CT DENSITY IN LUNG CANCER PATIENTS AFTER RADIOTHERAPY SENSITISED BY METOCLOPRAMIDE: A SUBGROUP ANALYSIS OF A RANDOMISED TRIAL

CT-DICHTE VON PATIENTEN MIT BRONCHIALKARZINOM NACH STRAHLENTHERAPIE IN KOMBINATION MIT STRAHLENSENSITIVIERENDER METOCLOPRAMIDBEHANDLUNG

Running title: CT density after radiotherapy of lung cancer

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ABSTRACT

Aim: To investigate the lung tissue response measured with CT after radiotherapy (RT) combined with metoclopramide.

Patients and Methods: Patients with NSCLC (tumour stage IIIA and B), included in a multicenter randomised phase III trial investigating the use of metoclopramide as a radiosensitising agent, were examined with repetitive post-RT CT scans. The analysis comprised data up to 100 days post-RT for a subgroup of 16 patients treated with a total dose of 60 Gy given in 1.82 Gy per fraction.

Results: Large radiation doses to subvolumes were associated with denser lung tissue measured with CT ($p<0.001$). Opposed to this finding, the volume of lung tissue irradiated with significant doses (v_{40Gy}) was negatively correlated with the average increase in lung tissue density ($p=0.003$). Patients randomised to metoclopramide injections also experienced less increase in lung tissue density ($p=0.01$).

Conclusion: There was an increase in the density of irradiated lung tissue with radiation dose and time after radiotherapy. Metoclopramide and significant radiation doses to larger lung volumes (v_{40Gy}) seemed to protect against fibrosis development.

Key words: Radiotherapy, lung cancer, late toxicity, computed tomography

ZUSAMMENFASSUNG

Ziel: Computertomographische Messung von Strahlenreaktion in Lungengewebe nach Strahlentherapie in Kombination mit Metoclopramid.

Patienten und Methodik: Patienten mit nicht-kleinzelligem Bronchialkarzinom (Tumorstadium IIIa und b), inkludiert in eine randomisierte Phase III Multizenterstudie zur Untersuchung des strahlensensitivierenden Effektes von Metoclopramid, wurden mit wiederholten post-therapie CT`s untersucht. Follow-up Daten 100 Tage nach Beendigung der Strahlentherapie einer Untergruppe von 16 Patienten, die mit einer Totaldosis von 60 Gy appliziert in Tagesdosis von 1,8 Gy behandelt wurden standen zur Analyse zur Verfügung.

Ergebnisse: Hohe Strahlendosis gegen Teilvolumina resultierten in höherer CT-Dichte im bestrahlten Lungengewebe ($p<0,001$). Im Gegensatz dazu korrelierte das mit signifikanter Dosis bestrahlte Lungenvolumen (V_{40Gy}) negativ mit der Zunahme der CT-Dichte im bestrahlten Lungengewebe ($p=0,003$). Bei Patienten, die in den Therapiarm mit Metoclopramid randomisiert wurden registrierte man eine weniger ausgeprägte Zunahme der CT-Dichte im bestrahlten Lungengewebe ($p=0,01$).

Schlussfolgerung: Wir fanden einen Zusammenhang zwischen der Zunahme von gemessener CT-Dichte im bestrahlten Lungengewebe, der applizierten Strahlendosis und der Zeit nach Bestrahlung. Metoclopramid und das mit signifikanter Dosis bestrahlte Lungenvolumen (v_{40Gy}) scheinen einen protektiven Effekt auf die Entwicklung von Lungenfibrose zu haben.

Schlüsselwörter: Strahlentherapie, Bronchialkarzinom, Spähttoxizitet, Computertomographie

INTRODUCTION

In patients with localised, inoperable non-small cell lung cancer (NSCLC), radical radiotherapy (RT) is the treatment of choice. Since radical radiotherapy may be limited by consequential pneumonitis and lung fibrosis, a better understanding of the relationship between the radiation dose and the development of late side effects, is needed [3, 4, 12, 17]. Previous studies have established CT as a tool to monitor the development of fibrosis/pneumonitis measured as changes in CT density [10, 19]. Dose-effect relationships have been derived for breast cancer and lymphoma patients [1, 18], and for patients with lung cancer [13, 15]. There are less detailed data describing the time dependency of the density changes after RT (post-RT) [14, 16]. Some authors have chosen to investigate populations of breast cancer and lymphoma patients, partially because of the well-known obstacles related to investigations of late side-effects in lung cancer patients [2, 18]: Firstly, the survival of lung cancer patients is low, and consequently, the patient materials are of low figures, and may thus be highly selected. Secondly, the lung function is influenced not only by RT, but also by tumour progression and other lung diseases frequently present in these patients. Nevertheless, certainly also for this patient group, further investigations on post-RT side effects are justified.

The enzyme adenosine diphosphate ribosyl transferase is activated by DNA damaging agents. From in vitro studies, metoclopramide has been shown to inhibit this enzyme resulting in increased cytotoxic effect of radiation and chemotherapeutic drugs (6, 11). A phase I/II study indicated that metoclopramide could be used safely as a radiosensitiser and that the drug could have positive treatment effects (8).

