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Effect of Radiotherapy on Carotid Arteries – An Observational Study

Radyoterapinin Karotis Arterleri Üzerindeki Etkisi – Gözlemsel Bir Çalışma

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Abstract

Intoduction: Survival rates of patients with head and neck cancer have recently increased with the introduction of new technologies and developments in comprehensive treatment modalities in RT. Observing late side effects, too, has become inevitable. Vascular damages and their clinicalresults are the prevalent effects of RT.
Objective: Carotid artery lesions and stenosis could develop after radiotherapy and can be detected viaintima-media thickness. Within the scope of this research, we aimed to elucidate the planning technique to minimize the radiation dose to be exposed to the carotid arteries.
Methods: This study included42 patients with stage T1-2 N0 M0 glottic cancer who applied to our institution. CA diameters of the patients were measured before and after RT. The measurements were performed 2 cm above the CA bifurcation level, and the largest diameter (cm) was recorded. All measurements were performed on CT scans. Actual treatment images (slice thickness, 2.5 cm) acquired using a computerized tomography (CT) simulator were transferred into the Hi-Art Tomotherapy treatment system. Dose-volume histograms were used for dose comparisons.
Results: A comparison of doses administered to the RCAs and LCAs revealed that the Dmean, V35-Gy, V40-Gy, and V50-Gy values of RCA were significantly higher than those of LCA. Examination of the correlation between the RCA diameters after treatment and RT doses revealed a statistically significant correlation only for the V60-Gy dose ($r = 0.299$, $p = 0.054$). The RCA diameter was reportedly significantly narrower in smokers than nonsmokers ($p = 0.039$).A statistically significant significance was observed between smokers' RCA diameter and V60-Gy dose ($r = 0.458$, $p = 0.013$).A statistically significant correlation was also observed between age and only the RCA diameter in smokers ($p = 0.038$).
Conclusion: RT performed on the head and neck region is an important risk factor for arterial stenosis and the resulting CVEs. Smoking is one of the most important factors that increase this risk. Carotid artery doses should be considered while planning RT.

Keywords: Carotid Artery, Carotid Artery Stenosis, Radiotherapy.

Özet

Giriş: Son yıllarda, radyoterapide (RT) yeni teknolojiler ve kapsamlı tedavi modalitelerindeki gelişmeler ile baş-boyun kanserleri hastaların sağkalım oranları artmaktadır. Geç yan etkileri de gözlemlemek kaçınılmaz olmuştur. Vasküler hasarlar ve klinik yansımları da RT nin bu etkilerinden biridir ve artık çok sık görünür olmuştur.
Amaç: Radyoterapi sonrası karotis arter lezyonları ve darlıkları gelişebilmekte ve intima-media kalınlığı ile tespit edilebilmektedir. Bu araştırma kapsamında karotis arterlerin maruz kalacağı radyasyon dozunu en aza indirecek planlama tekniğinin aydınlatılmasını amaçladık.

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Yöntem: Bu çalışmaya kurumumuza başvuran evre T1-2 N0 M0 glottik kanserli 42 hasta dahil edildi. Hastaların KA çapları RT öncesi ve sonrası ölçüldü. Ölçümler KA çatallanma seviyesinin 2 cm üzerinden yapıldı ve en büyük çap (cm) kaydedildi. Tüm ölçümler CT taramalarında yapıldı. Bilgisayarlı tomografi (BT) simülatörü kullanılarak elde edilen gerçek tedavi görüntüleri (kesit kalınlığı, 2.5 cm)Hi-Art Tomoterapi tedavi sistemine aktarıldı. Doz karşılaştırmaları için doz-hacim histogramları kullanıldı.
Bulgular: Sağ KA ve sol KA'lara uygulanan dozlar karşılaştırıldığında, sağ KA'nın Dmean, V35-Gy, V40-Gy ve V50-Gy değerlerinin Sol KA'e göre anlamlı derecede yüksek olduğu görüldü. Tedavi sonrası RCA çapları ile RT dozları arasındaki korelasyon incelendiğinde sadece V60-Gy dozu için istatistiksel olarak anlamlı bir korelasyon olduğu ortaya çıktı (r=0,299, p=0,054). RCA çapının sigara içenlerde içmeyenlere göre anlamlı derecede daha dar olduğu bildirildi (p = 0,039). Sigara içenlerin RCA çapı ile V60-Gy dozu arasında istatistiksel olarak anlamlı bir fark gözlendi (r=0,458, p=0,013). Sigara içenlerde yaş ile sadece RCA çapı arasında da istatistiksel olarak anlamlı bir korelasyon gözlendi (p=0,038).
Sonuç: Baş-boyun bölgesine yapılan RT, arteriyel stenoz ve bunun sonucunda ortaya çıkan serebro-vasküler olaylar açısından önemli bir risk faktörüdür. Sigara içmek bu riski artıran en önemli faktörlerden biridir. RT planlanırken karotis arter dozları dikkate alınmalıdır.

