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Aortic Dose Constraints when Reirradiating Thoracic Tumors

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Abstract

Background and Purpose—Improved radiation delivery and planning has allowed, in some instances, for the retreatment of thoracic tumors. We investigated the dose limits of the aorta wherein grade 5 aortic toxicity was observed after reirradiation of lung tumors.

Material and Methods—In a retrospective analysis, 35 patients were identified, between 1993 and 2008, who received two rounds of external beam irradiation that included the aorta in the radiation fields of both the initial and retreatment plans. We determined the maximum cumulative dose to 1 cm³ of the aorta (the composite dose) for each patient, normalized these doses to 1.8 Gy/fraction, and corrected them for long-term tissue recovery between treatments (*NID_R*).

Results—The median time interval between treatments was 30 months (range, 1–185 months). The median follow-up of patients alive at analysis was 42 months (range, 14–70 months). Two of the 35 patients (6%) were identified as having grade 5 aortic toxicities. There was a 25% rate of grade 5 aortic toxicity for patients receiving composite doses ≥ 120.0 Gy (vs. 0% for patients receiving <120.0 Gy) (*P*=0.047).

Conclusions—Grade 5 aortic toxicities were observed with composite doses ≥ 120.0 Gy (*NID_R* 90.0 Gy) to 1 cm³ of the aorta.

Keywords

reirradiation; aortic toxicity; radiation toxicity; lung cancer

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Conflicts of Interest Notification: The authors declare no conflicts of interest

INTRODUCTION

Radiation therapy for lung cancer has improved progressively over the past 20 years, and increased conformality in radiation planning and delivery has contributed to improved outcomes, particularly for those patients who are not candidates for surgery [1–3]. These improvements in conformality have led to an increase in the use of radiation for retreatment of locally recurrent disease [4]. This trend underscores the need for treating physicians to understand the nature and kinetics of long-term repair of occult radiation injury of critical adjacent structures such as the spinal cord, esophagus, and aorta [5]. Guidelines for radiation planning would be particularly useful when these structures are exposed to high cumulative doses. At this time, little is known about cumulative toxicity to the aorta from repeated irradiation, and hence appropriate dose constraints in this setting are not established [6–9].

To fill this gap in knowledge, we sought to determine the frequency of high-grade toxicity after high cumulative radiation doses to the aorta among patients being retreated for recurrent lung cancer. Our hypothesis was that both cumulative dose and time between the first and second radiation courses are important in influencing the incidence of high-grade toxicity and that dose constraints could be estimated based on these clinical data.

METHODS

Patients

Upon approval by the institutional review board, we searched our institutional database of individuals who had undergone radiation therapy for newly diagnosed non-small cell lung cancer (NSCLC) from March 1993 through August 2008. Of the 360 patients screened, 35 had had a second course of radiation therapy for recurrent disease and met the additional criteria of having at least 1 year's follow-up time, having received both courses at fractionation schedules between 1.2 and 3.0 Gy, and having had the aorta in the treatment fields of both courses.

Target volume delineation

Beginning in 2004, all treatment simulations were done with 4D CT systems (Discovery ST, GE Medical Systems, Milwaukee, WI; or Brilliance 64, Philips Healthcare, Andover, MA); before that time, treatment simulations had been done with conventional 2D planning. The 4D CT simulations involved obtaining sets of 10 respiration phase datasets, with maximum intensity projections and averaged CT values, and transferring those data to a Pinnacle version 8.0 treatment planning system (Phillips Medical Systems, Andover, MA). Gross tumor volumes (GTVs) were contoured on the end-of-expiration-phase CT scan, which were then expanded to form the clinical target volume (CTV). The CTV contours were then reproduced onto the other respiratory-phase scans by using an in-house deformable image registration algorithm [10]. The lung, heart, spinal cord, and on occasion the aorta were contoured in the original plans. We re-contoured the aorta manually on the planning CT images to include the ascending component, the arch, and the descending component, from the superior extent of the CTV to at least 5 cm below the inferior extent of the CTV.

Quantification of aortic dose

The dose to the aorta was calculated from composite plans for each patient. The composite plans included the dose distributions from both the first and second treatment plans. Dose distributions of the different plans were summed as they were mapped to a single image set (the composite plan) via the optical flow method [11]. For each patient, the maximum dose to 1.0 cm³ of the aorta was estimated from a tabular dose-volume histogram on the initial treatment plan, on the retreatment plan, and on the composite plan. These values are referred

to as unadjusted or raw doses. We further corrected these doses by normalizing them to 1.8 Gy/fraction and by α/β value of the linear-quadratic model, with correction for incomplete repair between two daily fractions when applicable, and a time-based recovery of occult injury between the two courses of radiation. Generation of these normalized isoeffective doses with recovery factor (NID_R), otherwise known as the biologically effective dose [12], is described further below.

