Original Article

Post-treatment lymphocytopaenia, integral body dose and overall survival in lung cancer patients treated with radical radiotherapy

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ARTICLE INFO

ABSTRACT

Introduction: Post-treatment lymphocytopaenia is a recognized complication of thoracic radiotherapy likely due to irradiation of a large volume of circulatory blood. We hypothesize that post-treatment absolute lymphocyte count (ALC) is associated with integral body dose and overall survival (OS) in lung cancer patients treated with radical radiotherapy.

Materials and methods: Data on clinicopathological variables, dosimetric parameters, and pre and post-treatment blood counts were collected retrospectively in 217 lung cancer patients (131 with non-small cell lung cancer and 86 with small cell lung cancer) treated with radical radiotherapy. Induction chemotherapy followed by radiotherapy and concurrent chemoradiotherapy were delivered in 89 (42%) and 99 (47%) patients respectively. Multiple stepwise regression analysis was performed separately for ALC and absolute neutrophil count (ANC) to derive a model for prediction of post-treatment count and multivariate analysis was performed for OS using a Cox regression model.

Results: There was a significant decline in post-treatment counts for both ANC and ALC ($p < 0.001$). Multiple stepwise linear regression analysis confirmed pre-treatment ALC, body integral dose and use of concurrent chemotherapy as significant predictors of post-treatment ALC ($R^2 = 0.33$, $F(4,212) = 26.6$ $p < 0.001$). Pre-treatment ANC, integral heart dose and number of fractions were significant predictors of post-treatment ANC ($R^2 = 0.18$, $F(3,213) = 16.38$ $p < 0.001$). Low post-treatment ALC, high pre-treatment ANC, high planning target volume integral dose and lower number of fractions were predictive of inferior OS.

Conclusions: There is a negative correlation between integral body dose and post-treatment ALC which is an adverse prognostic factor in lung cancer patients treated with radical radiotherapy.

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Radiotherapy is used in the curative treatment of localized non-small cell lung cancer (NSCLC) patients not suitable for surgery and in the majority of patients with limited-stage small cell lung cancer (SCLC) [1,2,3]. Despite some advances in the fields of radiotherapy and systemic treatment, most patients with localized lung cancer will eventually develop disease progression and survival remains poor [4,5]. The dose of radiation delivered to tumour is limited by the toxicity of adjacent organs such as heart, oesophagus, spinal cord and uninvolved lung and as a result attempts at escalating dose have failed to translate into improvements in outcome [3,6].

Lymphocytopaenia is a well-recognized complication of thoracic radiotherapy that is associated with a poor outcome [7]. In a small study of NSCLC patients treated with radiotherapy, a post-treatment absolute lymphocyte (ALC) count less than 0.5×10^9/L showed a non-significant trend towards inferior survival [8]. Post-treatment ALC and ALC nadir during treatment were associated with a poor outcome in another study of SCLC patients treated with chemoradiotherapy [9]. A high pre-treatment neutrophil lymphocyte ratio (NLR) has also been identified as a poor prognostic factor in both NSCLC and SCLC patients treated with radical chemoradiotherapy [10,11]. However, these studies used dichotomized variables with inconsistent cut-off values and their results have not been validated in independent cohorts [8,9,10,11].

Lymphocytes are highly radiosensitive cells with a LD90 (lethal dose required to reduce survival fraction by 90%) of 3 Gy [12]. Radiation-induced post-treatment lymphocytopaenia should

therefore correlate with total dose delivered and total number of circulating lymphocytes exposed to radiotherapy. The high radiosensitivity of lymphocytes suggests that fractionated radiotherapy would enhance treatment-induced lymphocytopaenia.

In contrast to lymphocytopaenia, which is caused by increased cell death due to apoptosis, radiation-induced neutropaenia is the result of direct bone marrow suppression leading to reduced granulopoiesis [13]. Use of concurrent myelotoxic chemotherapy and volume of bone marrow irradiated are the most significant predictors of post-treatment neutropaenia [13]. Fractionation should be protective against radiation-induced neutropaenia as it permits greater recovery of haemopoetic tissue in-between fractions of radiotherapy.

Since the pulmonary circulation receives half of the cardiac output, a large volume of blood is irradiated during thoracic radiation compared to other regions of the body. Unlike other dosimetric variables, the integral body dose, defined as the product of mean body dose and body volume, is a robust parameter that is likely to be a predictive parameter of post-treatment lymphocytopaenia. Furthermore, a large volume of blood circulates through the heart during a fraction of thoracic radiotherapy and therefore integral heart dose is another plausible predictor of post-treatment lymphocytopaenia.