Anahtar Kelimeler: Karotis Arter, Karotis Arter Stenozu, Radyoterapi.

INTRODUCTION

Radiotherapy (RT) is the most commonly used method for treating non-metastatic head and neck cancers. T1-2N0M0 glottic cancers are particularly treated with RT as the treated volume is small and acute or late toxicity is low (1). Radiation Accelerates the formation of a the rosclerotic plaques and causes an increase in the number of inflammatory cells. A the rosclerotic plaque formation with this inflammatory natüre is more prone to bleeding than a the rosclerotic plaques developing in the normal population and occur in a shorter time (2). Carotid artery lesions developed after radiotherapy can be easily distinguished from normal a the rosclerotic lesions on angiography. Carotid artery lesions that develop after RT are located in the irradiated carotid segment, in the distal part of the carotid artery, and affect a long segment. Due to RT, bifurcationin volvement is rare in carotid system a the rosclerotic lesions (3).

Additionally, RT increases the risk of stenosis in the carotid arterial system. They showed that the risk of ischemic stroke with RT increased significantly compared to the general population. Carotid plaques and increased carotid intima-media thickness (IMT) appearto be independent predictors of cerebrovascular disease (4).

However, organs at risk within the exposed areas can always be affected by RT. RT performed on the neck region negatively affects the carotid artery (CA) and increases this risk. Increasing RT doses result in atherosclerosis by causing thickening in the intima–media layer of the CA. Carotid artery stenosis (CAS) is a late complication reported after RT for head and neck cancers (5). These lead to the increased prevalence of cerebrovascular events (CVE) caused by RT on the neck region and were reported between 2.5% and 12% (6).

Furthermore, the expected prevalence of CVE within 10 years was evaluated and found to be 34% with RT alone, 25% with surgery + RT, and 26% with surgery alone. The mechanism of vascular damage by RT is well known. However, the mechanism of the damages caused in the CA is not clear. CA diameter measurements before and in the late period after RT are accurately investigated via computerized tomography angiography (CTA), and magnetic resonance imaging(MRI) is commonly used to determine stenosis (7).

In RT applications, it should be possible to distribute the desired dose in the target volüme and to protect the surrounding or gans and healthy tissue. If the target level is in close proximity to the dose delivered, the dose should be reviewed very accurately and with the most appropriate RT applications.. These Patients Pose a risk in terms of stenosis and ischemic disease that may develop due to RT, especially in the chronic period (8).

Carotid artery has two main branches: internal and external carotid arteries. The“internal carotid arteries” are formed, consisting of 4 main vessels containing brain oxygen. “External carotid arteries”nourish the neck area, face, and radiant skin. These arteries, which are of great vital importance, are close neighbors the vocal cord. RT treatment of early-stage glottic laryngeal cancer is a condition for large contiguous carotid arteries (9). Within the scope of this research, we aimed to elucidate the planning technique to minimize the radiation dose to be exposed to the carotid arteries.

METHOD

This study included 42 patients with stageT1-2 N0 M0 glottic cancer who applied to our institution. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Ethics committee approval has been granted from our institution. As this was a retrospective research informed consent has been obtained from participants.

CA diameters of the patients were measured before and after RT. The measurements were performed 2 cm above the CA bifurcation level, and the largest diameter (cm) was recorded. All measurements were performed on CT scans (Figure 1). Actual treatment images (slice thickness, 2.5 cm) acquired using a computerized tomography (CT) simulator were transferred into the Hi-Art Tomotherapy treatment system.