The normalized isoeffective dose to the aorta was calculated as $NID = D \cdot (d + \alpha/\beta)/(d_0 + \alpha/\beta)$, where D = the original dose to 1 cm³ of the aorta, d = the original dose to 1 cm³ of the aorta divided by the number of prescribed fractions, d_0 = 1.8 Gy/fraction, and the alpha/beta ratio, α/β , = 3. For treatment with two daily fractions, a correction term ($H_m=0.35$) was introduced to take incomplete repair of sublethal damage into account [13].

Each patient's composite aortic dose was further corrected for differences in retreatment intervals (defined as the end date of the first treatment and the start date of the second treatment) by applying a *recovery factor* to the initial NID distribution. To our knowledge, the kinetics of repair of the aorta has not been sufficiently studied to accurately predict the extent to which it recovers after irradiation. Because of the lack of published studies in this area, we estimated recovery kinetics based on those of the spinal cord, a structure that is analogous to the vasculature with respect to the serial nature of its organization of structural subunits [14] and the α/β ratio [15, 16].

We used animal models as a guide [17] to correct for the time between treatments. Specifically, we used an algorithm based on conservative estimates of spinal cord long-term recovery kinetics in the rhesus monkey published by Ang *et al.* [17], namely $R\% = 13.737\ln(t) + 15.994$, where $R\%$ represents the percent recovery of the aorta and t is the time (in months) between the first and second treatments. We plotted the conservative time-based estimates of ~50% recovery of occult injury induced by 44 Gy at 1 year, ~60% at 2 years, and ~65% at 3 years and identified the line of best fit. That line-of-best-fit algorithm was used to estimate the extent of aortic recovery for patients whose retreatment intervals were <36 months; for those whose retreatment interval was ≥ 36 months, we estimated recovery at a flat 65%. The recovery factor was then applied to the aortic dose from the first treatment such that the composite $NID_R = NID_{1st\ treatment} \cdot (1 - R\%) + NID_{2nd\ treatment}$.

Aortic toxicity

Patients had been routinely evaluated for evidence of toxicity, aortic and otherwise, once a week during radiotherapy and then approximately every 3 months for the first 2 years after treatment, every 6 months for the following 3 years, and yearly thereafter. For this study, we limited our endpoint to high-grade aortic toxicity which was defined as hemoptysis secondary to aortic damage; exsanguination secondary to aortic rupture; aortic aneurysm in the irradiated region; or aortic dissection.

Statistical analysis

Data were analyzed with Stata/MP 12.0 statistical software (StataCorp LP, College Station, TX). Two-tailed Fisher's exact test was used to evaluate associations between the proposed dose constraints and the incidence of grade 5 aortic toxicity. *P*-values of 0.05 or less were considered to indicate statistical significance.

RESULTS

Patient and treatment characteristics are presented in Table 1. Median patient age was 63 years (range, 38–73 years), and the median follow-up time for patients alive at the time of

analysis was 42 months (range, 14–70 months). Thirty-one percent of patients had a history of hypertension, 23% had preexisting cardiovascular abnormalities, and 34% were taking anticoagulation therapy at the time of retreatment. Notably, none of the patients studied had connective tissue disorders such as Marfan syndrome, Ehlers-Danlos syndrome, large-vessel vasculitis, or other potentially confounding collagenopathies.

Median raw and adjusted aortic doses are listed in Table 1 and Figure 1. The median raw composite dose to 1.0 cm³ of the aorta was 110.0 Gy (range, 74.5–142.7 Gy) ($NID_R=73.6$ Gy [range, 38.6–99.4 Gy]). Eight patients (23%) received raw composite doses of 120.0 Gy or more, two of whom (25%) had grade 5 aortic toxicity. There was no grade 5 aortic toxicity observed in any of the patients receiving raw composite doses <120.0 Gy ($p=0.047$) (Fig. 1A). Seven patients (20%) had an NID_R 90.0 Gy, two of whom (29%) had grade 5 aortic toxicity. No grade 5 aortic toxicity was observed in any of the patients receiving NID_R <90.0 Gy ($p=0.035$) (Fig. 1B).

