research article

Is carotid stiffness a possible surrogate for stroke in long-term survivors of childhood cancer after neck radiotherapy?

Lorna Zadravec Zaletel[1], Matjaz Popit[2], Marjan Zaletel[2]

[1] Radiotherapy Department, Institute of Oncology Ljubljana, Ljubljana, Slovenia
[2] Department of Vascular Neurology, University Medical Centre Ljubljana, Ljubljana, Slovenia

Radiol Oncol 2018; 52(2): 136-142.

Received 16 October 2017
Accepted 18 December 2017

Correspondence to: Assist. Prof. Lorna Zadravec Zaletel, M.D., Ph.D., Radiotherapy Department, Institute of Oncology Ljubljana, Zaloška 2, SI-1000 Ljubljana. Phone: +386 4 1436 575; Fax: +386 1 5879 304; E-mail: lzaletel@onko-i.si

Disclosure: No potential conflicts of interest were disclosed.

Background. The risk for cerebrovascular late effects among childhood cancer survivors is considerable. According to recent studies it is not clear which marker could be reliable for the screening of cerebrovascular diseases among the long-term survivors of childhood cancer. The purpose of this study is to analyse arterial stiffness and intima-media thickness as possible early markers of later occurring stroke in long-term survivors of childhood cancer after neck radiotherapy.

Patients and methods. Twenty-three patients, treated for Hodgkin disease (HD) in childhood, were included. They had received radiation therapy to the neck with 20–65 (median 30) Gy. Twenty-six healthy controls, matched in age, sex, body mass index, arterial hypertension, smoking history and total cholesterol levels were compared. High-resolution colour-coded duplex sonography and power Doppler sonography of the carotid arteries were performed and intima-media thickness, number and quality of plaques were measured. Arterial stiffness indices were calculated.

Results. Plaque deposits and/or arterial wall calcinations were found in 24 out of 43 (55.8%) irradiated vessels in cancer survivors group and 0 out of 52 vessels in the group of healthy controls ($p < 0.01$). We found significant group differences for all the stiffness parameters we used ($P < 0.05$), but there was no difference in intima-media thickness between cases and controls ($p = 0.92$). In a multivariate model, carotid pulse wave velocity was positively associated with smoking.

Conclusions. The arterial stiffness has appeared as a possible surrogate marker for stroke in long-term survivors of childhood cancer. Smoking habit might have an additional negative influence on vascular aging in the group of patients after neck radiotherapy.

Key words: carotid stiffness; carotid artery disease; childhood cancer survivors; late effects; neck irradiation

Introduction

The survival of children with cancer has improved over the past decades and almost 80% of this population now survives beyond 5 years.[1,2] But cumulative incidence of a chronic health condition thirty years after the cancer diagnosis is 73% as evidenced by the Childhood Cancer Survivor Study (CCSS).[3] Cardiovascular complications are serious late effects in childhood cancer survivors. The risk of stroke is increased in survivors of paediatric Hodgkin disease (HD), leukaemia and brain tumours who received radiation to the brain and/or neck.[4] Compared with the siblings, the RR of late-occurring stroke among HD survivors was 4.32, among those treated with mantle irradiation the RR was 5.62, for leukaemia survivors the RR of stroke was 6.4 and that one for brain tumour survivors was as high as 29.0 in comparison with siblings.[5,6] In the CCSS cohort of long-term survivors of childhood cancer (LTSCC) the RR of severe or life-threatening cerebrovascular accident was 9.3 in

comparison with siblings.[3] One of possible mechanisms of stroke in young adult survivors of childhood cancer may be a radiation-induced injury to the carotid artery.

The increased risk of carotid artery disease and stroke after radiation therapy (RT) in adult head and neck cancer and HD patients is well documented[7-12], but these radiation-related late effects have only recently been documented in adult survivors of childhood cancer.[13-16]

The detection of an appropriate surrogate marker for stroke is necessary in order to introduce it into follow-up guidelines. This could enable us to detect LTSCC who are at risk of developing cerebrovascular events. Many studies in adults and some in LTSCC found IMT as possible surrogates. Anyway the results are not consistent. Arterial stiffness was proposed as a possible surrogate for cardiovascular morbidity in LTSCC.[17,18] However, the stiffness indices were not systematically studied. Therefore, we analysed indices of arterial stiffness besides intima-media thickness as possible early markers of later occurring stroke.

