HEART DOSE ASSOCIATED WITH OVERALL SURVIVAL IN LOCALLY ADVANCED NSCLC PATIENTS TREATED WITH HYPOFRACTIONATED CHEMORADIOThERAPY

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SUMMARY

Association of heart dose and overall survival was investigated in a cohort including 469 locally-advanced NSCLC patients receiving daily low-dose hypofractionated chemo-radiotherapy. Significant associations were found over a range of dose parameters. Multivariate analysis showed significant associations of heart_V_{2Gy}:HR=1.007%\(^{-1}\) (95% CI: 1.002-1.013; p=0.006), age:HR=1.026year\(^{-1}\) (1.011-1.042; p=0.001) and GTV volume:HR=1.001cc\(^{-1}\) (1.000-1.002; p=0.006) with overall survival.
INTRODUCTION

An increased risk of heart disease decades after thoracic radiotherapy is well established in breast cancer and Hodgkin lymphoma patients [1,2]. More recently it was shown that in breast cancer patients there is an increased risk already in the first 5 years after treatment [1], suggesting that the dose to the heart could also be a concern for patients with a shorter life expectancy. Recently the RTOG 0617 trial, randomizing between 60/74 Gy with/without cetuximab, showed that in patients treated for locally advanced non-small cell lung carcinoma (NSCLC), an increased dose to the heart was associated with reduced overall survival (OS) [3]. The heart V$_5$ and V$_{30}$, i.e., the volume of the heart receiving at least 5 Gy and 30 Gy respectively, were both prognostic for OS. These patients were treated at 2 Gy per fraction over 6-7 weeks with weekly dose chemotherapy concurrent with radiotherapy, 51% concurrent with Cetuximab, followed by consolidation chemotherapy. Several studies that included at least 120 locally advanced stage NSCLC patients have confirmed or negated these associations. Tucker et al. did not find an association between heart dose and OS in a multivariate analysis but an association with the Mean Lung Dose (MLD) instead [4]. Their patient group received weekly chemotherapy concurrent with 60-74 Gy radiotherapy in 1.8-2 Gy per fraction. Wang et al. did find an association between mean heart dose and cardiac events for 127 patients treated with induction and/or concurrent weekly chemotherapy with radiotherapy [5]. Finally, Speirs et al. found that the heart V$_{50}$ was significantly higher for patients with cardiac toxicity, and they found an association between the heart V$_{50}$ and OS for 322 patients who received weekly chemotherapy with radiotherapy (neoadjuvant, concurrent and/or adjuvant), or radiotherapy alone [6]. At our institute, locally advanced NSCLC patients receive a different treatment regimen of daily low-dose cisplatin chemotherapy concurrent with hypofractionated radiotherapy. In this study we investigated the association between OS and heart dose for locally advanced NSCLC patients for this treatment regimen.

METHODS

Patient cohort

A retrospective analysis was carried out for patients treated at our institute between 2009 and 2014 for locally advanced NSCLC, stage IIA-IIIB. The treatment consisted of hypofractionated schedule of 66 Gy delivered in 24 fractions of 2.75 Gy with concurrent daily low-dose cisplatin (6mg/m$^2$), 5 days a week (overall treatment time (OTT) 32 days). Patients that received other schedules because of e.g. poor condition and/or normal tissue constraints were excluded. Follow-up (FU) consisted of three-monthly consultations for two years and six-monthly thereafter. Cause of death was not recorded. Patients receiving radiotherapy to the thoracic region for recurrent disease were censored at the start date of this treatment, to avoid the complications associated with the addition of dose given in separate treatment courses. Therefore, also patients that received RT to the thorax or breast region before the current treatment for NSCLC were excluded. Other exclusion criteria were failure of automatic extraction of treatment plans and FU, or when the treatment was adapted or stopped before completion.

Treatment planning and delivery

All contouring and treatment planning was carried out on a mid-ventilation (prior to August 2011) or a mid-position CT scan using contrast enhancement and a registered FDG-PET scan for target delineation [7]. The GTV-PTV margins for the primary tumor were 12 mm plus a quarter of the
peak-to-peak amplitudes in left-right, cranio-caudal and anterior-posterior directions as measured on the 4D CT scan [8]. For the involved lymph nodes, isotropic 12 mm GTV-PTV margins were used, irrespective of respiratory motion. The dose constraints for the heart were derived from Emami et al. [9]: a maximum of 40 Gy to the whole heart, i.e., heart $D_{\text{max}} \leq 40$ Gy, and the limits $D_{66\%} \leq 50$ Gy and $D_{33\%} \leq 66$ Gy. No additional effort was made during the treatment planning process to reduce the dose to the heart further, instead a major effort was directed at lowering the MLD. Treatment plans were created using Pinnacle\textsuperscript{3} (v7.6+, Philips Medical Systems, Best, The Netherlands) which uses a collapsed-cone dose calculation algorithm. All patients were treated using 5 to 7 beam step-and-shoot IMRT with 4-7 segments per beam with 10 MV photons. Position verification and setup corrections were carried out using weekly offline Cone-Beam CT (CBCT) guidance and a shrinking action level protocol up to February 2012 and daily online CBCT guidance from then on.