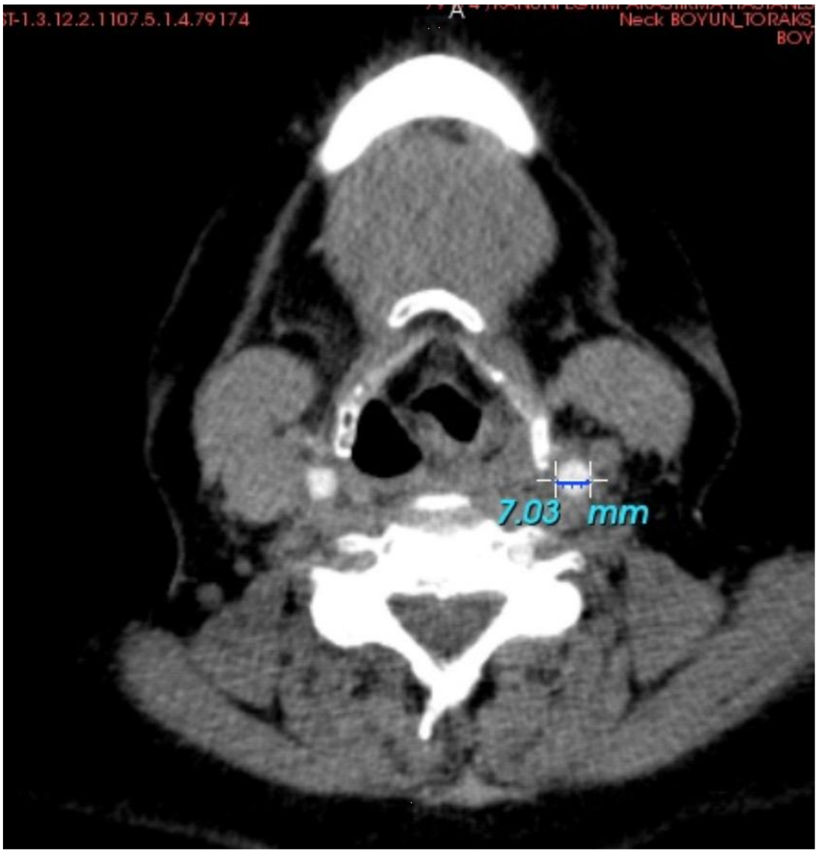

Figure 1. Carotid Artery Diameter In Computed Tomography

The same physician contoured clinical target volume (CTV) to encompass the thyroid (anteriorly, with a 5-mm margin)cricoids cartilage, arytenoid cartilage, false vocal cords, anterior and posterior commissures, true vocal cords, and 1–1.5 cm of the subglottis. The borders were extended superiorly to the hyoid bone and inferiorly to the bottom of the cricoids. Each CTV was modified to encompass a pre-delineated gross tumor volume. The CTVs were truncated within 3 mm of the skin surface to avoid a high skin dose in patients without anterior commissure involvement. Planning target volumes (PTV) were achieved by adding a 5-mm margin around the CTV. The spinal cord and CAs were defined as the critical structures. The organat-risk volumes of the spinal cord and CAs were delineated to exceed PTV by 1 cm superiorly and inferiorly (Figure 2).