Patients and methods

Subjects

Patients were eligible for the study if they had been treated for HD in Slovenia between 1975 and 1986, under the age of 16, and had received RT to the neck. Fifty-six patients were treated for HD at the age of 16 or less during this time range. Sixteen patients died, 32 out of 40 living patients received neck RT and were eligible for the study. Eight patients refused to participate in the study; one female patient was excluded from the study because she had significant carotid artery stenosis, managed with carotid angioplasty with stenting. Stenting was done 33 years after the patient was treated for HD with a neck RT with 30 Gy and chemotherapy (ChT) with nitrogen mustard, oncovin, procarbazine and prednisolone (MOPP).

None of the patients reported stroke or transient ischemic attack (TIA). Twenty-three (7 females, 16 males) patients were included. They were 3 to 16 (median 11) year old at diagnosis and had evaluation 27 to 38 (median 33) years later at the age of 29 to 48 (median 43) years. They received neck RT with 20 to 65 (median 30) Gy. Eighteen (78%) patients received ChT, only two got ChT with anthracyclines. We recruited 26 healthy controls matched in age, sex, body mass index (BMI), arterial hypertension, smoking history and total cholesterol levels. Study procedures were approved by the National Medical Ethics Committee of the Republic of Slovenia.

Clinical and laboratory investigations

All participants completed a questionnaire to assess cardiovascular risk factors. A positive family history of cerebrovascular disease was defined as a cardiac or cerebral ischemic event in a first-degree relative younger than 65 years. We measured height, weight and blood pressure. Eight hour fasting blood samples were collected for measurement of total cholesterol. Cancer survivors and healthy controls were matched in age, sex, BMI, arterial hypertension, smoking history, total cholesterol levels. Diagnosis and treatment information were abstracted from patient's medical records.

Carotid measurements

High-resolution colour-coded duplex sonography and power Doppler sonography (equipped with an echo tracking system, Alpha 10, Aloka, Tokyo, Japan) of the carotid arteries was performed in all patients. Intima-media thickness (IMT), carotid diameter measurements and arterial stiffness measurements were performed longitudinally, strictly perpendicular to the ultrasound beam, with both walls clearly visualized bilaterally 2 cm below the bifurcation, on the far wall of the common carotid artery (CCA). For reproducible measurements, high-quality images were acquired along a CCA segment of minimum length of 1.5 cm. IMT was measured in accordance with the Mannheim consensus statement. The distances between the characteristic echoes from the lumen-intima and media-adventitia interfaces were measured. The final IMT value was based on the mean value of three maximal IMT measurements in three frames. Arterial stiffness was automatically measured from the modification of the arterial diameter between the systolic and diastolic phases on CCA segments. Carotid diameter waveforms were assessed by means of an ultrasound and converted to carotid pressure waveforms using an empirically derived exponential relationship between pressure and arterial cross section. Blood pressure measurements were obtained simultaneously with ultrasound measurements. The derived carotid pressure waveform was calibrated from brachial end-diastolic and mean arterial pressures by iteratively changing the wall rigidity coefficient.[19] This allowed the calculation of the arterial stiffness in-

TABLE 1. Risk factors in controls and cancer survivors

Charasteristics and risk factors	Controls	Survivors	P value
Total	26	23	
Sex (male (%))	6 (77)	7 (70)	0.40
Smoking (%)	8 (30.8)	7 (30.4)	0.613
Family history (%)	5 (20)	0	0.031
Arterial hypertension (%)	4 (15.4)	6 (26.1)	0.354
Diabetes mellitus	0	0	
Age (years)	42.65 ± 5.38	40.22 ± 6.56	0.16
Total cholesterol (mmol/l)	5.7 ± 1.00	5.6 ± 1,01	0.646
Body mass index	25.4 ± 2.98	24.9 ± 1.85	0.595

dices obtained as mean values of the last six measurements:

β, the stiffness index, is relatively independent of transient blood pressure changes:

$$\beta = \ln\frac{Ps}{Pd}\cdot\frac{Dd}{Ds-Dd}$$

where Ps and Pd are systolic and diastolic pressures (in mmHg), and Ds and Dd are systolic and diastolic carotid diameters.[20]

Ep (kPa), the pressure-strain elasticity modulus, is similar to Young's elastic modulus, regarded as a measure of intrinsic rigidity/stiffness of the arterial wall and inversely related to arterial elasticity[20,21]:

$$Ep = \frac{(Ps-Pd)Dd}{Ds-Dd}$$

AC, arterial compliance (mm²/kPa), is calculated from the arterial cross-section area and blood pressures. It exhibits an absolute stroke change in arterial lumen area for a given pressure and evaluates the role of the artery as a hollow structure[20]:

$$AC = \frac{\pi(Ds^2-Dd^2)}{4(Ps-Pd)}$$

PWV, the one-point pulse wave velocity (m/s), is calculated from the time delay between two adjacent distension waveforms from water hammer equation with the use of the β stiffness parameter[22]:

$$PWV = \sqrt{\frac{V\Delta P}{\rho\Delta V}}$$

where ϱ is blood density = 1050 kg/m³.