In this study we investigated the correlation between integral body dose, integral heart dose and integral PTV dose and post-radiotherapy absolute lymphocyte count (ALC) and absolute neutrophil count (ANC). We also investigated the impact of post-radiotherapy ALC and ANC on overall survival in lung cancer patients treated with radical radiotherapy.

Materials and methods

Patients

Lung cancer patients treated with radical radiotherapy (with or without chemotherapy) from 2010 to 2014 at the Christie Hospital, Manchester, UK were retrospectively reviewed. Patients were included in this study if their radiotherapy dosimetric data and pre-treatment and post-treatment full blood count were available. Patients treated with stereotactic ablative radiotherapy, post-operative radiotherapy and radiotherapy for recurrent disease were excluded from the study. Patients with oligometastatic disease, treated with radical thoracic radiotherapy to the primary disease were included in the study.

Data collection

Clinicopathological data on age, gender, performance status, histology, stage, use of induction and concurrent chemotherapy were obtained. Radiotherapy dose and fractionation regimens, planning target volume (PTV), heart and whole body mean dose and volume were collected directly from the treatment plans for the patients. The heart was be contoured along with the pericardial sac with its base defined as the superior aspect of pulmonary artery and the contour extended inferiorly to the apex of the heart. Integral dose was defined as the product of the mean dose and total volume of each structure (PTV or organ at risk). Pre-treatment and post-treatment ALC and ANC values were also recorded. Pre-treatment count was defined as the latest blood count prior to commencement of radiotherapy and post-treatment count was defined as the earliest blood count after completion of radiotherapy. Patients without blood counts within 60 days prior to commencement of treatment and/or within 60 days after completion of treatment were excluded from the study.

Statistical analysis

Differences between pre-treatment and post-treatment ANC and ALC counts were tested by using the Kolmogorov–Smirnov test. The association with post-treatment counts and the following dependent variables were tested separately for ANC and ALC with univariate simple linear regression analysis: pre-treatment count, number of fractions delivered, integral heart dose, integral PTV dose, integral body dose, histology, age, use of induction or concurrent chemotherapy, volume of lung receiving at least 20 Gy (V20) and mean lung dose. Multiple stepwise linear regression analysis of variables significant on univariate analysis was performed to derive a model for prediction of post-treatment counts

Finally, to determine prognostic impact, time-to-event analysis was carried out for overall survival (OS) using the Kaplan–Meier method. Univariate and multivariate analyses were performed using Cox regression analysis for the following variables: age, gender, histology, stage, performance status, use of induction or concurrent chemotherapy pre-treatment ANC, pre-treatment ALC, post-treatment ANC, post-treatment ALC, integral heart dose, total body integral dose, PTV integral dose and number of fractions.

All Statistical analyses were carried out using the statistical software R version 3.4.1.

Results

The study cohort comprised 131 patients with NSCLC and 86 patients with SCLC treated with radical radiotherapy with or without chemotherapy. The clinicopathological, dosimetric and blood count data of the whole cohort are listed in Table 1. 99 (46%) patients received concurrent chemotherapy while induction chemotherapy was used in 89 (41%) patients and 29 (13%) patients were treated with radiotherapy alone. A fraction size exceeding 2.1 Gy (hypofractionation) was used in 104 (48%) patients, while 23 patients (11%) received twice daily fractions. 89 (85%) patients treated with hypofractionated regimens received induction chemotherapy, but none received concurrent chemotherapy.

The median date of pre-treatment counts was 4 days prior to commencement of radiotherapy (range 0–52 days), while that of post-treatment counts was 6 days after completion of treatment (range 1–60 days).There was a statistically significant decline in post-treatment counts for both ANC and ALC ($p < 0.001$). However, the drop in post-treatment count was clinically more significant for ALC than for ANC. For example 127 (58.5%) patients had a post-treatment ALC below 0.5×10^6 but only 36/217 (16.6%) patients had post-treatment ANC below 1.5×10^6.

The results of the simple linear and multiple stepwise linear regression analyses of correlation with post-treatment ALC and ANC are described in Table 2. A high Integral heart dose, integral PTV dose and body integral dose were all significantly associated with low post-treatment ALC on univariate simple linear regression. However with multiple stepwise linear regression analysis, pre-treatment ALC ($\beta = 0.34$, $p < 0.001$), body integral dose ($\beta = -0.24$, $p < 0.001$) and use of concurrent chemotherapy ($\beta = -0.33$, $p < 0.001$) were significant factors associated with post-treatment ALC ($R^2 = 0.33$, $F(4,212) = 24.6$ $p < 0.001$). Pre-treatment ANC ($\beta = 0.15$, $p = 0.01$), integral heart dose ($\beta = -0.19$, $p = 0.003$) and number of fractions ($\beta = -0.31$, $p < 0.001$) were significant factors associated with post-treatment ANC ($R^2 = 0.18$, $F(3,213) = 16.38$, $p < 0.001$).