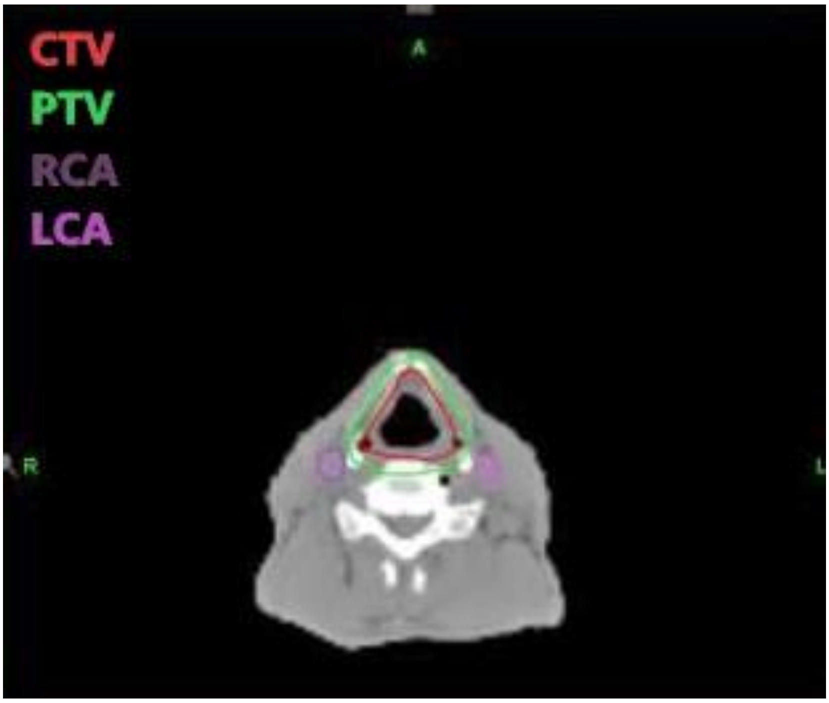

Figure 2. Volume definition

CTV: Clinical Target Volume **PTV:** Planning Target Volumes **RCA:** Right Carotid Artery **LCA:** Left Carotid Artery.

Dose-volume histograms were used for dose comparisons. For each CA, Dmean(mean dose),Dmax(maximum dose), and V35 (percentage of volume receiving 35 Gy), V40 (percentage of volume receiving 40 Gy), V50 (percentage of volume receiving 50 Gy), V60 (percentage of volume receiving 60 Gy), and V70 (percentage of volume receiving 70 Gy) values were investigated. All plans were normalized such that >95% of the CTV received 100% of the prescribed dose. A totalof200 cGy was applied to each fraction, and treatment was completed with a total of 66 or 70 Gy.

Statistical Analysis

Statistical analyses were performed using the SPSS version 13 software package. The conformity of the variables to normal distribution was analyzed using visual (histogram and probability graphs) and analytical (Kolmogorov–Smirnov test) methods. The significance tests of the differences between the two averages were conducted using Student's t-test or paired t-test for parametric-interval data, Mann–Whitney U-test or Wilcoxon test for nonparametric-interval data, and Chi-square test for ordinal/nominal data (or Fisher's exact test for smaller samples). Correlation coefficients (r) and statistical significance of parametric data were calculated using Pearson's test, whereas those of nonparametric data were calculated using Spearman's test. Conditions with type-1 error levels<5% ($p<0.05$) were considered significant.

RESULTS

A total of 42 male patients with stage T1-2 N0 M0 glottic cancer have been enrolled in this study.The median follow-up duration was 44.5 (9–995.5) months. CA measurements were performed in the final follow-up month. Of the 42 patients, 14 (33.3%) received 66-Gy RT, whereas 28 (66.7%) received 70-Gy RT. The demographic characteristics of the patients are denoted in Table 1. The median right carotid artery (RCA) diameter was 8.1 mm(range 7–9.9 mm) before and 7.6 mm (range 6.5–8.5 mm) after RT. The median left carotid artery (LCA) diameter was 8 mm(range 6.5–9 mm) before and 7.05 mm(range 6–8 mm) after RT. Comparative examination of the CA diameters before and after RT revealed a statistically significant decrease in the RCA and LCA diameters after RT ($p<0.001$).

Table 1. Patient Characteristics of the Study Population

		Value
Age (years) **Mean (range)**		62 (45–81)
T stage	**T1**	32 (76.2%)
	T2	10 (%23.8%)
Stage	**1**	32 (76.2%)
	2	10 (23.8%)
Smoking	**No**	13 (31%)
	Yes	29 (69%)
CAD	**No**	33 (78.6%)
	Yes	9 (21.4%)
CHF	**No**	41 (97.6%)
	Yes	1 (2.4%)
MI	**No**	38 (90.5%)
	Yes	4 (9.5%)
HT	**No**	29 (69%)
	Yes	13 (31%)
DM	**No**	38 (90.5%)
	Yes	4 (9.5%)
HL	**No**	30 (71.4%)
	Yes	12 (28.6%)
PAD	**No**	42 (100%)
	Yes	-

CAD: Coronary Artery Disease, **CHF:** Congestive Heart Failure**, MI:** Myocardial Infarction, **HT:** Hypertension, **DM:** Diabetes Mellitus, **HL:** Hyperlipidemia, **PAD:** Pulmonary Artery Disease.