AI, the augmentation index (%), is a simple method commonly used to measure the effects of wave reflection and an indirect index of aortic elasticity [21]:

$$AI = \frac{\Delta P}{PP}$$

where ΔP is the pressure difference between peak systolic pressure and an early inflection point that indicates the beginning upstroke of the reflected pressure wave, and PP is pulse pressure.[20]

Beside these indices we examined the carotid arteries for plaque deposits and wall calcinations with the same ultrasound.

Statistical analysis

For the comparison of cases and controls we used chi-square (for categorical variables) and t-test (for continuous variables). In controls we examined carotids from both sides, so we analysed 52 non-irradiated vessels. In cases only carotids on irradiated side of the neck were examined. Twenty patients had bilateral neck RT, 3 unilateral only, so data for 43 vessels was included in our study.

All results were analysed using SPSS Version 21 software (SPSS, Chicago, IL, USA). For the group of cases we performed univariate linear and logistic regression analysis to detect associations between variables. After that we developed multivariate models for carotid PWV and wall calcinations and/or plaques. Variables with P-values < 0.25 from our univariate analysis were introduced into multivariate models.

For intergroup relationships we chose PWV as the most representative and usually used stiffness index and wall calcinations and/or plaques as atherosclerosis surrogate.

Results

Subjects

A total of 49 people (23 cases, 26 controls) were included in our population study. In our comparison of cases and controls no significant group differences were found for age, sex, BMI, total cholesterol, arterial hypertension and smoking history ($P < 0.05$). But there was a difference in family history between both groups ($p = 0.031$). Namely 20% of controls and none of survivors had positive family history (Table 1).

Carotid artery disease

Plaque deposits were present in 9 out of 43 (20.9%) vessels in cancer survivors group and in 0 out of 52 vessels in the group of healthy controls (0%; Figure 1). The results were analysed with the Pearson chi-square test which showed a significant group difference ($p < 0.01$).

Arterial wall calcinations were present in 17 out of 43 (39.5%) vessels in cancer survivors group

and in 0 out of 52 vessels in the group of healthy controls (0%; Figure 1). These results were also analysed with the Pearson chi-square test which showed a significant group difference ($p < 0.01$).

Plaque deposits and/or arterial wall calcinations were found in 24 out of 43 (55.8%) vessels in cancer survivors group and 0 out of 52 vessels in the group of healthy controls (0%; Figure 1) (significant group difference ($p < 0,01$).

As a measure of carotid stiffness the following parameters were used: beta stiffness index, pressure-strain elastic modulus (Ep), augmentation index (AI), pulse-wave velocity (PWV) and arterial compliance (AC). We analysed the results with the t-test, which showed significant group differences for all the stiffness parameters we used ($P < 0.05$; Table 2), but there was no difference in IMT between cases and controls ($p = 0.92$).

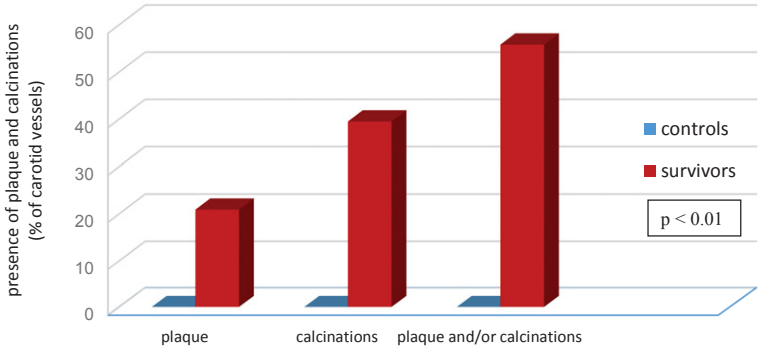

FIGURE 1. Plaques and wall calcinations in cancer survivors and controls.