In this retrospective study, the results from an analysis on our institution's follow-up data from a multicentre, randomised phase III study, are presented. The primary goal of the multicentre study was to explore the overall survival effect of metoclopramide as a

radiosensitiser in the treatment of NSCLC [8]. The present paper concentrates on the influence of the radiosensitiser and radiotherapy on normal lung tissue as measured as CT density changes.

MATERIALS AND METHODS

During 1995-1998, 30 NSCLC patients from our institution were enrolled in a multicentre, randomised phase III study aimed at investigating the efficacy, safety and tolerability of intramuscular injections of neutralised metoclopramide 100 mg/ml (Neu-Sensamide^{TM}) as a radiosensitising agent [6]. Neu-Sensamide^{TM} was produced by Oxigene Europe AB. Inclusion criteria were inoperable NSCLC, squamous cell carcinoma, stage IIIA and IIIB, age >30 years and Karnofsky performance scale ≥ 80. The local ethics committee approved the protocol, and all participating patients gave informed consent before entering the study. All available follow-up data were transferred to the central study group at Oxigene Europe AB in Lund, Sweden for later analysis and publication. The multi-centre study was closed prematurely due to financial matters. No follow-up data have been published from the central study group.

Sixteen of the 30 patients from our hospital had sufficient data for a local analysis, i.e. complete radiotherapy records and CT examinations. Three of the 16 patients were female and the median age was 68 years (range 46-81 years). The remainder 14 patients had insufficient follow-up data (partly because of withdrawal from the study related to rapid disease progression during or shortly after radiotherapy and partly because of inadequate RT files).

Radiosensitiser

Seven patients were randomised to receive intramuscular injections of neutralised metoclopramide, 2 mg/kg given 1 hour prior to RT, 3 times per week. Four patients complied with the protocol, one patient was not given the sensitiser the last week and two patients refused to continue with the sensitiser after few injections due to side-effects (fatigue, muscle pain, headache and indigestion).

Radiotherapy

All patients were given megavoltage (6-15 MV) conformal RT applying 2-4, usually 3, radiation fields. The ICRU central axis dose was 60 Gy given in 1.82 Gy per fraction 5 days per week. The RT dose planning was performed with Treatment Management System v3.1 (Helax) based on CT scans acquired with 10 mm slice thickness and 10 mm distance between the slices. The clinical target volume comprised the gross tumour volume (GTV) plus a 10 mm margin accounting for subclinical disease. The multi-leaf collimators were set to obtain an additional margin of minimum 5-10 mm, and normally 20 mm to account for set-up errors and penumbra. Dose-volume histograms (DVH) of both lungs as a single organ, and only the affected lung excluding the GTV were calculated. All doses presented in this study have been corrected according to the LQ formula with $\alpha/\beta = 3$ Gy for late side effects and dose per fraction equal to 2 Gy [7].

Follow-up CT scans

For each patient, follow-up CT scans were intended to be performed 12 and 16 weeks after the start of RT (i.e. approximately 35 and 65 days after the end of RT lasting 6.5 weeks). In addition, several patients had extra diagnostic post-RT CT scans related to suspected tumour progression. After advice from our statistician (DTK), we chose to set a cut-off at 100 days

when plotting the data and 90 days for the statistical analysis. A median number of 2.5 CT examinations per patient, were available (Table 1). CT scans were performed with Cytec 3000 (General Electrics) in a private radiology clinic. The Cytec 3000 was a sequential CT scanner. Normally, the slice thickness was 5mm.

We chose to present radiation-induced alterations in lung tissue density as changes in the Air-filled fraction (f_{air}) according to [18]:

$$f_{air} = 1 - \rho = -0.001 \cdot N_{CT}$$

where ρ is the electron density relative to water and N_{CT} is the measured CT number in Hounsfield units. The advantage of f_{air}, is that the relative effect seldom attains values over 100% in contrast to the relative change in tissue density, ρ [18]. Volumes of interests (VOI) for CT number measurements were defined on the RT planning computer. VOIs identified normal lung tissue in regions of homogeneous dose close to the tumour and were delineated on 3 adjacent CT slices with the middle slice containing the ICRU central axis dose. VOIs corresponding to regions covered by either 1 or several radiotherapy fields were chosen for each patient (Figure 1). The VOI size was typically 30-100 cm^3. The 2 Gy equivalent mean dose and whether the VOI was anteriorly, centrally or posteriorly located, were recorded. The standard deviation (SD) of the VOI dose distribution was always lower than 10%. A median number of 3 VOIs for each patient were defined (Table 1).

Hard-copy RT planning CT images of the VOI were compared with post-RT CT images. Corresponding CT images were identified by visually comparing bony and soft tissue anatomy, and the VOI could thus be digitally delineated on post-RT CT images. The overall mean CT number of the VOI was obtained from multiple small circular areas covering the VOI (Figure 1).

Ideally, the f_{air} obtained after RT should have been normalised according to the individual's baseline value obtained prior to RT (pre-RT). Unfortunately, it was not possible to obtain the baseline CT numbers from the images in the RT planning system. Therefore, the f_{air} was normalised according to a global f_{air} of 0.802, the mean f_{air} from all lung VOIs receiving a radiation dose less than 8 Gy. To investigate the uncertainty of this normalisation procedure, data from The Netherlands Cancer Institute were used. These data included f_{air} of low-dose (<8 Gy) areas of the lung from both pre-RT CT scans and 3-4 months post-RT. Thus, the ideal normalisation method could be compared with the method applied in the present study. The uncertainty introduced by not having access to the baseline f_{air} is measured to be 4% (R^2=0.96; Figure 2).

