Cancer Medicine Journal

Research Article | Vol 3 Issue 1

High Cardiac Radiation Dose Significantly Impacts Survival in NSCLC Patients Treated with Hypofractionated Chemoradiotherapy

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Abstract

Purpose: Concurrent chemoradiotherapy is the standard of care for locally advanced non-small cell lung carcinoma (NSCLC). The primary objective of the current study was to investigate the impact of high radiation dose to the heart in patients with locally advanced non-small cell lung cancer (NSCLC) treated with hypofractionated concomitant chemoradiotherapy (2.75 Gy per fraction).

Material and Methods: Data on 98 patients treated as per SOCCAR regimen (55 Gy in 20 daily fractions along with split dose of cisplatin and vinorelbine chemotherapy) were analysed. Mean heart dose (MHD) and V_{50Gy} (the percentage of heart volume receiving radiation dose ≥ 50 Gy) were correlated with overall survival.

Results: V_{50Gy} to ≥15% heart volume significantly affected the survival (hazard ratio 2.1 with 95% CI 0.9 - 4.9, p = 0.028). For patients with long-term survival (>600 days), value of V_{50Gy} even <15% was associated with poor prognosis (median survival not reached in 34 patients with V_{50Gy} <10% versus 1518 days in 23 patients with V_{50Gy} ≥10%: hazard ratio 3.9 with 95% CI 1.4 - 10.9, p = 0.005). Receipt of MHD of ≥25 Gy also showed a trend towards poor survival but this wasn't significant (hazard ratio 1.7 with 95% CI 0.80 - 3.6, p = 0.196).

Conclusion: To the best of author's knowledge, this is the first study showing detrimental impact of high cardiac radiation dose in non-small cell lung cancer patients treated with hypofractionated concomitant chemoradiotherapy. In particular, the impact was even more marked in long-term survivors.

Keywords: ***NSCLC; Chemoradiotherapy; Hypofractionated; Cardiac dose; Heart dose***

Received Date: November 12, 2019; **Accepted Date:** November 28, 2019; **Published Date:** December 05, 2019

Citation: Muhammad Shahid Iqbal, High Cardiac Radiation Dose Significantly Impacts Survival in NSCLC Patients Treated with Hypofractionated Chemoradiotherapy. Cancer Med J 3(1): 23-30.

Introduction

Lung cancer remains the leading cause of cancer-related mortality worldwide, with 1.6 million deaths per year [1]. Concurrent chemoradiotherapy is the standard of care in medically inoperable locally advanced non-small cell lung cancer (NSCLC) [2]. However, loco-regional failure remains a challenge as approximately up to one third of patients recur locally [2]. In order to try to improve the loco-regional control, dose-escalation has historically been considered an option. However, a recent dose escalation study, RTOG 0617 showed disappointing results with a higher dose chemoradiotherapy [3]. A multivariate analysis of this study showed the heart doses V_{5Gy} (the percentage of heart volume receiving ≥5 Gy) and V_{30Gy} (the percentage of heart volume receiving ≥ 30 Gy) were important predictors of patient survival. Based on findings of this study, Speirs et al. conducted a comprehensive retrospective analysis on 333 patients and found that heart dose V_{50Gy} (the percentage of heart volume receiving ≥50 Gy) was an independent predictor of survival [4]. These findings have led to increased recognition of the potential importance of high radiation dose to the heart in treating patients with NSCLC.

From experience of patients who have survived Hodgkin's lymphoma and breast cancer, it is well established that thoracic radiotherapy leads to an increased risk of cardiac disease [5,6]. There is sparsity of literature describing the impact of radiation dose to the heart in patients with lung cancer and most has evaluated patients with NSCLC who received chemoradiotherapy with 2 Gy per fraction which is the most common radiotherapy dose fractionation in these settings worldwide. Recently we published our report on 100 patients with NSCLC who were treated with hypofractionated chemoradiotherapy, 55 Gy in 20 daily fractions, i.e. 2.75 Gy per fraction, along with split dose of cisplatin and vinorelbine chemotherapy, as per SOCCAR regimen. The outcomes presented were comparable to conventional 2 Gy per fraction chemoradiotherapy studies [7].