At a median follow-up time of 42 months (range, 14–70 months) for patients who were alive at the time of this analysis, two patients had developed grade 5 aortic toxicity; both presented with hemoptysis secondary to aortic damage, and both died of exsanguination. This damage was attributed to radiation and not from malignant invasion, as both patients had no radiographic signs of active thoracic disease at time of death. Both of these patients had stage IIIA NSCLC [18].

One of the patients with grade 5 aortic toxicity received a raw composite dose to 1 cm³ of the aorta of 120.0 Gy ($NID_R=94.9$ Gy). The patient died of aortic rupture 39 months after the last radiation treatment. Treatment plans and the composite dose-volume histogram for this patient are shown in Figure 2. The first treatment simulation was done with conventional 2D planning, and the second treatment simulation was done with 4D CT system planning for this patient.

The other patient with grade 5 aortic toxicity received a raw composite dose to 1 cm³ of the aorta of 127.0 Gy ($NID_R=90.6$ Gy). This patient died of aortic rupture 9 months after the last radiation treatment. Treatment plans and the composite dose-volume histogram for this patient are shown in Figure 3. For this patient, the first and second treatment simulations were done with 4D CT systems.

DISCUSSION

Our major findings from this study can be summarized as follows. First, we demonstrated that aortic toxicity after reirradiation is relatively rare, even when composite doses to the max 1.0 cm³ of the aorta exceed 100 Gy. Second, our findings suggest that radiation damage to the aorta can persist for many years after treatment, which implies that this damage is not fully repaired over time. Finally, composite dose thresholds of 120.0 Gy as a raw dose and 90.0 Gy when the dose is corrected for long-term recovery during the retreatment interval can serve as rudimentary cutoff points above which patients are more likely to experience aortic toxicity.

To date, most of the studies attempting to establish dose constraints and mechanisms of damage for vascular structures have been preclinical [19, 20]. Werber and colleagues, for example, assessed radiation-induced carotid artery toxicity in rabbits and found that this structure can tolerate doses up to 130.0 Gy [21]. In the current study, 8 patients (23%) received raw composite doses of 120.0–142.7 Gy to the aorta, and 6 of these patients (75%) tolerated these doses without observable toxicity.

Clinical reports on the reirradiation dose tolerance of the aorta in humans are sparse [9, 22, 23]. Trombetta and colleagues suggested that the tolerance of the aorta may be greater than previously anticipated, concluding that the aorta may tolerate more than 120.0 Gy, but they cautioned against reirradiation because of the occurrence of aortic rupture in 1 of 29 patients so treated [6]. Similar to Trombetta's case of aortic rupture, we found 2 patients with serious aortic sequelae from raw composite doses 120.0 Gy (NID_R 90 Gy). This study provides the first set of objective clinical data on cumulative doses associated with aortic toxicity when considering retreatment of thoracic tumors with external beam irradiation.

Other than the limitations inherent in any retrospective analysis, our study had several additional shortcomings. First and most importantly, our conclusions are based on a small number of events, which limits our ability to generalize our findings with regard to dose constraints and recovery. That being said, given the paucity of clinical information on this topic, we believe that our findings are important in that they form a basis for understanding the incidence of high-grade aortic toxicity among patients contemplating repeated radiation therapy to the thorax. Another limitation was our follow-up period. Although our median follow-up time for the 11 patients who were living at the time of analysis was 42 months, longer follow-up may reveal additional instances of toxicity. Finally, the algorithm used to account for long-term aortic recovery in establishing the NID_R was developed from the repair kinetics of the spinal cord, which limits its applicability to other tissues such as the aorta.

In conclusion, we found that most of the patients in this study tolerated retreatment irradiation to the aorta without observable toxicity especially when the raw composite doses were kept below 120.0 Gy (NID_R <90.0 Gy). Our findings should be evaluated with both longer follow-up and confirmed in prospective studies of larger numbers of patients.

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Fig. 1.

Proportion of patients who did or did not develop aortic toxicity at defined composite doses.

(**A**) Treatment of 1 cm³ of aorta to 120 Gy (without normalization of isoeffective dose or correction for aortic recovery), produced aortic toxicity in 25% of patients (*P*=0.047 vs. raw dose <120 Gy). (**B**) Treatment of 1 cm³ of aorta to 90 Gy (when the dose had been normalized to 1.8 Gy/fraction and corrected for long-term aortic recovery) resulted in aortic toxicity in 29% of patients (*P*=0.035 vs. *NID_R* <90 Gy).