Analysis

As the guidelines for manual contouring of the heart had varied slightly over the years, the manual heart contour that was used for treatment planning was not used for dose parameter analysis. Instead analysis was done on a consistent heart contour, following Feng et al.’s heart atlas [10]. This contour was segmented automatically using the staple algorithm in ADMIRE (ADMIRE Research 2015, Elekta AB, Stockholm, Sweden). To this end, 50 patients who had their heart contoured according to the heart atlas were selected as atlases for the automatic segmentation of all patients. These 50 atlases were non-rigidly registered to the patient CT, and subsequently the 50 registrations were combined into one contour. For all patients, the normal lung tissue (lung-GTVs) dose-volume histograms (DVHs) were retrieved from the archived records, and DVHs for the heart were obtained using in-house software (Match42) [11]. We considered the relative volume parameters $V_{0.5\text{Gy}}$, $V_{1\text{Gy}}$, $V_{2\text{Gy}}$, $V_{3\text{Gy}}$, $V_{4\text{Gy}}$ and $V_{5\text{Gy}}$ to $V_{55\text{Gy}}$ in 5 Gy increments and the equivalent uniform dose (EUD) [12,13] with parameter $n$ ranging between {0.1, 0.2, 0.5, 0.8, 1, 2, 3, 4, 5, 10}. We used the physical dose as given in our 2.75 Gy fractions and enabled a comparison to RTOG 0617, where 2 Gy fractions were given. The endpoint of this study is overall survival. First, we performed univariate analyses for all heart dose parameters. The dosimetric parameter with the highest likelihood was split on the median into two groups and the difference between the groups was tested in a log-rank test. Second, the dosimetric parameter with the highest likelihood was tested for potential confounders: age, gender, GTV volume (primary tumor + involved nodes) and MLD [14]. Finally, a multivariate Cox regression was performed including the dosimetric parameter and all significant confounders. To compare to Tucker et al. [4], we also test the association between MLD and overall survival, and included MLD in a separate multivariate analysis. All tests for significance were conducted at the 5% significance level using SPSS (IBM SPSS, Version 22.0. Armonk, NY, USA).

RESULTS

Four-hundred and sixty-nine patients were included (Table 1), with an average age of 65 year, WHO performance of mostly 0 or 1, and mostly stage IIA-IIIB. The median OS was 21 months (95% CI:17.8-24.2), and the 1 and 2 year Kaplan-Meier estimates [15] of OS rate were 69% and 46% respectively. Median follow-up was 55 months.

The univariate analysis based on relative heart volume parameters yielded significant results for all parameters ranging from $V_{0.5\text{Gy}}$ to $V_{45\text{Gy}}$, with $V_{5\text{Gy}}$ HR = 1.007 %\textsuperscript{-1} (95% CI: 1.003-1.010;p<0.001),
while the highest likelihood was found for the $V_{2\text{Gy}}$; HR = 1.008 %$^{-1}$ (95% CI: 1.004-1.012; $p<0.001$). Univariate analysis based on EUD parameter were significantly associated to OS for n-values from 0.1 to 10, with the highest likelihood for EUD$_{n=0.5}$; HR = 1.021 Gy$^{-1}$ (95% CI: 1.009-1.033; $p<0.001$).

The median $V_{2\text{Gy}}$ was 59.7%, and the Kaplan-Meier plot split on this median is shown in figure 1. The two groups were significantly different ($p<0.001$), with a median OS of 30 and 17 months for the $V_{2\text{Gy}} < 59.7\%$ and $V_{2\text{Gy}} \geq 59.7\%$ respectively.

Age, gender and GTV volume were significant confounders in the associations of $V_{2\text{Gy}}$ with OS and were included in a multivariate Cox regression. The heart $V_{2\text{Gy}}$, age and GTV volume were significantly associated with OS; $V_{2\text{Gy}} = HR 1.007 \%^{-1}$ (95% CI: 1.002-1.013; $p=0.006$), age=HR 1.026 year$^{-1}$ (95% CI: 1.011-1.042; $p=0.001$) and GTV volume= HR 1.001 cc$^{-1}$ (95% CI:1.000-1.002; $p=0.006$).

MLD was significantly associated to OS; HR 1.047 Gy$^{-1}$ (95% CI: 1.017-1.079; $p=0.002$). Inclusion in a multivariate Cox regression also including heart $V_{2\text{Gy}}$, age, gender and GTV volume only yielded the heart $V_{2\text{Gy}}$, age and GTV volume as significantly associated to OS, as shown above.