In the current study, we evaluated the dosimetric effect of radiation dose to the heart in NSCLC treated with hypofractionated concomitant chemoradiotherapy. The primary aim of the study was to test the hypothesis that V_{50Gy} heart dose and mean heart dose (MHD) were predictors of survival in this specific patient population treated with 2.75 Gy per fraction.

Material and Methods

All 100 patients had histological confirmation of NSCLC. The treatment regimen was as per SOCCAR regimen [8]. It consisted of 55 Gy in 20 daily fractions at 2.75 Gy per fraction concurrent with split dose cisplatin (20 mg/m^2 intravenous with fractions 1-4 and 16-19) and vinorelbine (15 mg/m^2 intravenous on the day of fraction 1, 6, 15 and 20) followed by two cycles of consolidative chemotherapy (cisplatin 80 mg/m^2 day 1 and vinorelbine 25 mg/m^2 on days 1 and 8, three weeks apart). We elaborated the methodology in detail in our previously published study [7]. For the purpose of current manuscript, only the additional methods used in the new analyses are described below.

Out of 100 total patients treated with hypofractionated chemoradiotherapy, radiotherapy data was available in 98 patients. In the remaining two patients, radiotherapy plans could not be retrieved. On all cases, heart as organ at risk was outlined by either a clinical oncologist or an experienced dosimetrist. For quality assurance, the senior author (MSI) checked the heart contouring as per Feng et al. [9]. Until December 2015, radiotherapy was delivered using 3D conformal radiotherapy (n = 71) and after this date, the remaining 27 patients were treated with volumetric arc therapy (VMAT). The radiotherapy plans were exported in DICOM (digital imaging and communication in medicine) format from two planning systems, Masterplan® and Raystation® to ProKnow® to facilitate the extraction of tables of dose and volume data for easy analysis. Additional intersection volumes

were created between heart and PTV (planning target volume) and ProKnow® generated histogram data was exported for analysis. Survival was assessed from the date of first consultation, with a data cut-off of 1/12/2018. Mean heart doses of 10 Gy, 15 Gy, 20 Gy, 25 Gy and 30 Gy and cut-off of Heart V_{50Gy} of 5%, 10% and 15% was used to explore significance on overall survival (OS). SPSS (IBM SPSS Statistics 24.0.0.2) was used to generate Kaplan-Meier curves with a Mantel-Cox Log rank comparison to compare survival, with a 5% significance level used for exploratory analysis.

Results

The median age of patients was 63 years (range 43 - 75). All patients had a WHO performance status of 0 or 1. Ninety five percent of the patients had stage III NSCLC and 97% of all patients completed radiotherapy. With a median follow-up of 27 months, one and two-years overall survival (OS) were 81% and 58% respectively. Median OS was 43.4 months. Gender, age, performance status, histology or stage (II, IIIA and IIIB) did not influence survival. The number of chemotherapy cycles received was significant prognostic factor. We reported these results in detail in our previously published study [7].