Statistics

To evaluate the reduction in Air-filled fraction the measurement times were pooled: within 30 days, 31-60 days and 61-90 days after end of RT. A repeated measurement analysis of variance was undertaken using the highest radiation (>40 Gy) dose to the VOI for each time interval, whether radiosensitiser dose was administered or not, CT post-RT examination time and VOI location (central, anterior, posterior) as explanatory variables.

p-values from 2-sided tests are presented, and should be considered hypothesis generating as no power calculations had been performed for the comparisons reported in this paper. The data were analysed with SPSS v10.1.0 and SAS v.9.1.3.

RESULTS

Air-filled fraction

The impact of the radiosensitiser and the radiation dose to the course of the Air-filled fraction (f_{air}), has been visualised in plots for each patient according to whether the patient received

radiosensitiser or not. The reduction in f_{air} increased with radiation dose ($p<0.001$), and the effect was more pronounced for those patients not given metoclopramide ($p=0.01$; Figure 3). The normal lung volume (both lungs delineated) irradiated with significant radiation doses (20-60 Gy) was negatively correlated with the reduction in f_{air}. The most significant parameter was v_{40Gy} ($p=0.003$; Figure 4). The time dependence of f_{air} was analysed using an interaction variable; time and whether metoclopramide was given or not. The reduction in f_{air} increased with the time interaction variable ($p=0.04$; Figure 5). There was a larger reduction in f_{air} for those VOIs located in the posterior position in the lung ($p=0.01$). There was no significant difference in f_{air} values comparing the central with the anterior position ($p=0.17$).

DISCUSSION

Air-filled fraction

In the present study we found that the density change (ρ) in the lung measured as an Air-filled fraction ($f_{air}=1-\rho$) change, was dependent on radiation dose. Normal lung tissue irradiated with more than 30 Gy was denser 50-100 days after treatment compared to tissue irradiated with a smaller doses (Figure 3a). This has also been demonstrated in previous studies. Theuws et al. [18] found that the effect measured as a relative change in f_{air} attained values significantly different from zero for doses larger than 20 Gy. Their results were derived from a material of lymphoma and breast cancer patients but were also confirmed in a study by Seppenwoolde et al for NSCLC patients [15]. In a study by Boersma et al., the dose-effect relation increased from zero effect at approximately 30 Gy (1). Rosen et al. found a threshold for physician-identified radiographic fibrosis at 30-35 Gy, but significant density changes were also detected for smaller doses [13].

Opposed to the positive correlation between local radiation dose to smaller lung volumes, there was a negative correlation between the normal lung volumes irradiated with significant

doses (v_{40Gy}) and the reduction in f_{air}. A possible explanation is an antitumour effect of the radiotherapy making the conditions for the normal lung tissue more favourable.

The CT examinations were performed at various time points post-RT but due to the limited patient number, an exact quantification of the relationship between reduction in f_{air} and time, was not possible. Skoczylas et al. [16] measured a change in optical density on follow-up x-rays of breast cancer patients treated with RT. These investigators found a monotonous increase in effect from 1 month reaching a plateau at 4-5 months and then decreasing moderately at 8-10 months. These findings are in agreement with a CT study by Rotstein et al., examining breast cancer patients at 3 and 9 months after RT [14].

The decrease in f_{air} was significantly larger for the posterior 1/3 of the lung. All patients were examined and treated in the supine position. Theuws et al. have demonstrated this effect previously [18]. Their explanation was a gravity-dependent density gradient causing a relative increase in lung mass (oedema) in the posterior region after irradiation.

There was a statistically significant association between high doses of metoclopramide, and the least reductions in f_{air}. Animal experiments have reported no increase in effects on normal tissue when combining RT with metoclopramide [11]. A possible explanation for the relationship between metoclopramide dose and f_{air}, is an antitumour effect similar to the negative correlation between normal lung volumes encompassed by the 40 Gy isodose (v_{40Gy}) and the reduction in f_{air}. The tumours were mostly centrally located (stage IIIA and IIIB), and the patients enduring the drug treatment, could get increased blood perfusion and airflow to the neighbouring normal tissues in the lung. These effects of tumour shrinkage have been shown by De Jaeger et al and Seppenwoolde et al. [5, 15]. The resulting improved physiological conditions after RT could make the lung tissue more resistant to development of fibrosis/pneumonitis. Tumour volumes before and after RT could have elucidated our data further. Regrettably, tumour volumes were not available in the present material.

In conclusion, there was an increase in the density of lung tissue with radiation dose and time after radiotherapy. This effect was more pronounced for the posterior lung volumes. Metoclopramide and irradiation of large lung volumes with significant doses seemed to protect against fibrosis/pneumonitis development. However, the number of patients in the analysis was low. Therefore, the results must be interpreted with caution.

