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An Institutional Audit of Maximum Heart Dose in Patients Treated With Palliative Radiotherapy for Non-small Cell Lung Cancer

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Abstract. *Background/Aim: Recent studies suggested that high unintended radiation doses to the heart may reduce survival of patients with non-small-cell lung cancer (NSCLC) irradiated with curative intent. In the palliative setting, limited information is available. Therefore, we analyzed a single-institution cohort of 165 patients. Patients and Methods: Patients in this retrospective study received palliative (chemo)radiotherapy (at least 30 Gy). Typical radiation doses were 10-13 fractions of 3 Gy and 15 fractions of 2.8 Gy. Heart dose constraints were not employed during treatment planning. The maximum dose to 1 cc of the heart was registered and converted into the equivalent dose in 2-Gy fractions (EQD2). Results: The median heart dose (maximum to 1 cc) was 26 Gy (range=11-42 Gy). This dose corresponded to 28-108% of the prescription dose. After conversion into EQD2, the median maximum heart dose to 1 cc was 26 Gy, range=10-58 Gy). Neither higher T-stage nor higher N-stage predicted for higher maximum heart EQD2. The maximum heart EQD2 was not associated with overall survival. Conclusion: The current practice of focusing on sparing of lungs and esophagus appears acceptable in the context of palliative regimes. To further strengthen this strategy, additional studies looking at cardiac substructures and other dosimetric variables such as mean dose are warranted.*

Radiotherapy for non-small-cell lung cancer (NSCLC) requires a balance between efficacy and safety, meaning that the dose to critical organs-at-risk (OAR) must be calculated and weighed against the desire to cover the target volume with a high dose (1). The probability of tumor control is not an isolated parameter. Achieving a safe dose to the lungs, esophagus and spinal cord has long been regarded essential in the treatment-planning process (2). Due to better treatment delivery techniques, it has become possible to respect the OAR dose constraints while trying to escalate the dose to the target volume (3). However, researchers have also realized that an unintentional dose to the heart may compromise the success of high-dose radiotherapy for NSCLC (4-6). Recent recommendations include heart-sparing approaches but, unlike in the curative setting, fewer data are available for the large group of patients who receive palliative radiotherapy. Intermediate radiation doses of between 30 and 60 Gy, such as the Norwegian CONRAD regime (42 Gy in 15 fractions) (7), are endorsed in current guidelines (8), preferably in combination with platinum-based chemotherapy. In clinical practice of palliative radiotherapy, OAR contouring and prioritization, as well as treatment delivery technique vary between institutions (9-12). In order to study the radiotherapy heart dose in a real-world practice setting, we performed a retrospective analysis of patients who received palliative radio- or chemoradiotherapy.

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Patients and Methods

We included 165 consecutive patients irradiated with palliative three-dimensional conformal radiotherapy or chemoradiotherapy to an equivalent dose of at least 30 Gy in 10 fractions between 2009 and 2019. Patients treated with low-dose radiotherapy, primarily two fractions of 8.5 Gy, were excluded. In the case of combined bimodal treatment, most patients received the Norwegian CONRAD regime (15 fractions of 2.8 Gy, four cycles of carboplatin/vinorelbine before and during radiotherapy) (7). The individual treatment concept was recommended by the hospital's lung cancer Multidisciplinary Tumor Board. Treatment plans were calculated with Varian Eclipse TPS® (Varian Medical Systems, Palo Alto, CA, USA) and no intensity-modulated or arc-based techniques were employed. The dose was prescribed to the reference point. A minimum dose of 95% to the clinical target volume was attempted. Mandatory OAR contouring

included left and right lung and spinal canal. Esophageal and heart contouring was at the discretion of the treating physician. If these organs were contoured, the physician was to specify the desired dose constraints at the time of prescribing treatment in the electronic radiotherapy record (Varian Aria®). For the purpose of a recent retrospective toxicity assessment (13), patients without contoured OAR had their original plan recalculated after complete contouring. The heart contours did not include the aorta, pulmonary arteries and veins. Eventually, all 165 patients had their maximum dose to 1 cc of the heart registered (absolute dose in Gy and as a percentage of the prescribed dose). We then calculated the 2-Gy equivalent dose (EQD2) according to the linear-quadratic model with an alpha/beta value of 2 Gy (14). IBM SPSS v.25 (IBM, Armonk, NY, USA) was employed for statistical analyses. The latter included univariate Cox regression for associations between heart EQD2 (continuous variable) and overall survival. Significance was defined as $p<0.05$. Actuarial overall survival from the start of radiotherapy was also calculated according to the Kaplan–Meier method. Survival curves were compared by log-rank test. At the time of this analysis, 18 patients were alive (censored observations after a median follow-up of 14.4 months, minimum 4 months). Date of death was known for all remaining patients.