Heart V50 Gy

As expected, there was a wide range (0 to 27.20) of the percentage of heart volumes receiving 50 Gy as shown in Figure 1. Five patients did not receive 50 Gy to any part of their heart ($V_{50Gy} = 0$) and 2 patients received 50 Gy to 27% of their heart volume ($V_{50Gy} = 27\%$). The number of patients receiving 50 Gy to 20% heart volume or more was small (n = 8) and this puts a limit on the highest dose that can be analysed. The analysis showed that in patients where V_{50Gy} cardiac dose was <5% (n = 22, against remaining 76 patients where V_{50Gy} was ≥5%), it didn't affect the survival (hazard ratio 1.57 with 95% CI 0.8 - 2.9, p = 0.198). Similarly, V_{50Gy} <10% (n = 59, versus 39 patients with V_{50Gy} cardiac dose ≥10%) didn't affect the survival either (hazard ratio 1.55 with 95% CI 0.9 - 2.8, p = 0.128). However, in patients where V_{50Gy} was ≥15% (n = 14, compared to remaining 84 patients where V_{50Gy} was less than 15%), it was associated with worst survival (hazard ratio 2.1 with 95% CI 0.9 - 4.9, p = 0.028). A further analysis of cases where heart V_{50Gy} was ≥20% failed to show significance (hazard ratio 1.5 with 95% CI 0.6 - 4.0, p = 0.356). The most likely explanation of this could well be because of low number of patients in this patient group (n = 8) which limited the meaningfulness of analysis. These results are summarised in Table 1. Figure 2 shows the comparison in survival between the patient groups receiving 50 Gy to less than 15% of their heart volume compared to that receiving ≥15%. Our analysis also showed that the effect of V_{50Gy} cardiac dose was evident in all volumes over time (compared to the reference group) for patients who survived ≥600 days, and this effect was more marked using a threshold of 10%, for example at 900 days survival (HR was 6.4 with 95% CI 2.0 - 25) (Figure 3).

Mean heart dose (MHD)

We also analysed the impact of MHD on survival. The average of the individual patient's mean heart doses was 15 Gy (range: 1 Gy - 37 Gy). A range of cut off doses (mean 10 Gy, 15 Gy, 20 Gy, 25 Gy and 30 Gy to the whole heart) were evaluated to test for the existence of a prognostic value. Because of the limited number of patients with higher mean doses to the heart (only two patients received ≥30 Gy), the analysis was limited to the maximum of 25 Gy. Therefore we assessed the 14 patients who received ≥25 Gy to the whole heart and found no significant difference in survival compared to patients receiving MHD <25 Gy (801 days versus 1560 days (hazard ratio 1.7 with 95% CI 0.8 - 3.6, p = 0.196) (Figure 4 and Table 2). However, visualisation of the Kaplan Meier curves suggested that the hazard ratios were not equal over time. We observed a differential impact in the risk on short term and long term survival with no observable effect until 2 years but worse survival beyond 2

years in patients receiving ≥25 Gy MHD. There was a similar, though less strong, effect for the mean heart dose of 20 Gy and 15 Gy. The relative risks for the various thresholds are shown in Table 2.

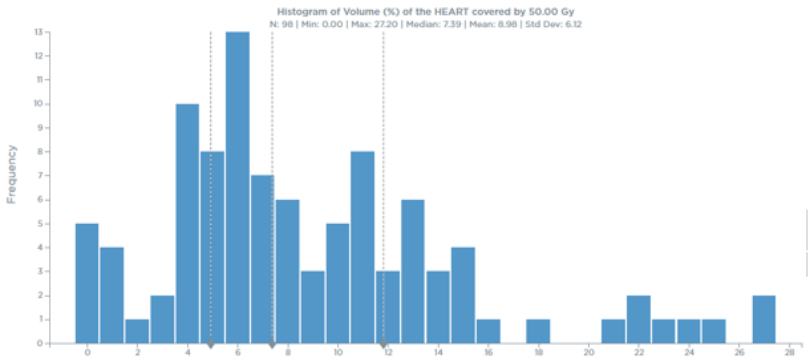

Figure 1: Range of percentage of the heart receiving 50 Gy in cohort.

% heart receiving 50 Gy (V_{50Gy})	V = 5%	V = 10%	V = 15%	V = 20%
Number of patients with ≥V_{50Gy}	76	39	14	8
Number of patients <V_{50Gy}	22	59	84	90
Hazard ratio with 95% CI	1.57(0.8 - 2.9)	1.55(0.9 - 2.8)	2.1(0.9 - 4.9)	1.5(0.6 - 4.0)
Log Rank (Mantel Cox)	0.198	0.128	0.028	0.356

Table 1: The impact on the risk of death overtime having received 50 Gy to more than 5%, 10%, 15% or 20% of the heart.