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Patient ID	Metoclopramide (mg)	Mean Lung Dose (Gy)	# post-RT CT	#CT-VOI
1	3198	NA	2	3
2	2160	18.2	3	3
3	1920	21.5	3	3
4	0	16.4	3	4
5	616	16.3	1	2
6	0	15.9	3	3
7	0	17.6	3	2
8	320	19.3	2	4
9	0	NA	1	3
10	2160	19.8	3	2
11	0	9.8	3	2
12	0	NA	2	4
13	0	11.1	2	2
14	0	13.3	2	4
15	0	22.6	1	3
16	1800	10.6	3	3
		Mean Dose = 16.3 Gy	#CT = 37	#VOI = 47

Table 1: Radiosensitiser dose, mean radiation dose to both lungs, frequency of CT scans and number of VOIs per patient.

Tabelle 1: Radiosentiziser Dosis, mittlere Lungendosis, Anzahl durchgeführter CT Untersuchungen und Anzahl VOI’s pro Patient.

LEGENDS

Figure 1: The CT number of each VOI was calculated as the mean CT number of multiple circular regions covering the VOI.

Figure 2: Data from Netherlands Cancer Institute (NCI) demonstrating the uncertainty introduced by not having access to the pre-RT (baseline) CT examination. The relative reduction in Air-filled fractions without baseline have been normalised according to the mean CT number given less than 8 Gy, as in the present study. The NCI data are derived from 129 volumes in 14 patients.

Figure 3: The relative reduction in Air-filled fraction (f_{air}) as a function of radiation dose 50-100 days post-RT. a) Patients not given metoclopramide (n=9). b) Patients given metoclopramide (n=7). In the case of > 1 VOI, the mean f_{air} was used.

Figure 4: The relative reduction in Air-filled fraction (f_{air}) averaged over VOI>40 Gy and time 50-100 days, as a function of v_{40Gy}, the normal lung volume fractions irradiated with more than 40 Gy. The Pearson´s correlation coefficient was R^2=0.56 (n=13).

Figure 5: The relative reduction in Air-filled fraction (f_{air}) for VOI>40 Gy, as a function of time after end of radiotherapy schedule. In the case of > 1 VOI for a specific time, the mean f_{air} was used. a) Patients not given metoclopramide (n=9). b) Patients given metoclopramide (n=7).

ABBILDUNGEN

Abbildung 1: Die Hounsfield-Einheiten für jedes einzelne VOI berechnet sich aus der mittleren Hounsfield-Einheiten zirkulärer Regionen über jedem VOI.

Abbildung 2: Daten des niederländischen Krebs Institus (NCI) beschreiben Unsicherheiten die mit den nicht zugänglichen pretherapeutischen CT- Untersuchungen zusammenhängen. Wenn pretherapeutische CT- Daten fehlen, so ist die relative Reduktion der Air-filled Fraction (f_{air}) der Gruppe < 8 Gy, wie auch in unserer aktuellen Studie, im Verhältnis zur mittleren Hounsfield-Einheiten normalisiert. Die niederländischen Daten wurden aus 129 Volumina von 14 Patienten generiert.

Abbildung 3: Die relative Reduktion der Air-filled fraction (f_{air}) als Funktion der Strahlendose 50-100 Tage nach Strahlentherapie. a) Patienten ohne Metoclopramid (n=9). b) Patienten mit Metoclopramid (n=7). Im Falle von > 1 VOI, wurde die mittlere f_{air} benutzt.

Abbildung 4: Relative Reduktion der Air-filled fraction (f_{air}) für VOI > 40 Gy und Zeit 50 - 100 Tage als Funktion von V_{40Gy}, normales Lungevolumen bestrahlt mit mehr als 40 Gy. Pearsons Korrelationskoeffizient R^2=0,56 (n=13).

Abbildung 5: Relative Reduktion der Air-filled fraction (f_{air}) für VOI > 40 Gy als Funktion der Zeit nach Strahlentherapie. Im Falle von > 1 VOI für eine gegebene Zeit, wurde die mittlere f_{air} benutzt. a) Patienten ohne Metoclopramid (n=9). b) Patienten mit Metoclopramid (n=7).

Fig 1:

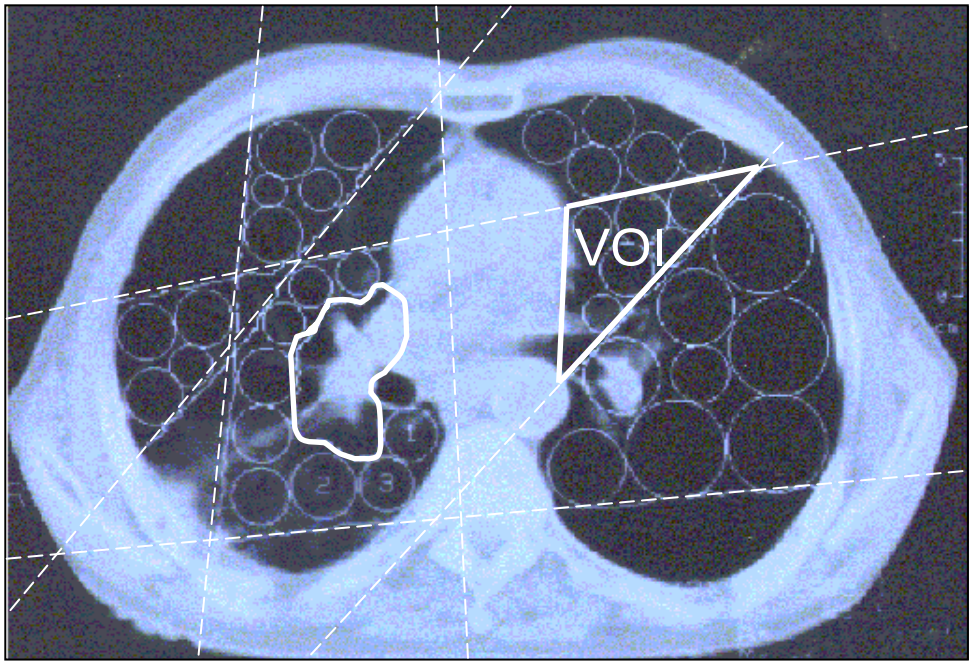


Fig2

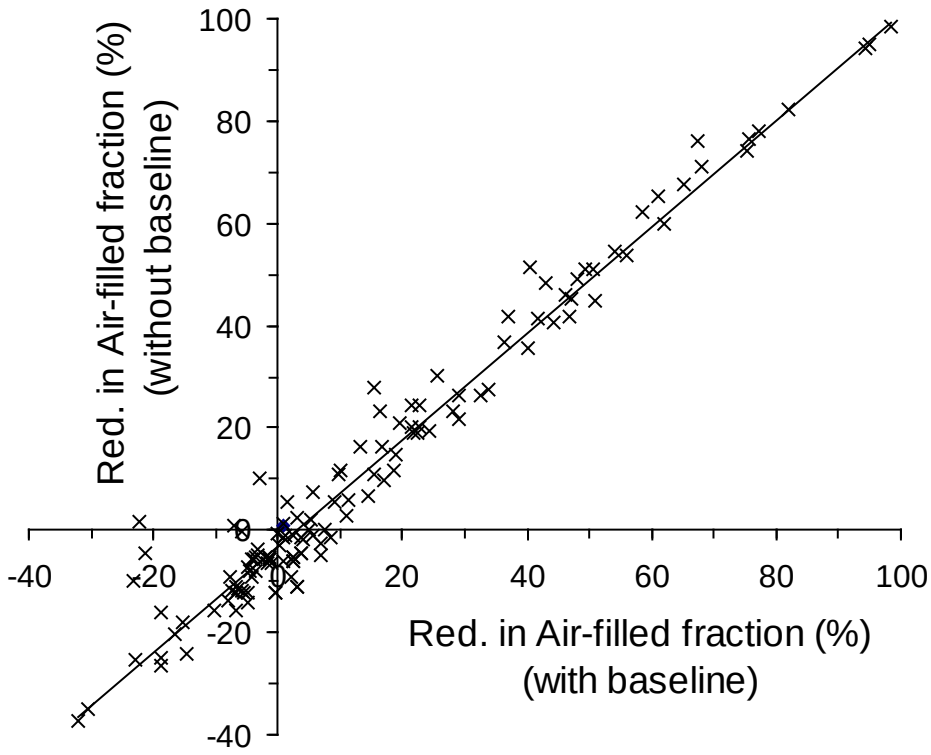

Red. in Air-filled fraction (%)
(without baseline)
Red. in Air-filled fraction (%)
(with baseline)
100
80
60
40
20
0
-20
-40
-40
-20
0
20
40
60
80
100

Fig3a:

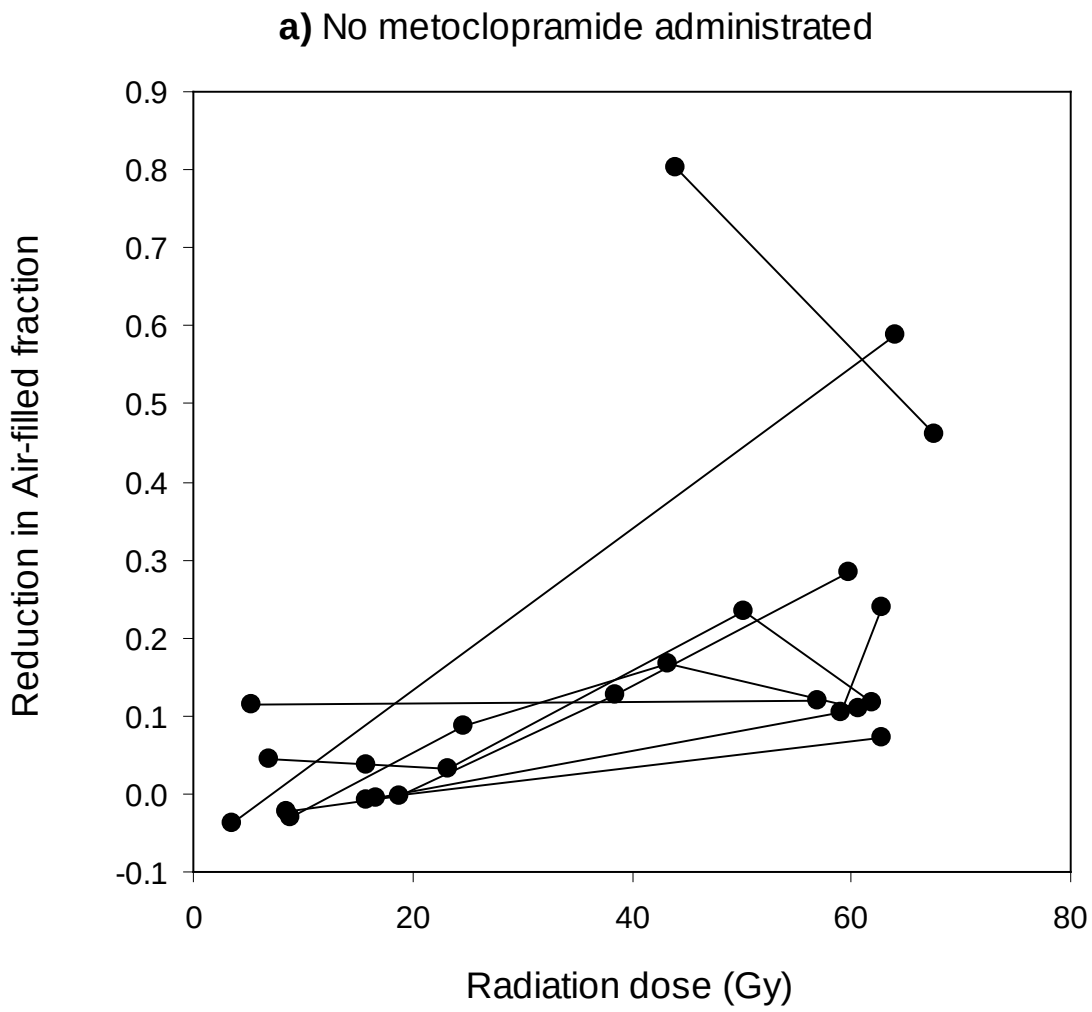

a) No metoclopramide administrated
Reduction in Air-filled fraction
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
-0.1
0
20
40
60
80
Radiation dose (Gy)

Fig3b:

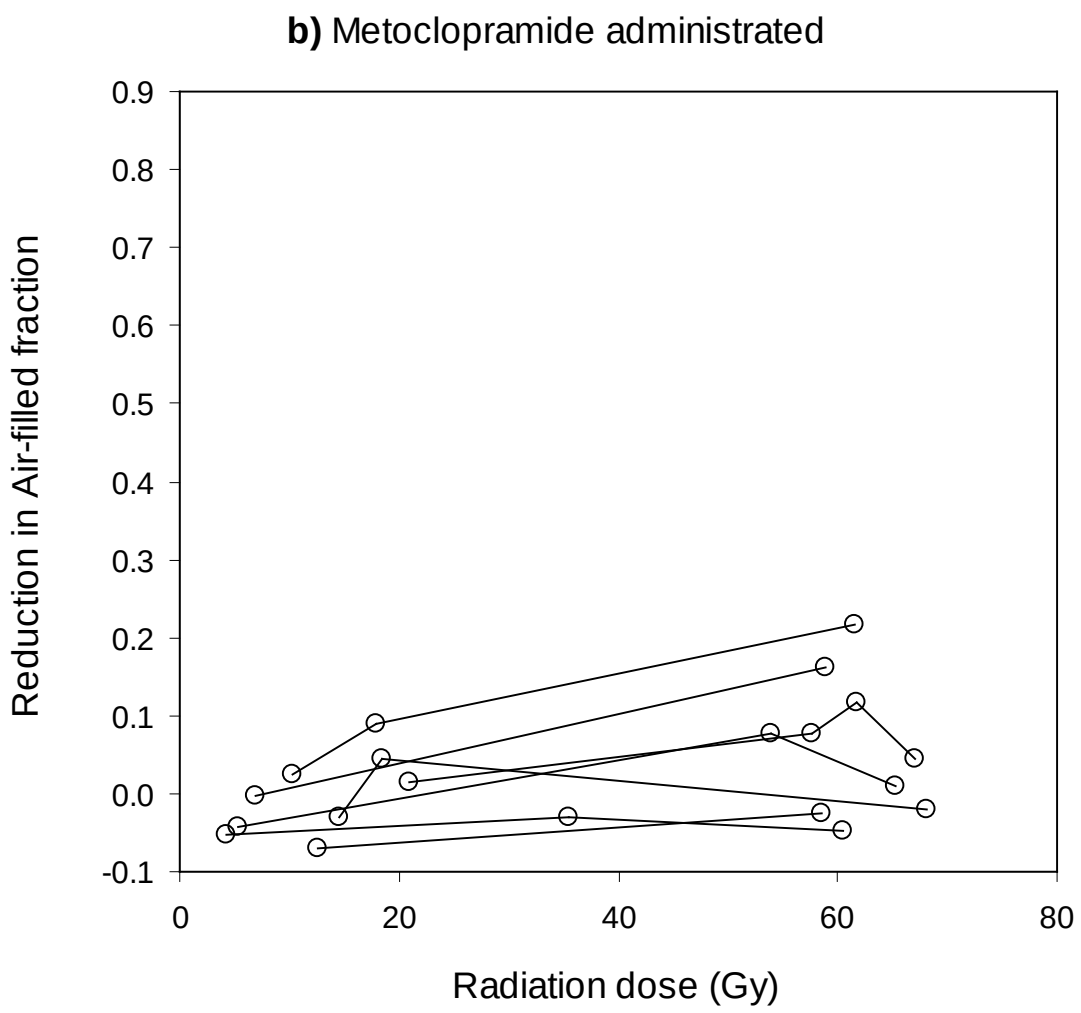

b) Metoclopramide administrated
Reduction in Air-filled fraction
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
-0.1
0
20
40
60
80
Radiation dose (Gy)