Univariate and multivariate models for the group of cancer survivors

Among cancer survivors, we found a positive association between carotid PWV and gender ($P = 0.03$). No significant relationships were found for smoking, arterial hypertension, total cholesterol, age at diagnosis, age at evaluation, BMI, chemotherapy (yes, no) and size of RT dose (higher than 30 Gy or lower/equal to 30 Gy) (Table 3). In a multivariate model of carotid PWV only smoking was a significant factor; PWV was higher in smokers (Table 4). In a univariate and multivariate model of wall calcination and/or plaque, none of the factors had significant relationships (Tables 3, 5).

Discussion

The principal finding of present study is statistically significant higher values of carotid artery stiffness parameters in LTSCC of HD after neck RT. This is in agreement with two recent studies[16,17] Vatanen *et al.* found increased carotid artery stiffness in the cohort of 19 high-risk neuroblastoma patients compared with the control group, no differences in stiffness parameters were observed when comparing total body RT with non-total body RT survivors, but the number of patients in the two groups was small.[17] Krystal *et al.* evaluated carotid-femoral PWV in a cohort of 68 LTSCC, including non-irradiated patients, and healthy controls. LTSCC >18 years old at evaluation had significantly higher PWV compared to controls >18 years old and 70% of LTSCC >18 years had elevated PWV compared to established norms. In a univariate analysis, only exposure to RT and time off therapy were significantly associated with greater PWV. These associations did not hold after adjusting for age, sex, and BMI z-score.[18] In the present study all included patients were treated for HD with neck RT with or without ChT. Therefore, our group is more homogeneous regarding primary diagnosis, type of treatment in comparison with the above-mentioned studies, and it is population based. According to these observations it seems that PWV might be a surrogate marker for stroke in long-term survivors of HD after neck RT.

IMT did not show up as a possible surrogate marker for stroke in survivors of HD after neck RT. Namely, in our study there was no significant difference in IMT between the group of survivors and controls. Many authors offered IMT as a possible surrogate marker for stroke[14-17], however there are

TABLE 2. T-test for IMT and stiffness parameters

	Group	N	Mean	Std. dev.	P value
IMT	0	52	0.546	0.056	0.92
	1	43	0.548	0.132	
Beta stiffness	0	52	6.732	1.437	0.008
	1	43	8.014	3.035	
Ep	0	52	88.149	20.348	0.008
	1	43	109.767	53.331	
AC	0	52	0.774	0.264	0.034
	1	43	0.651	0.293	
AI	0	52	6.722	6.820	0.000
	1	43	20.130	12.833	
PWV	0	52	5.733	0.702	0.009
	1	43	6.300	1.334	

In the second column controls are coded with 0 and cases with 1.
AC = arterial compliance; AI = augmentation index; Ep = pressure-strain elastic modulus; IMT = intima-media thickness; PWV = pulse-wave velocity

TABLE 3. Univariate model for carotid pulse-wave velocity (PWV) and wall calcinations and/or plaque

	PWV		Wall calcinations and/or plaque	
	Linear regression estimate (SE)	p value	Odds ratio (95%CI)	p value
Gender	0.055 (0.448)	0.03	1.121 (0.303–4.145)	0.864
Smoking	0.741 (0.424)	0.088	2.679 (0.681–10.534)	0.158
Arterial hypertension	-0.037 (0.472)	0.938	0.570 (0.143–2.268)	0.425
Age at Dg (years)	0.019 (0.052)	0.718	1.094 (0.936–1.278)	0.258
Age at evaluation (years)	-0.047 (0.032)	0.151	1.078 (0.975–1.192)	0.143
Total cholesterol	0.021 (0.205)	0.920	0.702 (0.381–1.294)	0.257
Body mass index	0.021 (0.118)	0.862	0.926 (0.655–1.309)	0.664
Chemo (yes/no)	0.365 (0.484)	0.455	0.455 (0.100–2.072)	0.309
RT (2 groups*)	-0.551 (0.431)	0.208	1.680 (0.452–6.249)	0.439

*Size of radiotherapy dose (higher than 30 Gy or lower/equal to 30 Gy)

some contradictions. Indeed, in a cohort of LTSCC Krawczuk *et al.* failed to find any differences in IMT between irradiated and nonirradiated females.[23] In another article authors did not observe significant differences in IMT between cancer survivors treated with chemotherapy only versus those treated with chemotherapy and radiotherapy.[24] Beside that in articles with significant differences in IMT between irradiated and nonirradiated patients those differences were very small and still in a normal range.