Table 1. Patient characteristics

<table>
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<td>0-91</td>
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<td>%</td>
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GTV = Gross tumor volume
Figure 1. Kaplan Meier plot of overall survival for patients with a $V_{2 Gy} > \text{median}$ and $V_{2 Gy} < \text{median}$.
DISCUSSION

We found significant associations between heart dose and overall survival in our cohort that included 469 locally advanced NSCLC patients treated with daily concurrent hypofractionated chemoradiation. The dosimetric parameter with the highest likelihood was the V$_{2\text{Gy}}$ and patients with a V$_{2\text{Gy}}$ higher than the median had a significantly lower OS than patients with a V$_{2\text{Gy}}$ lower than the median. In literature, the V$_{5\text{Gy}}$, V$_{30\text{Gy}}$, V$_{50\text{Gy}}$, and the mean heart dose have been reported [3,16,6]. These studies were done on (mainly) stage III NSCLC patients that received (concurrent) chemoradiotherapy. Although radiotherapy and chemotherapy schedules varied, these and our study show that heart dose is independently associated with OS [3,6] or cardiac toxicity [16].

Comparable to the RTOG 0617 trial, we found significant associations between heart V$_{5}$ and OS, both with HRs of 1.007 %$^{-1}$ [3]. The higher V parameters V$_{30\text{Gy}}$, found in the RTOG 0617 trial, was also significantly associated with OS in our cohort, but the V$_{50\text{Gy}}$ found by Speirs et al. was not [3,6]. The HR of the strongest predictor, V$_{2\text{Gy}}$, changed only by 0.001 between the univariate and the multivariate analysis, indicating a stable association. Three major differences between our cohort and the RTOG 0617 cohort are 1) our patients received daily, not weekly, low-dose chemotherapy. This is better tolerated than full dose chemotherapy given concurrently [17]. 2) Our patients received exclusively IMRT, where in the RTOG 0617, about half of the patients received IMRT, and the other half 3D-CRT. Because heart dose is penalized in an IMRT plan, 3D-CRT may cause more dose to the heart, especially when the GTV is in close proximity to the heart. 3) The patients in our analysis were treated with a hypofractionated schedule up to a total dose of 66 Gy in 24 fractions with an overall treatment time (OTT) of only 32 days. The OTT of the radiotherapy course in the RTOG 0617 was 6 and 7.5 weeks to deliver 60 to 74 Gy, and the majority received consolidation chemotherapy (2 courses), which might have caused extra cardiac toxicity [18]. Despite these differences, these studies both show a very similar association between heart dose and OS.

We did not convert our doses to EQD2-doses, as we wanted to enable a comparison to the physical doses used by Bradley et al. [3]. However, given the low fraction doses to the heart found to be associated with OS, EQD2 conversion would have limited effect. Therefore our conclusion that the associations between dose and OS are strongest for the low V parameters remains valid.

We associated cardiac dose to OS in this analysis, as was done in the RTOG 0617 study and other literature [3,4,6]. Since we did not have access to the cause of death for most of the patients analyzed, we could not exclude deaths caused by other factors than heart toxicity. To enable the determination of dose constraints for future planning studies, non-cancer death or even cardiac associated death and not OS is preferred. Stam et al. investigated associations between heart dose and non-cancer death in early stage NSCLC patients that received stereotactic body radiotherapy (3x18Gy). Albeit a different patient cohort (early and not locally advanced NSCLC patients), and a different treatment (radiotherapy and not chemoradiotherapy), this cohort also showed an association between heart dose and survival, namely non-cancer death [11]. Differences are that the early stage NSCLC patients showed the strongest association with survival with the D$_{1\%}$ (dose to 1% of the heart volume) [11], which is comparable to the high V parameters, where our cohort of advanced stage NSCLC patients showed the strongest association with the low V parameters.
Since this was a retrospective analysis, we might be sensitive to a bias in patient selection or FU. The cases excluded from analysis (10%) were those where automated retrieval of treatment plans and FU failed, which should be uncorrelated to survival. Other cases excluded were patients that did not finish their intended treatment due to plan adaptation or being unable to tolerate the treatment. These exclusions might lead to an overestimation of the OS of the whole group since the patients that could not complete the treatment were excluded. However, we suspect that the exclusion of these groups is unrelated to dose to the heart, and would therefore not influence the association with OS in our cohort.

Opposed to Tucker et al. (468 patients) [4], in our paper (469 patients) and in the paper by Speirs et al. (322 patients), heart dose did remain significant even if MLD was included in the multivariate analysis. These opposing results indicate that the interplay between heart and lung doses should not be ignored, as demonstrated by Cella et al. for the risk of lung fibrosis and valvular dysfunction [19,20] and by Ghobadi et al. for pulmonary toxicity [21]. Prospective investigation into the association between heart dose and cardiac toxicity is warranted.

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REFERENCES