Table 3 shows the results of the univariate and multivariate overall survival analysis. Low post-treatment ALC, high pre-treatment ANC, high PTV integral dose and low number of fractions delivered were associated with lower survival on multivariate analysis. The Kaplan–Meier survival plots for pre-treatment

Table 1
Baseline characteristics of study population.

Age, median (range)	64 years (24–88)
Gender	
Male	113 (52%)
Female	104 (48%)
Histology	
Small cell lung cancer	86 (40%)
Non-small cell lung cancer	131 (60%)
Stage	
I	4 (2%)
II	43 (20%)
III	156 (72%)
IV	14 (6%)
Eastern Cooperative Oncology Group Performance Status	
0	60 (28%)
1	129 (59%)
2	26 (12%)
3	2 (1%)
Induction chemotherapy	89 (41%)
Concurrent chemotherapy	99 (46%)
Number of fractions delivered, median (range)	30 (16–34)
Fractionation	
Hypofractionation (>2.1 Gy per fraction)	104 (48%)
Conventional (1.8–2.1 Gy per fraction)	90 (41%)
Twice daily	23 (11%)
Mean dose to planning target volume, median (range)	55.4 Gy (39.2–69.5)
Planning target volume, median (range)	0.4 l (0.05–1.2)
Planning target volume integral dose, median (range)	22.3 l.Gy (2.7–70.8)
Heart integral dose, median (range)	13.6 l.Gy (0.5–35.2)
Body integral dose, median (range)	183.1 l.Gy (61.1–398.1)
Pre-treatment absolute lymphocyte count, median (range)	$1.7 \times 10^9/l$ (0.3–6.8)
Post-treatment absolute lymphocyte count, median (range)	$0.5 \times 10^9/l$ (0.1–2)
Pre-treatment absolute neutrophil count, median (range)	$6.1 \times 10^9/l$ (1.2–19.8)
Post-treatment absolute neutrophil count, median (range)	$3.6 \times 10^9/l$ (0.1–18.5)

neutrophilia and post-treatment lymphocytopaenia, when dichotomized at median, are depicted in Figs. 1 and 2 respectively.

Discussion

Multiple stepwise regression analysis confirmed our hypothesis that body integral dose correlates negatively with post-treatment lymphocytopaenia. However, unexpectedly, an association was also found between higher integral heart dose and lower post treatment ANC.

In a study of NSCLC patients treated with radical radiotherapy, higher volume of lung tissue receiving 5 Gy (V5) and higher volume of gross tumour were found to be significant predictors of lymphocyte count nadir during treatment [14]. Similar results were reported in a study of patients with malignant glioma where it was found that higher cerebral blood volume was associated with radiotherapy-induced lymphocytopaenia [15]. In a study in oesophageal cancer, lymphocyte count nadir was lower for photon therapy in comparison to those treated with protons [16]. Mean body dose, which was higher in patients treated with photons, significantly correlated with lymphocyte nadir [16]. While our findings are in agreement with these previous studies, we demonstrate for the first time an association between integral body dose and post-treatment lymphocytopaenia. Furthermore, neither mean lung dose nor lung V20 were significantly associated on with post-treatment ALC or ANC on multivariate analysis in our

Table 2
Regression analysis of predictor variables of post-treatment absolute lymphocyte count and post-treatment absolute neutrophil count.

Variable	Post-treatment absolute lymphocyte count				Post-treatment absolute neutrophil count			
	Univariate		Multivariate		Univariate		Multivariate	
	β	p value	β	p value	β	p value	β	p value
Age	0.18	0.006	–	–	0.16	0.02	–	–
Histology (SCLC)	0.15	0.03	–	0.06	–	0.15	–	–
Performance status	–	0.38	–	–	–	0.35	–	–
Stage	–	0.29	–	–	–	0.96	–	–
Pre-treatment count	0.30	<0.001	**0.34**	**<0.001**	0.17	0.01	**0.15**	**0.01**
Number of fractions	−0.4	<0.001	–	–	−0.37	<0.001	**−0.31**	**<0.001**
Integral heart dose	−0.24	<0.001	–	–	−0.25	<0.001	**−0.19**	**0.003**
Integral PTV dose	−0.37	<0.001	–	–	–	0.59	–	–
Integral body dose	−0.37	<0.001	**−0.24**	**<0.001**	–	0.14	–	–
Mean Lung Dose	−0.03	<0.001	–	–	−0.12	<0.001	–	–
Lung V20	−1.31	<0.001	–	–	–	0.08	–	–
Induction chemotherapy	0.27	<0.001	–	–	1.2	0.001	–	–
Concurrent chemotherapy	−0.38	<0.001	**−0.33**	**<0.001**	−1.84	<0.001	–	–