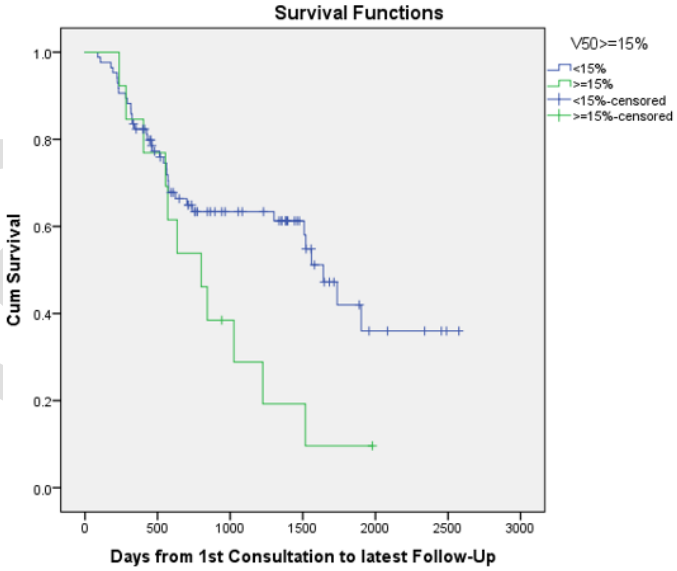

Figure 2: Kaplan-Meier overall survival curves for patients received V50 Gy cardiac dose to <15% or ≥15 Gy according to the heart V50 Gy.

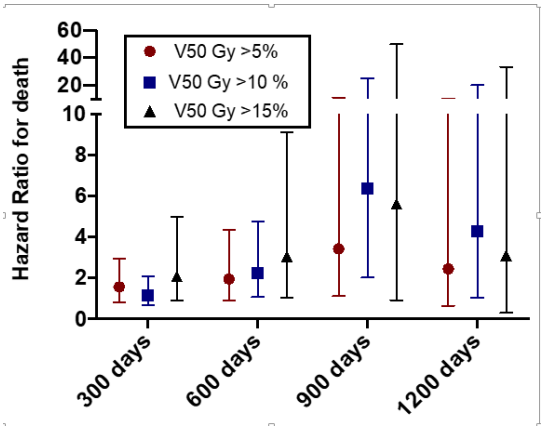

Figure 3: The change in risk of death overtime having received 50 Gy to more than 5%, 10% or 15% of the heart. Risk shown as the hazard ratio with 95% confidence interval compared to the reference group of patients who have received 50 Gy to volume of the heart below the threshold percentage.

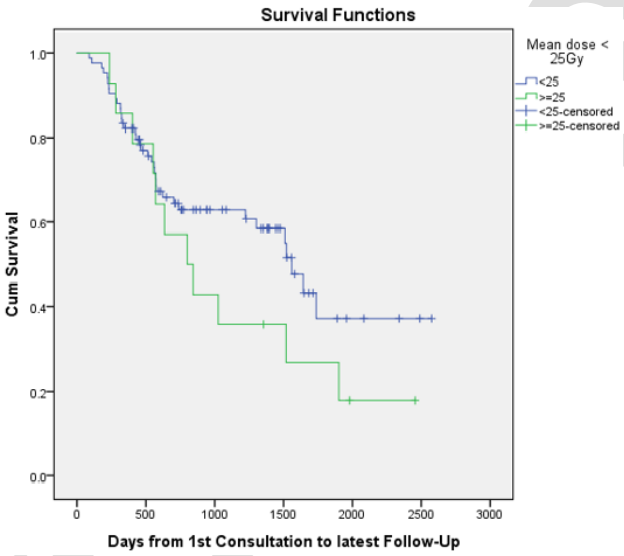

Figure 4: Kaplan-Meier curve showing overall survival of patients according to whether they received ≥ or <25 Gy mean heart dose.

