −15.5 (±70.6)<br>−231.9 to 26.7 |
| Relative change MV40 (%) | −35.9 (±37.8)<br>−91.8 – 35.9 |
| MV50 preCTx ($cm^3$) | 90.2 (±62.1)<br>6.6–235.2 |
| MV50 postCTx ($cm^3$) | 27.8 (±55.7)<br>3.9–224.7 |
| Absolute change MV50 ($cm^3$) | −25.3 (±48.2)<br>−169.9 – 20.3 |
| Relative change MV50 (%) | −44.1 (±38.4)<br>−95.6 – 46.7 |
| CT volume preCTx ($cm^3$) | 190.6 (±111.0)<br>5.0–441.4 |
| CT volume postCTx ($cm^3$) | 113.8 (±62.5)<br>11.3–237.3 |
| Absolute change CT volume ($cm^3$) | −47.2 (±105.3)<br>−327.4 – 61.4 |
| Relative change CT volume (%) | −40.3 (±63.8)<br>−77.9 – 126 |

follow-up, 4 patients had both locoregional and distant progression, 5 patients had distant failure only, and one patient had locoregional failure only. Given the retrospective nature of this trial in combination with the limited patient numbers, we considered it inappropriate to perform a meaningful analysis regarding the correlation of an early response with (site of) progression.

## Discussion

Concurrent chemoradiotherapy for SCLC is associated with considerable toxicity. Therefore, an early anticipation to the expected benefit from this treatment, before the start of the most toxic part of the therapy, would be of great value. To our knowledge, this is the first study evaluating the predictive value of an early CT and PET response on final outcome after therapy. In the present study, we found that both the response to chemotherapy on CT and on PET, before the start of concurrent chemoradiotherapy, was correlated with overall survival. Two earlier studies evaluated the predictive ability of an FDG response after one cycle of chemotherapy [30,31]. However, in these studies patients with stage I–IV disease were investigated. Therefore, the results reflect the predictive value of an early FDG response in a heterogeneous patient population, receiving either palliative chemotherapy or radical chemoradiotherapy. Furthermore, both studies used CT response after completion of therapy as a reference, not survival. Both studies concluded that the metabolic response was correlated with the response according to RECIST.

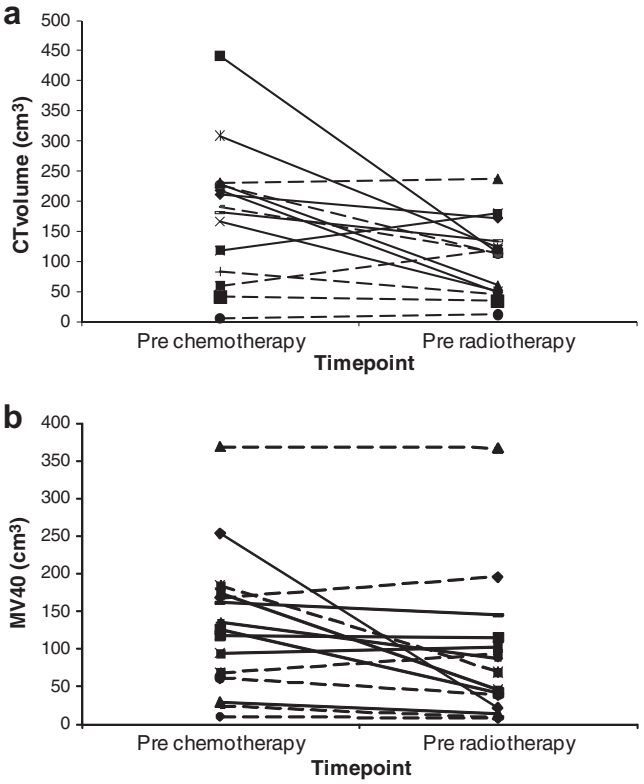


**Fig. 1.** Early change in CT- and metabolic volume per individual patient. (a) Early volume change on CT. (b) Early metabolic volume change (MV40). Continuous line: OS above median; dotted line: OS below median.

In the present study, both the CT-volume change early during chemotherapy (HR: 1.01, $p = 0.007$) and the change in metabolic volume (HR: 1.02, $p = 0.042$ and 0.048 for MV40 and MV50, respectively) showed a correlation with overall survival. One should be cautious in interpreting these results given the limited amount of patients in this study. Nonetheless, the absence of a clear superiority of PET over CT in predicting final outcome is remarkable and in contrast to the findings in NSCLC [26–28]. In comparison to NSCLC, however, SCLC is characterised by a rapid volume response to chemo- and radiotherapy. Therefore, a response to therapy could be more rapidly visible on CT than it is in NSCLC, which might restrict the added effect of PET. This hypothesis is supported by the study of Fischer et al., who found that early response assessment after one cycle of chemotherapy with CT and PET showed a comparable correlation with the final evaluation on basis of RECIST [31].

Given the retrospective nature of this trial, no specific rules on the timing and frequency of follow-up were applied. Neither were

their prescriptions on the types of imaging to be performed. For this reason, in combination with the limited patient numbers, we considered it inappropriate to perform a meaningful analysis regarding the correlation of an early response with (site of) progression. We emphasise the importance to address this correlation of an early response with the sites of progression in future clinical trials to appropriately adapt therapy. The small sample size in this study did not allow multivariate analysis of potential confounding factors, such as stage or tumour volume. The influence of these factors should be tested in future prospective trials.

Early response assessment with FDG might be compromised by its limited ability to discriminate between inflammation and tumour activity. Therefore, it is worthwhile to investigate alternative tracers that correspond more specifically with tumour proliferation, such as markers of DNA-synthesis ($^{18}$F-fluorothymidine) and amino-acid tracers, or with hypoxia [32].

Literature shows that the time from the start of any therapy to the end of radiotherapy (SER) is an important predictor for survival in stage I–III SCLC [33,34]. Therefore, one could argue that ideally, RT should start at day 0 of chemotherapy. In clinical practice, however, this is hardly ever possible taking into account the time needed for RT planning. Especially in SCLC, which is characterised by its rapid, be it often temporary, response to chemotherapy, suspending the start of chemotherapy treatment until the start of RT is not an option. Hence, this unavoidable time delay between the start of chemotherapy and RT underscores the importance of the assessment of an early response to treatment in clinical practice.

Based on the results of the current study, we have initiated a prospective study in a larger patient cohort. This future study would allow a more thorough evaluation of different methods of response evaluation of PET, as well as multivariate analysis of different potentially predictive variables, with the final aim to select patients early during treatment that could benefit from dose intensification or alternative treatment.

In conclusion, this hypothesis generating study shows not only the metabolic response on PET, but also the CT response early after the start of chemotherapy, before the start of RT, show a significant correlation with survival in SCLC. A prospective study is planned in a larger patient cohort to allow multivariate analysis, with the final aim to select patients early during treatment that could benefit from dose intensification or alternative treatment.

## Conflict of interest notification

Actual or potential conflicts of interest do not exist.

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