Fig. 2. Axial views of thoracic treatment plans for a woman who died of radiation-induced aortic damage. The aorta is contoured in yellow. **(A)** The initial plan involved treatment to 50.4 Gy (green isodose line; blue isodose line is 39.6 Gy). **(B)** The second plan involved treatment to 66.0 Gy (blue isodose line; green isodose line is 69.0 Gy). **(C)** The composite plan illustrates a green hot spot in the aorta (arrow) that received 120.0 Gy. **(D)** Dose volume histogram for the composite plan. GTV, gross tumor volume.

Fig. 3. Axial views of thoracic treatment plans for a man who died of radiation-induced aortic damage. The aorta is contoured in yellow. **(A)** The initial plan involved treatment to 60.4 Gy (blue isodose line; green isodose line is 59.0 Gy). **(B)** The second plan involved treatment to 63.0 Gy (blue isodose line; green isodose line is 68.0 Gy). **(C)** The composite plan illustrates a green hot spot in the aorta (arrow) that received 127.0 Gy. **(D)** Dose volume histogram for the composite plan. GTV, gross tumor volume.

Table 1**Patient and Treatment Characteristics**

	No. of Patients (% or range)			
	All Patients (n=35)		Patients with Aortic Toxicity (n=2)	
Age, years, median (range)	63 (38–73)		68 (66–70)	
Sex				
Male	17 (49%)		1 (50%)	
Female	18 (51%)		1 (50%)	
Hypertension				
Yes (blood pressure ≥ 140/90)	11 (31%)		0	
No (<140/90)	24 (69%)		2 (100%)	
Preexisting CV abnormalities	8 (23%)		2 (100%)	
Abdominal aortic aneurysm	2 (6%)			
Aortic valve replacement	1 (3%)			
Cardiac arrhythmias*	2 (6%)		1 (50%)	
Coronary artery disease	3 (9%)		1 (50%)	
Anticoagulation therapy	12 (34%)		2 (100%)	
Aspirin	15 (44%)			
Clopidogrel and aspirin	2 (6%)		1 (50%)	
Warfarin	3 (9%)		1 (50%)	
Hyperlipidemia				
Yes	4 (11%)		1 (50%)	
No	31 (89%)		1 (50%)	
Diabetes				
Yes	4 (11%)		1 (50%)	
No	31 (89%)		1 (50%)	
Vital status at analysis				
Alive	11 (31%)			
Dead	24 (69%)		2 (100%)	
Cause of death				
Aortic rupture	2 (6%)		2 (100%)	
Cardiac	3 (9%)			
Pulmonary	4 (11%)			
Infection	1 (3%)			
Cancer-related	10 (29%)			
Unknown	4 (11%)			
Follow-up interval, median (range)				
All patients	17 mo (2–70 mo)			
Patients alive at analysis	42 mo (14–70 mo)			
Patients dead at analysis	12 mo (2–45 mo)		24 mo (21–64 mo)	
	1 st Trtmt	2 nd Trtmt	1 st Trtmt	2 nd Trtmt

	No. of Patients (% or range)			
	All Patients (n=35)		Patients with Aortic Toxicity (n=2)	
Concurrent chemotherapy				
Yes	24 (69%)	21 (60%)	1 (50%)	1 (50%)
No	11 (31%)	14 (40%)	1 (50%)	1 (50%)
Prescribed dose, Gy median (range)	54 (45–70)	60 (30–70)	55.4 (50.4–60.4)	64.5 (63–66)
Fraction size, Gy median (range)	1.8 (1.2–3.0)	2.0 (1.5–3.0)	1.8	1.9 (1.8–2.0)
No. of Fractions median (range)	30 (15–58)	30 (10–42)	31 (28–33)	34 (33–35)
Max dose to 1 cm ³ of aorta, median (range)				
Raw dose, Gy	56.0 (25.5–76.2)	49.9 (3.5–74.3)	55.0 (51.0–59.0)	68.5 (68.0–69.0)
Composite raw dose, Gy	110.0 (74.5–142.7)		123.5 (120.0–127.0)	
NID _R	23.9 (7.0–37.5)	53.8 (2.2–79.3)	21.2 (20.6–21.7)	71.6 (70.0–73.2)
Composite NID _R	73.6 (38.6–99.4)		92.8 (90.6–94.9)	
Duration of radiation therapy, median (range)	39 d (14–52 d)	38 d (14–53d)	46 d (40–52 d)	44 d (39–48 d)
Interval to re-treatment, median (range)	30 mo (1–185 mo)		43 mo (21–64 mo)	

Abbreviations: NID_R, dose normalized for fraction size and adjusted for tissue recovery between trtmts

* Atrial fibrillation and premature ventricular contractions