Mean heart dose (Gy)	10	15	20	25
Number of patients ≥ specified dose	71	41	24	14
Number of patients < specified dose	27	57	74	84
Median survival ≥ specified dose	1302	1224	1026	801
Median survival < specified dose	Not reached	1560	1560	1560
Hazard ratio with 95% CI	1.78(0.97 - 3.3)	1.4(0.77 - 2.5)	1.4(0.72 - 2.7)	1.7(0.80 - 3.6)
Log rank (Mantel Cox)	0.056	0.273	0.293	0.196

Table 2: The impact of mean heart dose on overall survival.

Effect of cardiac dose on long term survival

The survival curves for both V_{50Gy} and mean heart dose show a clear difference between the effect of heart dose between short term survival and long term survival with separation at between 500 days and 600 days depending on the percentage of heart exposed to 50 Gy. The total number of patients who were alive and under active follow-up at 600 days was 57 and the remaining

41 patients had either died (n = 31) or were lost to follow-up (n = 10). We further analysed the impact of V_{50Gy} on survival in patients surviving more than 600 days (n = 57). The number of patients receiving 50 Gy to >15% of the heart is small (n = 8), limiting the ability to determine the exact percentage at which the effect is most significant. However, the analysis does show that the effect exists (Table 3). Figure 5 shows the Kaplan-Meier curve using the threshold of 10% V_{50Gy} where the median survival has not yet been reached in the 34 patients who received V_{50Gy} of <10% (with an average follow-up in this group of 2205 days) versus median survival of 1518 days in the 23 patients where the V_{50Gy} was ≥10%.

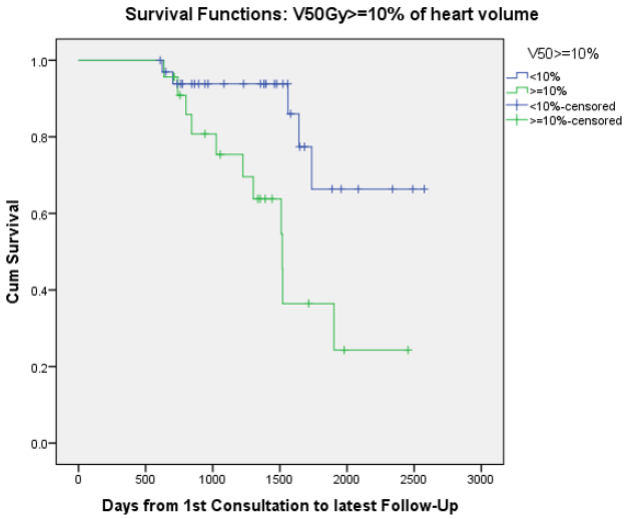

Figure 5: Long term survival as a function of volume of heart receiving 50 Gy comparing those with ≥10% of heart receiving 50 Gy with those with <10%.

% heart receiving 50 Gy (V_{50Gy})	V = 5%	V = 10%	V = 15%
Number of patients ≥ indicated V	41	23	8
Number of patients < indicated V	16	34	49
Hazard Ratio with 95% CI	4.0(1.4 - 11.0)	3.9(1.4 - 10.9)	4.0(0.74 - 22.9)
Log Rank (Mantel Cox)	0.045	0.005	0.001

Table 3: In patients surviving more than 600 days the impact on survival of the percentage volumes of heart receiving 50 Gy.