PTV, planning target volume. SCLC, small cell lung cancer. β, standardized coefficient.
V20, Proportion of volume receiving at least 20 Gy.
Statistically significant values are highlighted in bold.

Table 3
Univariate and multivariate analyses of overall survival.

Variable	Univariate		Multivariate	
	HR [95% CI]	*p* value	HR [95% CI]	*p* value
Age	–	0.31	–	0.07
Gender	–	0.96	–	0.71
Histology (SCLC)	–	0.89	–	0.4
Performance status	–	0.21	–	0.71
Stage	–	0.3	–	0.67
Number of fractions	**0.96 [0.94–0.98]**	**0.001**	**0.93 [0.88–0.99]**	0.03
Integral PTV dose	**1.01 [1–1.02]**	**0.04**	**1.02 [1–1.04]**	0.05
Integral body dose	–	0.19	–	0.74
Integral heart dose	–	0.91	–	0.69
Induction chemotherapy	**1.47 [1.08–1.99]**	**0.01**	–	0.81
Concurrent chemotherapy	**0.6 [0.44–0.82]**	**0.001**	–	0.31
Pre-treatment ALC	–	0.06	–	0.48
Pre-treatment ANC	**1.09 [1.04–1.14]**	**<0.001**	**1.07 [1.02–1.12]**	**0.009**
Post-treatment ALC	**0.63 [0.4–0.98]**	**0.04**	**0.41 [0.23–0.75]**	**0.004**
Post-treatment ANC	**1.07 [1.02–1.13]**	**0.006**	–	0.19

SCLC, small-cell lung cancer. PTV, Planning target volume. HR, Hazard Ratio. CI, Confidence Interval. ALC, absolute lymphocyte count. ANC, absolute neutrophil count.
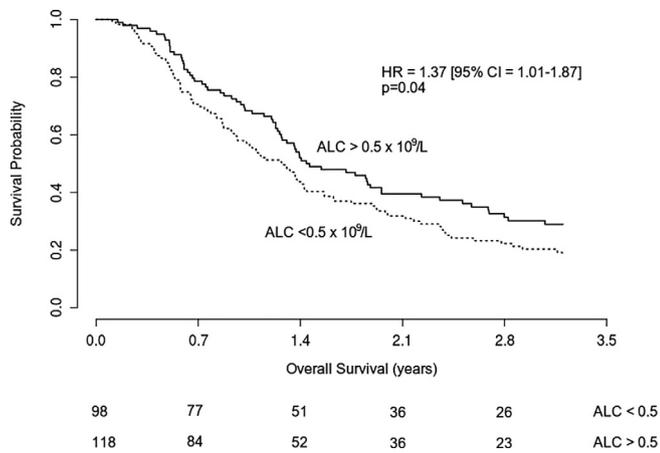Statistically significant values on multivariate analysis are highlighted in bold

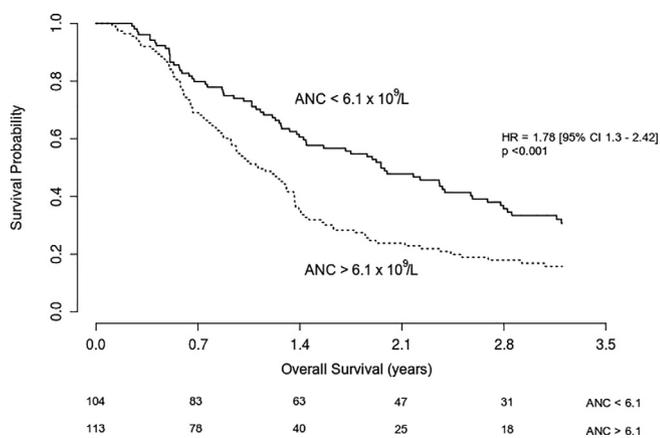**Fig. 1.** Overall survival with post-treatment absolute lymphocyte count dichotomized at median.