In the present population based study, 56% of long-term survivors of HD after neck RT had morphological carotid wall changes as calcinations and/or plaques and none of controls. Many authors reported on higher incidence of atherosclerotic changes in patients treated with neck RT for head and neck cancers or HD in adulthood[7-12,24,25], and in LTSCC who were treated with RT as well.[13-15,17]

TABLE 4. Multivariate model for carotid pulse-wave velocity (PWV)

	Estimate (SE)	p value
Sex	-0.538 (0.471)	0.261
Smoking	0.937 (0.436)	0.031
Age at evaluation (years)	-0.050 (0.034)	0.155
RT (2 groups*)	-0.622 (0.439)	0.165

*Size of RT dose (higher than 30 Gy or lower/equal to 30 Gy)

TABLE 5. Multivariate model for wall calcinations and/or plaque

	Odds ratio (95%CI)	p value
Smoking	2.765 (0.680–1.238)	0.155
Age at evaluation (years)	1.081 (0.974–1.201)	0.144

But to our knowledge this study is the first population based study of long-term survivors of HD after neck RT.

The high percentage of morphological carotid wall changes in patients of our cohort after neck RT show that atherosclerotic changes are accelerated by neck RT. All patients with morphological carotid wall changes were asymptomatic regarding stroke or TIA. But one female patient was excluded from the study because she experienced hemodynamically significant carotid artery stenosis, managed with carotid angioplasty with stenting. Stenting was done 33 years after the patient was treated for Hodgkin disease with neck RT with 30 Gy and MOPP chemotherapy. Carotid artery disease is a progressive vascular disease, so we can expect that patients with morphological carotid wall changes can be at a higher risk for carotid disease.

Inside the group of survivors we studied the relationship between the size of RT dose and PWV and found out that there was no significant association between the two in the univariate analysis. Also there was no significant relation between them in our multivariate analysis. To our knowledge, no study on LTSCC exists studying the influence of the size of RT dose on stiffness. Meeske *et al.* failed to observe the relationship between radiation doses and intima-media thickness in young patients who received lower (18 Gy) and higher (>30 Gy) doses of RT.[15] In addition, we found no correlation between the size of RT dose and plaque deposits and/or arterial wall calcinations in a univariate analysis. It seems that even a low dose of RT induces premature vascular changes. This is in concordance with the report of Vatanen *et al.* who described premature vascular aging (decreased ar-

terial lumen, arterial plaques and increased IMT) in adolescents and young adult survivors of neuroblastoma even after TBI of 10–12 Gy.[17]

We analysed the influence of treatment with ChT inside the group of patients as well and there was no significant association between treatment with ChT and PWV or plaque deposits and/or arterial wall calcinations. We were not able to sub-analyse the influence of ChT containing anthracyclines, because only 2 of our patients got it. Our observation is in agreement with the report of Krystal *et al.* who did not find anthracycline dose or chemotherapy exposure to be a risk factor for elevated PWV among LTSCC.[18] Brouwer *et al.* in LTSCC even found a negative association between carotid IMT and treatment with anthracyclines, both as categorical variables [yes/no] and per 100mg/m2 cumulative dose.[22] Further, Bowers *et al.* observed no association between ChT and the risk of stroke in patients treated for HD in childhood.[5] To our knowledge, only one study dealing with LTSCC suggested that anthracyclines causes impaired endothelial function, which is early event in atherogenesis.[26] In adult patients with breast cancer, Kalabova *et al.* found an association between anthracycline based ChT and increase laboratory risk factors as well as progression of atherosclerosis. They proposed that antracyclines induces oxidative stress that can lead to higher incidence of cardiovascular events.[27]

Inside the group of survivors we studied the association between traditional cerebrovascular risk factors and PWV. In a multivariate analysis, we found a significant association between smoking and PWV; it was pointed out that smoking habit might have an additional negative influence on vascular aging in the group of patients after neck RT. Interestingly, this finding is in accordance with report of Bowers *et al.* who found out that cigarette smoking may be related to an increased risk of stroke among survivors of HD in childhood. Namely, in this study smoking was undoubtedly recognized as a powerful and independent risk factor for stroke.[5]

We are aware of the limitations of our study. It included only 23 cases and 26 healthy controls, therefore further studies with a bigger sample are needed. The groups matched in the most common risk factors, except in family history of cardiovascular diseases. Further, we could not analyse the influence of follow-up time in the group of survivors, since all of them were treated in a 12-year period.