Table I. *Baseline parameters of study patients.*

Parameter	Value
Median clinical target volume, cc	
Median (range)	134.5 (10-1,185)
Median planning target volume, cc	
Median (range)	401.5 (95-1,950)
Median age, years	
Median (range)	69.5 (41-90)
Gender, n (%)	
Male	90 (55%)
Stage, n (%)	
<III	10 (6%)
III	76 (46%)
IV	79 (48%)
Radiation dose, n (%)	
Low	54 (33%)
Intermediate	33 (20%)
High	78 (47%)
Concomitant chemoradiotherapy, n (%)	
Yes	53 (32%)

Radiation dose: Low: 10 fractions of 3 Gy; Intermediate: 13 fractions of 3 Gy and comparable regimes; High: 15 fractions of 2.8 or 3 Gy.

Results

The baseline parameters are shown in Table I. Concomitant chemoradiotherapy was given in 32%. Most patients received radiotherapy alone. Commonly, intermediate or high palliative doses were prescribed, *e.g.* 13 fractions of 3 Gy or 15 fractions of 2.8 Gy. None of the patients had any heart as OAR dose constraints registered at the time of treatment planning. The median heart dose (maximum to 1 cc) was 26 Gy (range=11-42 Gy). This dose corresponded to 28-108% of the prescribed dose, meaning that the dose per fraction may have been as low as 0.78 Gy or as high as 3.24 Gy. After conversion into EQD2, the median maximum heart dose to 1 cc was 26 Gy (range=10-58 Gy). Stratified by prescribed radiation dose, the median maximum heart EQD2 to 1 cc was 25 Gy in patients prescribed low doses (primarily 10 fractions of 3 Gy), 21 Gy in those prescribed intermediate doses (commonly 13 fractions of 3 Gy), and 30 Gy in those prescribed high doses (the difference between the three groups was not significant). Neither higher T-stage nor higher N-stage predicted for higher maximum heart EQD2. The maximum heart EQD2 was not associated with overall survival. Subgroup analyses limited to patients with stage III irrespective of prescribed dose and stage III treated with high-dose radiotherapy did not reveal statistically significant associations either (Figure 1).

Discussion

This retrospective analysis evaluated the maximum heart dose in a routine care setting of palliative radio- or chemoradiotherapy in 165 patients with NSCLC. Treatment planning had been performed without heart dose constraints and in the vast majority of patients without contouring of the heart as an OAR. This practice resulted in highly variable maximum heart doses, which were independent of the prescribed dose to the target volume, T-stage and N-stage. However, studies performed in the curative setting have reported higher median maximum heart doses than the present one (5, 6). This fact is not surprising, given that curative radiotherapy often employs 60-66 Gy total dose, and that efforts are needed to limit the lung and esophageal dose, meaning that high heart doses are often unavoidable (15). Heart damage tends to manifest as a late toxicity, while potentially lethal radiation pneumonitis may develop within the first year (16, 17). Due to these considerations and the fact that early disease progression led to limited survival in the past, heart dose constraints have historically received less attention than other aspects of treatment planning. In a recent study, the maximum dose to the combined cardiac region encompassing the right atrium, right coronary artery and ascending aorta was found to have the greatest effect on patient survival (18). A maximum EQD2 of 23 Gy was identified for consideration as a dose limit in future studies. To date, there is no consensus about the importance of assessing different heart substructures. The same is true for the large set of dosimetric variables that can be evaluated (maximum dose, mean dose, volume or sub-volume of heart receiving a specific threshold dose). Moreover, these issues are complicated by heart motion, the fact that the treatment planning scans represent only a snap-shot, and the issue of daily set-up variation, *i.e.* uncertainties which may affect the actual dose to the heart (19). Patients with pre-existing heart disease should be considered more vulnerable than those without comorbidity.