Fig. 2. Overall survival with pre-treatment absolute neutrophil count dichotomized at median.

radiotherapy ANC. Since the heart lies in the middle of the chest, integral heart dose may be a surrogate marker of dose to vertebral bone marrow. Previous studies have shown that post-treatment neutropaenia is the result of suppressed haemopoiesis due to direct bone marrow toxicity [13] Unfortunately, the bone marrow was not contoured as a separate structure in our patients and we could not therefore assess any direct dosimetric association. However, there was no association between either higher body integral dose or higher PTV integral dose and lower post-treatment ANC, excluding any effect of the low dose bath or high dose volume on ANC. Furthermore, as mentioned previously, although post-treatment ANC showed a statistically significant decline from baseline, it did not reach clinical significance in most patients. These findings suggest that suppression of cancer-induced inflammation, in addition to suppression of bone marrow haemopoiesis may play a role in neutrophil counts regressing to baseline from their high pre-treatment values in a majority of patients, upon completion of treatment.

Contrary to expectations, number of fractions delivered did not correlate with post-treatment ALC on multivariate analysis while use of concurrent chemotherapy was significantly associated with lower post-treatment ALC. The converse was true in the case of ANC, with increased number of fractions delivered was associated with lower post-treatment counts while use of concurrent chemotherapy had no significant association on multivariate analysis. These findings are confounded by the fact that all patients who received concurrent chemotherapy were treated with higher numbers of fractions (30–33) while most other patients were treated with hypofractionated schedules with lower numbers of fractions (20). While 85% (89/104) of patients treated with hypofractionated regimens received induction chemotherapy followed by radiotherapy alone, 88% (99/113) of patients treated with conventional regimens received concurrent chemoradiotherapy. As such, our data do not permit any robust inference on the effect of fractionation and use of concurrent or induction chemotherapy on post-treatment ALC and ANC nor on OS.

While pre-treatment and post-treatment ANC and ALC both predicted inferior OS on univariate analysis only pre-treatment ANC, post-treatment ALC, PTV integral dose and number of fractions delivered emerged as significant prognostic variables on multivariate analysis. Since cancer induced inflammation as reflected by a high pre-treatment ANC is a manifestation of aggressive tumour biology it is a better predictor of adverse outcome than post-treatment ANC [17]. On the other hand, our results suggest that post-treatment ALC is a potentially better predictor of

study. In our opinion, integral body dose is a more robust dosimetric parameter in comparison to lung V5, V20, mean lung dose or gross tumour volume as it encompasses the effect of both the low dose bath and the high dose volume.

To our knowledge this is also the first study to demonstrate an association between higher integral heart dose and lower post-

persistent anti-tumour immune incompetence than pre-treatment ALC. The adverse impact of higher PTV integral dose is due to increased tumour burden associated with larger PTV volumes. Patients treated with hypofractionated regimens are more likely to have more advanced disease and increased co-morbidities which explain the association between hypofractionation and inferior OS.

The results of the PACIFIC trial, in which treatment with the anti-PD-L1 antibody durvalumab following radical chemoradiotherapy resulted in a significant improvement in survival highlights the importance of the anti-tumour immune response in consolidating the effects of radical radiotherapy [18]. Retrospective studies have also shown that higher pre-treatment ANC and lower post-treatment ALC are markers of poor outcome in patients with metastatic NSCLC and melanoma treated with the anti-PD1 antibody nivolumab [19,20]. In addition, it has also been shown that increases in ALC after 2–3 doses of immune modulating antibodies predict superior response to therapy [21,22]. In this context, our data suggest that post-treatment lymphocytopaenia leads to anti-tumour immune suppression and subsequently, an inferior OS.

Even though we successfully demonstrated significant associations between integral body dose and post-treatment ALC, there was no prognostic association between integral body dose or integral heart dose and overall survival. Given the heterogeneous nature of our patient population it is likely that many confounding factors impacted on overall survival. While all patients in the study cohort were treated with radical intent, hypofractionated regimens are offered to patients with relatively poor prognostic features and worse performance status. These patients receive a lower prescribed dose to PTV with higher doses per fraction and are therefore more likely to have a lower total integral body dose. In addition, post-treatment lymphocytopaenia was included in the multivariate survival model further negating some of the prognostic effects of integral body dose.

The absence of a validation cohort is a major limitation of our study and its retrospective nature precluded determination of disease-specific survival. However, we have demonstrated for the first time, a significant association between higher integral body dose and post-treatment decline in ALC in addition to confirming the prognostic effect of pre-treatment ANC and post-treatment ALC on multivariate analysis.

Funding

Conflict of interests

The authors declare no conflict of interest.

Acknowledgements

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