Discussion

To the best of authors' knowledge, this is the first study looking exclusively at the relationship between high cardiac radiation dose at 2.75 Gy per fraction concomitant chemoradiotherapy and survival for NSCLC treated with SOCCAR regimen. Our findings show a strong correlation between V_{50Gy} and long term survival. These findings are in consistent with previously described results by Spiers et al. [4] in their comprehensive analysis of radiation dose on the heart in NSCLC patients, using conventional 2 Gy per fraction chemoradiotherapy. Their analysis showed that increasing heart dose was an independent predictor of worse overall survival. In particular, heart V_{50Gy} was the strongest predictor (V_{50Gy} <25% *vs.* ≥25%, the one and two-year OS rates were 70.2% *vs.* 46.8% and 45.9% *vs.* 26.7% respectively; p<0.0001). Stam et al. [10], in their retrospective analysis on 569 patients treated with hypofractionated chemoradiotherapy (66 Gy in 24 fractions with concurrent daily low-dose cisplatin), studied the heart doses for parameters ranging from $V_{0.5Gy}$ to V_{45Gy}. In their analysis, the highest prognostic cut off was V_{2Gy}. V_{50Gy} wasn't an area of interest in their study. In another retrospective study by Tucker et al. [11], the effect of

heart doses on 2-years OS in NSCLC patients treated with chemoradiotherapy (60 Gy - 74 Gy in 1.8 Gy - 2 Gy per fraction) was studied. Their findings did not support an association between heart doses (mean heart dose, V_{5Gy} ≥50% and V_{30Gy} ≥25%) and 2-years OS. Again V_{50Gy} wasn't the area of interest in that study.

In a recently published systematic review by Zhang et al. [12], the authors found no consistent cardiac dosimetric parameters associated with overall survival, possibly as a result of difference in NSCLC patient population in the selected studies including non-cardiac comorbidities. We agree with the recommendations made in this systematic review that the radiotherapy target dose distribution should not be compromised in order to reduce heart dose. However, if heart dose can be minimised without compromising the therapy we suggest that this be of significant benefit to those patients surviving long term.

Durvalumab, an anti-PDL1 antibody, is now recommended in patients who complete concurrent chemoradiotherapy with response as consolidation treatment for a year, and has shown improved survival at 2-years after randomisation [13]. Immune myocarditis is a rare complication using single agent anti-PD1/PDL1 antibodies but is associated with a high mortality [14]. It will be important as durvalumab moves into routine clinical practice to assess whether patients who receive radiotherapy to large volumes of the heart are more prone to this rare complication.

Limitations of Study

Although this is a retrospective analysis which might potentially carry a bias, this is mitigated as we analysed all consecutive patients treated in our centre with this regimen. The only exclusion was two patients whose radiotherapy data was not available for the analysis. A limitation of the study is that two planning treatment methods were used to treat this cohort of patients; 3D conformal and VMAT. This has not been analysed in this study, since the purpose was to correlate heart dose to the outcome, irrespective of the technique to deliver that dose. It is a limitation that we solely analysed the effect of heart dose on survival and not cardiac toxicity as the information on acute and late cardiac toxicities were not available in detail. This should be the subject of further study. The selection of 600 days was a *post hoc* analysis performed after visualisation of the Kaplan-Meier curves and analysis of the change in hazard ratios over time and this should be looked at in future series.

Future Directions

Based on our findings, the authors suggest that effect of heart V50Gy on long term survivors should be the subject of prospective trials using conventional 2 Gy and where available, 2.75 Gy per fraction hypofractionated chemoradiotherapy regimens in NSCLC.

Conclusion

Accepting certain limitations, our study confirms that there is a significant impact of high cardiac radiation doses on survival especially on long-term survival for this cohort of NSCLC patients treated with hypofractionated chemoradiotherapy. With the introduction of consolidation durvalumab, high radiation dose to the heart may even have more impact on long-term survival. With the use of state-of-the-art radiation delivery techniques, every effort should be made to keep the cardiac dose as low as possible without compromising the target coverage required for tumour control.

Ethical Considerations

The data used in this retrospective study were collected through the radiotherapy datasets of patients treated in clinical practice. The patients' privacy and personal information were protected anonymously, so ethical approval was not required. The project was registered with institutional clinical effectiveness register as a service evaluation project. The registration number was 7413.

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