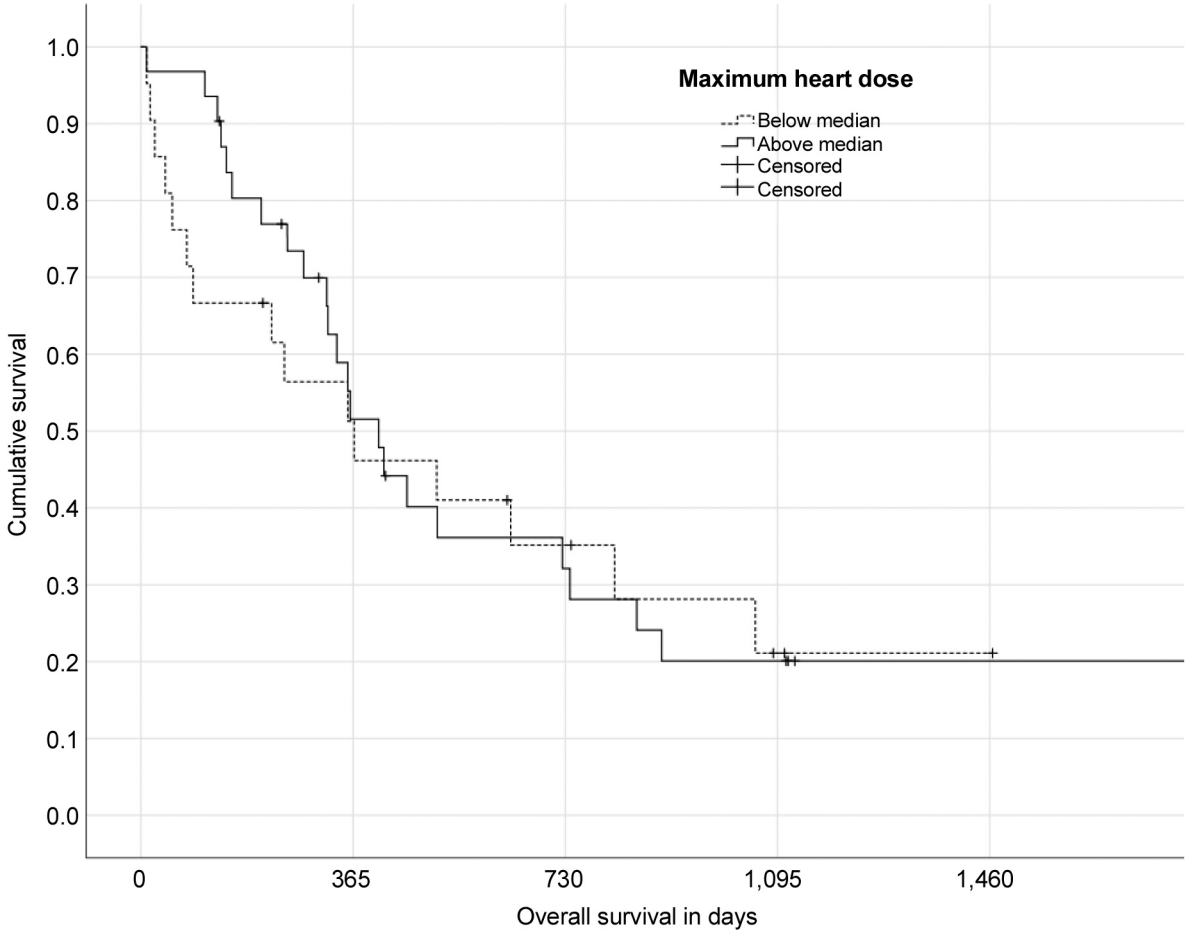

Figure 1. *Actuarial overall survival (Kaplan–Meier curves) for patients without distant metastases treated to high radiation doses such as 15 fractions of 2.8 Gy. Median survival was 12 months in 29 patients with a heart dose below the median (26 Gy) and 15 months in 29 patients with a heart dose above the median (p>0.1).*

We previously proposed a prognostic model that might be helpful in assessing patients before prescribing a 10-fraction or more regime, given that survival may be shorter than anticipated (20). Performance status, serum lactate dehydrogenase, C-reactive protein, presence of liver/adrenal gland metastases, and extrathoracic disease status significantly predicted survival and formed the basis of the score. Compared to these parameters, the present analysis suggests that maximum heart EQD2 is not a main driver of outcome after palliative (chemo)radiotherapy, not even in those with stage III disease. Despite inherent limitations of the retrospective study design, the limited size of the stage III subgroup, lack of information about pre-existing heart disease and the focus on maximum EQD2 rather than a range of dosimetric variables, this study provides important insights about a patient population that has received limited attention so far. Comparable to the rapidly evolving curative concepts, palliative (chemo)radiotherapy should also be as safe as possible and benefit from continuous technological advances (21), given that it often is prescribed to elderly patients with a wide range of comorbidities and compromised organ function.

Conclusion

The current practice of focusing on sparing of the lungs and the esophagus appears acceptable in the context of palliative regimes. To further strengthen this strategy, additional studies looking at cardiac substructures and dosimetric variables other than maximum dose are warranted.

Conflicts of Interest

The Authors declare that they have no conflicts of interest.

Authors' Contributions

CN participated in the design of the study and performed the statistical analysis. KSI collected patient data. CN and KSI conceived

the study and drafted the article. All Authors read and approved the final article.

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