Fig4:

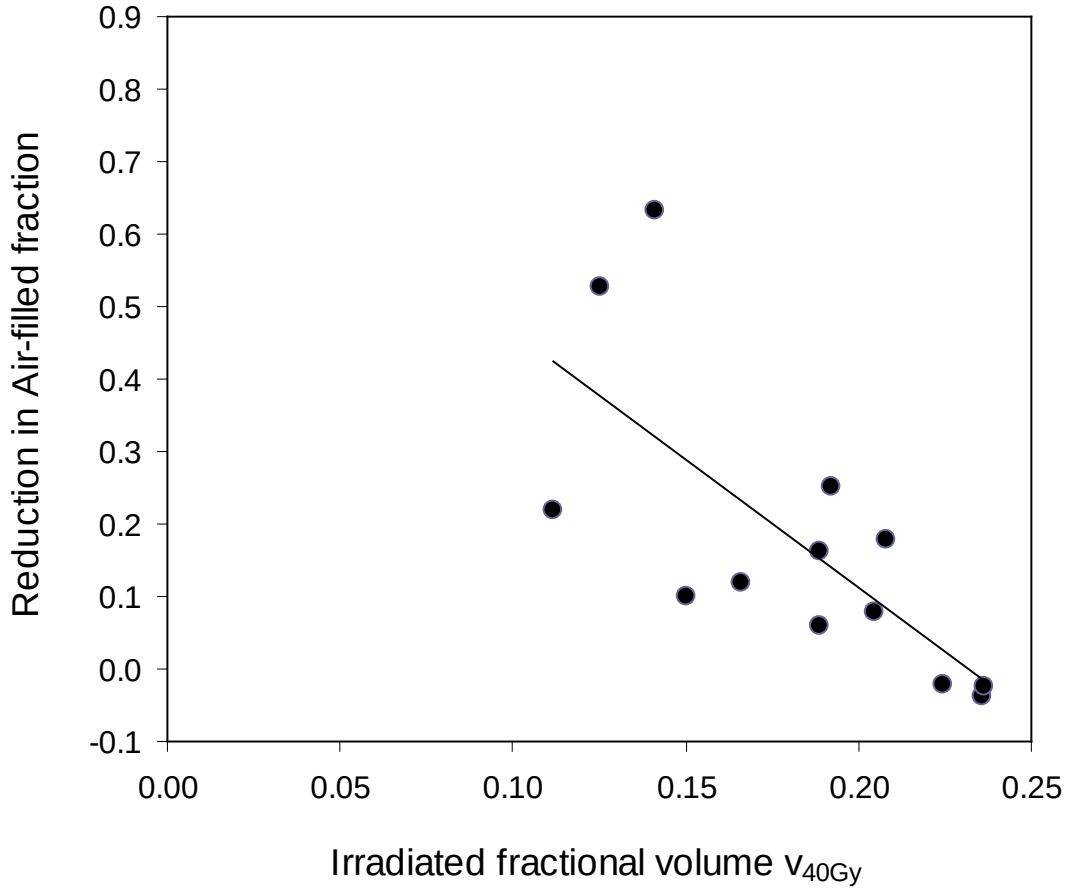

0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
-0.1
Reduction in Air-filled fraction
0.00
0.05
0.10
0.15
0.20
0.25
Irradiated fractional volume v40Gy

Fig5a:

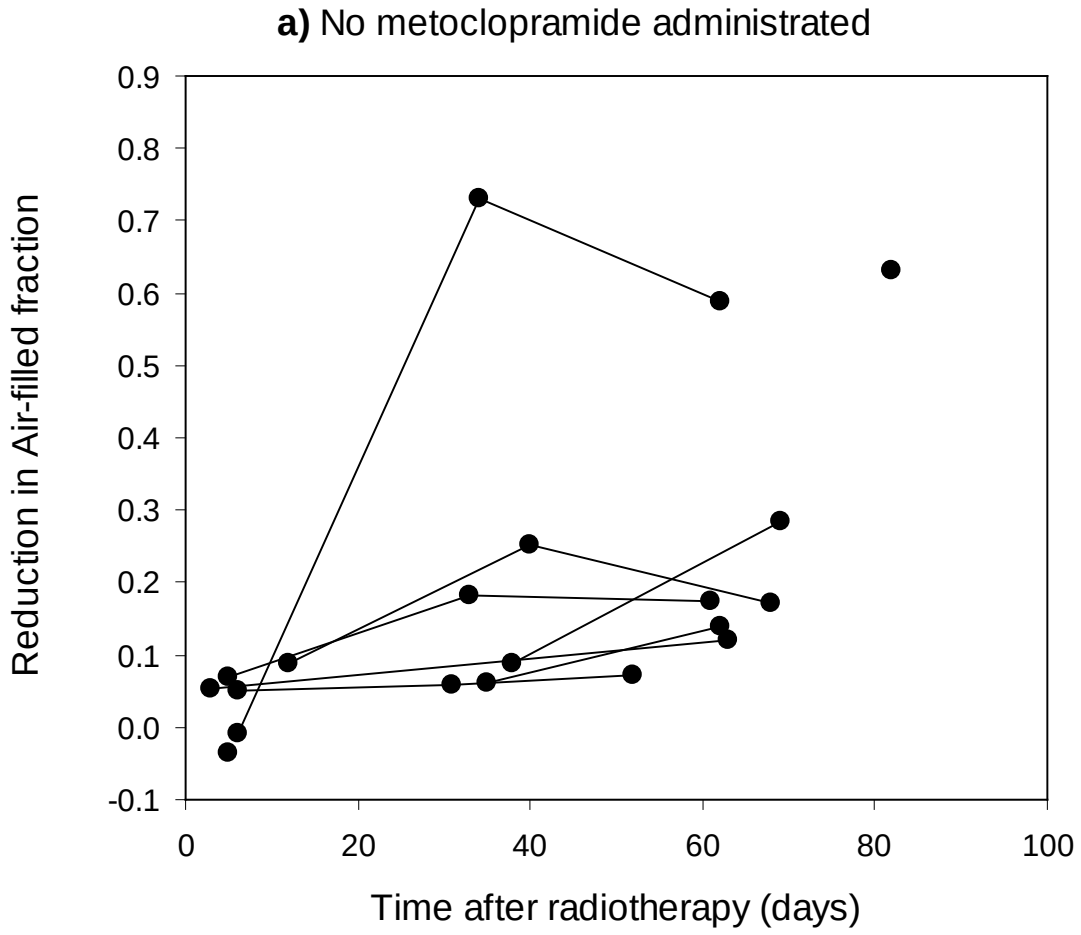
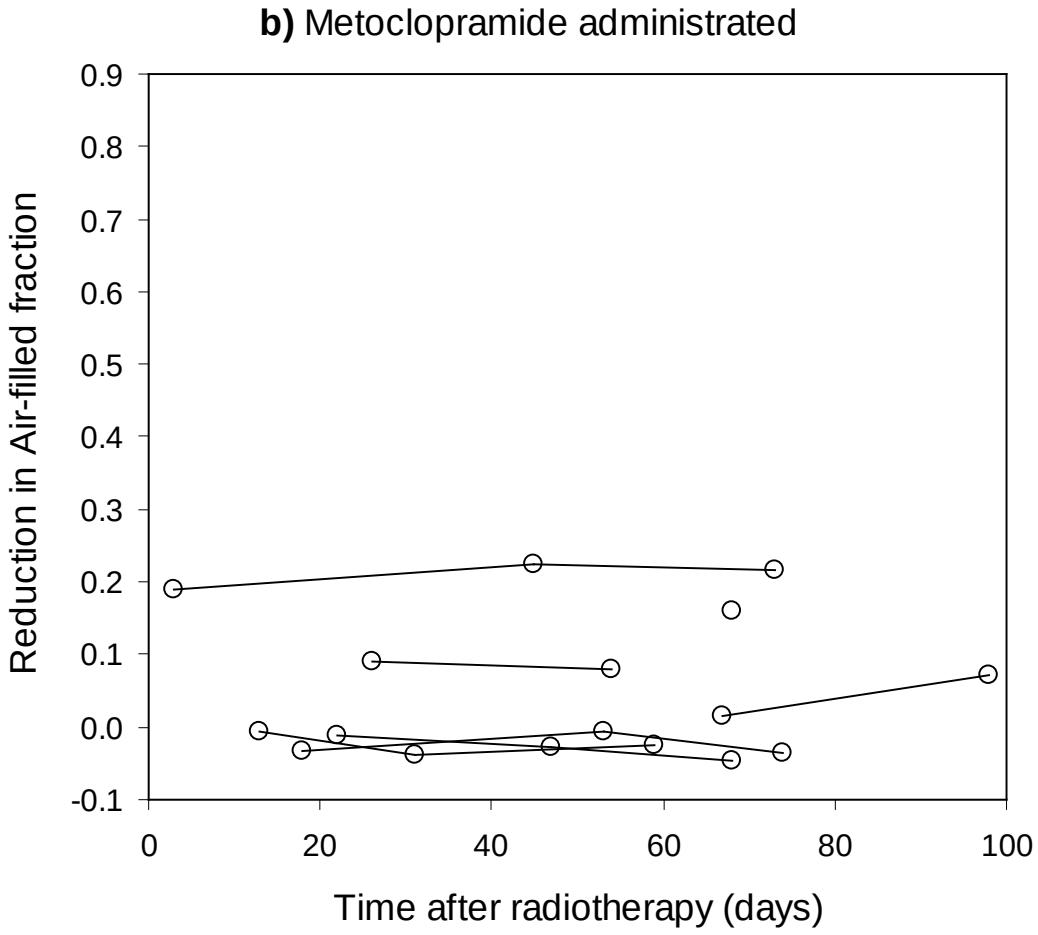

a) No metoclopramide administrated
Reduction in Air-filled fraction
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
-0.1
0
20
40
60
80
100
Time after radiotherapy (days)

Fig5b:


b) Metoclopramide administrated
Reduction in Air-filled fraction
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
-0.1
0
20
40
60
80
100
Time after radiotherapy (days)