A comparison of doses administered to the RCAs and LCAs revealed that the Dmean, V35-Gy, V40-Gy, and V50-Gy values of RCA were significantly higher than those of LCA. Examination of the correlation between the RCA diameters after treatment and RT doses revealed a statistically significant correlation only for the V60-Gy dose ($r = 0.299$, $p = 0.054$) (Table 2). No statistical significance was observed in the examination of the correlation between the RT doses and LCA diameters after RT ($p > 0.05$) (Table 3).

Table 2. Effect of RT Doses on RCA Diameters

	RCA Diameter	
	r value	**p value**
Dmax	0.025	0.873
Dmean	−0,085	0.590
V35Gy	0.013	0.934
V40Gy	0.097	0.540
V50Gy	0.034	0.828
V60Gy	0.299	**0.054***
V70Gy	−0.004	0.982
Total RT dose	0.088	0.579

***** = Statistically Significant, **r** = Correlation Coefficient
Dmax: maximum dose, **Dmean:** mean dose.

Table 3. Effect of RT Doses on LCA Diameters

	LCA Diameter	
	r value	**p value**
Dmax	0.222	0.159
Dmean	0.003	0.984
V35Gy	0.133	0.400
V40Gy	0.155	0.328
V50Gy	0.176	0.266
V60Gy	0.144	0.362
V70Gy	0.106	0.504
Total RT dose	−0.134	0.397

Dmax: maximum dose, **Dmean:** mean dose.

Age was not significantly correlated with the RCA diameter before RT (p > 0.05); however, it was significantly correlated with the RCA diameter after RT (r = 0.409, p = 0.007). Similarly, no statistically significant correlation existed between age and the LCA diameters before and after RT (p > 0.05). Furthermore, there was no statistically significant correlation between the time interval after RT and the CA diameters (p > 0.05). Evaluation of factors affecting CA diameters revealed only smoking as an influential habit. The RCA diameter was reportedly significantly narrower in smokers than nonsmokers (p = 0.039). There was no significant difference in the LCA between smokers and nonsmokers (p = 0.214) (Table 4). In the subgroup analysis investigating the effect of RT doses on the RCA diameters according to the smoking status, no statistically significant correlation was observed in non-smokers. However, a statistically significant significance was observed between the RCA diameter and V60-Gy dose in smokers (r = 0.458, p = 0.013).

Table 4. Factors Affecting Carotid Artery Diameter

			RCA Diameter	LCA Diameter
			p value	**p value**
T stage	T1	32 (76.2)	0.806	0.736
	T2	10 (23.8)		
Stage	1	32 (76.2%)	0.806	0.736
	2	10 (23.8)		
Smoking	No	13 (31%)	**0.039**	0.214
	Yes	29 (69%)		
CAD	No	33 (78.6%)	0.491	0.387
	Yes	9 (21.4%)		
CHF	No	41 (97.6%)	0.592	0.937
	Yes	1 (2.4%)		
MI	No	38 (90.5%)	0.433	0.204
	Yes	4 (9.5%)		
HT	No	29 (69%)	0.955	0.165
	Yes	13 (31%)		
DM	No	38 (90.5%)	0.667	0.643
	Yes	4 (9.5%)		
HL	No	30 (71.4%)	0.486	0.513
	Yes	12 (28.6%)		
RT Dose	66 Gy	14 (33.3%)	0.463	0.417
	70 Gy	28 (66.7%)		

CAD: coronary artery disease, **CHF:** congestive heart failure**, MI:** myocardial infarction, **HT:** hypertension, **DM:** Diabetes Mellitus, **HL:** Hyperlipidemia, **PAD:** Pulmonary Artery Disease.

In the subgroup analysis of the effect of RT doses on the LCA diameters according to the smoking status, no statistically significant correlation was observed in nonsmokers. However, a statistically significant significance was observed between smokers' LCA diameter and V40-Gy dose ($r = 0.376$, $p = 0.044$). No statistically significant significance was observed between age and the LCA and RCA diameters in nonsmokers ($p = 0.103$, $p = 0.127$).On the contrary, a statistically significant correlation was observed between age and only the RCA diameter in smokers ($p = 0.038$).

DISCUSSION

Most head and neck cancers are currently treated with RT. RT applied on the neck region causes some damage to the regional arteries. The results of radiation exposure on CAs are similar to the changes caused by age-related atherosclerosis. It has traditionally been accepted that the carotid artery is considerably resistant to fibrosis and narrowing, which are evident in smaller vessels undergoing comparable radiation exposure. However, RT reportedly causes rupture, thrombosis, and progressive stenosis in the CA. The exact mechanism of damage caused by RT remains unclear. Injuries to the vasa vasorum and consequent ischemic lesions of the arterial wall were considered structural appearances that differentiate arterial damage secondary to radiation from atherosclerosis (10).

Previously, the prevalence of CAS after RT was considered low. However, with the improvement in imaging techniques and increased clinicians' awareness, increasing attention has been paid to this field. Lam et al. reported that arterial stenosis was more common in the post-radiation group than in the pre-radiation group, which consisted of newly diagnosed patients with nasopharyngeal carcinoma (n=56/71 andn=11/51) (11). The overall prevalence of extra cranial artery disease was 78.9% (n=56/71), and significant stenosis (>50%) was only observed in the post-radiation group. One study retrospectively evaluated 45 patients five years after completion of RT and reported significant changes in the degree of maximal stenosis of the CA using peak systolic velocity and end diastolic velocity as parameters (12).Another retrospective study involving 23 patients reported a 21.7% prevalence of severe (70%–90%) CAS at a mean interval of 4.9 years after RT (13). Muzaffar et al. prospectively evaluated 36 patients following neck irradiation for head and neck cancer. The carotid intima–media thickness and plaque sizes were measured prior to irradiation and at one and two years after irradiation. Comparison with age- and sex-matched controls in epidemiological studies revealed a significant increase in the IMT of the treated patients at one year ($p < 0.001$) and twoyears following radiotherapy($p < 0.01$) (14).Bilora et al.obtained statistically insignificant study results for the measurement of the carotid system's intima-media thickness after radiotherapy($p > 0.05$) in patients with lymphoma (15).

Few studies have reported a considerably increased prevalence of CAS in patients who underwent RT than in those who did not.The currency of CAS was 17% to 25% in humans who underwent RT (16, 17). CAS was detected in our patients at a rate of 17%. The diagnosis of CAS still principally relies on imaging approaches. Carotid IMT, which can be relatively easily and noninvasively measured using Doppler ultrasonography, is a good indicator of atherosclerosis and a significant predictor of future vascular events (13). An increase in the CIMT is also one of the earliest visible features and can be observed within the first 2 years after RT (18). Conventional digital subtraction angiography remains the gold standard method in diagnosing CAS. MRI and CTA are also widely employed in diagnosing CAS (19).

Chang et al. reported a positive correlation between the total plaque score (index of atherosclerosis), RT use, RT dose, duration after RT, hyperlipidemia, and age (20). Steele et al. revealed that severe post-RT CAS was associated with age, smoking, heart disease, no prior oncologic surgery, cerebrovascular symptoms, and interval from RT. The risk of radiation-induced CAS seemingly depends on the primary malignancy site and the radiation doses. Here, smoking was revealed as the most important risk factor for CAS (21).

CONCLUSION

RT performed on the head and neck region is an important risk factor for arterial stenosis and the resulting CVEs. Smoking is one of the most important factors that increase this risk. Carotid artery doses should be considered while planning RT. Carotid artery diameters in the late period after RT should be measured with CT, and carotid artery stenosis related to RT should be considered. Comprehensive treatment plans should be performed, particularly for patients with a smoking history.

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Competing Interests: The authors declare that they have no competing interests.

Ethical Declaration: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.Ethics committee approval was granted from our institution on 08.10.2021 with protocol number 2933, and informed consent was obtained from all participants.

Author Contributions

Working Concept / Design	: GHU, ATK
Data collecting	: GHU, ATK
Data Analysis / Interpretation	: GHU, LS
Writing Draft	: GHU
Technical Support / Material Support	: GHU, ATK
Critical review of content	: LS, ATK
Literature Review	: GHU

Abbreviations

CA	: Carotid Artery
CAS	: Carotid Artery Stenosis
CIMT	: Carotid Intima – Media Thickness
CTA	: Computerized Tomography Angiography
CTV	: Clinical Target Volume
CVE	: Cerebro Vascular Events
IMT	: Intima – Media Thickness
LCA	: Left Carotid Artery
MRI	: Magnetic Resonance Imaging
PTV	: Planning Target Volumes
RCA	: Right Carotid Artery
RT	: Radiotherapy
SPSS	: Statistical Package for the Social Sciences

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