Patients with carotid disease are asymptomatic in early stages of the disease, and stroke is often the first sign. It would be reasonable to screen patients after neck RT with ultrasound for these radiation-related late effects. To our knowledge, among available long-term follow-up guidelines only current COG guidelines recommend that LTSCC who had neck RT with 40 Gy should undergo yearly neurologic examination and assessment for diminished pulses and the presence of carotid bruits and Doppler of carotid vessels if clinically indicated (http://www.survivorshipguidelines.org). It is obvious that recommendations for screening of carotid stenosis in those patients have to be adjusted. One of the possible screening tools in the future could be PWV, but further research in this field is needed. What is more, even a very low dose of RT can cause atherosclerotic changes, therefore we should change cut-off dose of 40 Gy to a lower one. However, it is beyond dispute that atherogenesis in LTSCC with controlling cardiovascular risk factors can be slowed down. This is very important because it was reported that LTSCC are predisposed to obesity, hypertension, dyslipidaemia and glucose intolerance[16,17], therefore carefully monitoring and correction of the common vascular risk factors such as diabetes, smoking, obesity, hyperlipidaemia, hypertension is mandatory. Promotion of healthy life style in long-term follow-up clinics is of vital importance as well.

Acknowledgement

Thanks to Slovenian Research Agency for funding and to Slovenian Cancer Registry for data. Thanks to Vesna Savić, dr. med. for help with data collection.

References

1. Gatta G, Botta L, Rossi S, Aareleid T, Bielska-Lasota M, Clavel J, et al. Childhood cancer survival in Europe 1999-2007: results of EUROCARE-5 - a population-based study. *Lancet Oncology* 2014; **15:** 35-47. doi: 10.1016/S1470-2045(13) 70548-5

2. Perme MP, Jereb B. Trends in survival after childhood cancer in Slovenia between 1957 and 2007. *Pediatr Hematol Oncol* 2009; **26:** 240-51. doi: 10.1080/ 08880010902900437

3. Oeffinger KC, Mertens AC, Sklar CA, Kawashima T, Hudson MM, Meadows AT, et al. Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med* 2006; **355:** 1572-82. doi: 10.1056/NEJMsa060185

4. Morris B, Partap S, Yeom K, Gibbs IC, Fisher PG, King AA, et al. Cerebrovascular disease in childhood cancer survivors. A Children's Oncology Group Report. *Neurology* 2009; **73:** 1906-13. doi: 10.1212/WNL.0b013e3181c17ea8

5. Bowers DC, McNeil DE, Liu Y, Yasui Y, Stovall M, Gurney JG, et al. Stroke as a late treatment effect of Hodgkin's disease: a report from the childhood cancer survivor study. *J Clin Oncol* 2005; **23:** 6508-15. doi: 10.1200/JCO.2005.15.107

6. Bowers DC, Liu Y, Leisenring W, McNeil E, Stovall M, Gurney JG, et al. Late-occurring stroke among long-term survivors of childhood leukemia and brain tumors: a report from the childhood cancer survivor study. *J Clin Oncol* 2006; **24:** 5277-82. doi: 10.1200/JCO.2006.07.2884

7. Cheng SW, Wu LL, Ting AC, Ting AC, Lau H, Lam LK, Wei WI. Irradiation-induced extracranial carotid stenosis in patients with head and neck malignancies. *Am J Surg* 1999; **178:** 323-8.

8. Dorresteijn LD, Kappelle AC, Boogerd W, Klokman WJ, Balm AJM, Willem J. Klokman WJ, Keus RB, et al. Increased risk of ischemic stroke after radiotherapy of the neck in patients younger than 60. *J Clin Oncol* 2002; **20:** 282-8. doi: 10.1200/JCO.2002.201.282

9. Carmody BJ, Arora S, Avena R, Curry KM, Simpkins J, Cosby K, et al. Accelerated carotid artery disease after high-dose head and neck radiotherapy: is there a role for routine carotid duplex surveillance? *J Vasc Surg* 1999; **30:** 1045-51. doi: 10.1016/S0741-5214(99)70042-X

10. Elerding SC, Fernandez RN, Grotta J, Lindberg RD, Causay LC, Mcmurtrey MJ. Carotid artery disease following external cervical irradiation. *Ann Surg* 1981; **194:** 609-15.

11. Wethal T, Nedregaard B, Andersen R, Fosså A, Lund MB, Günther A, et al. Atherosclerotic lesions in lymphoma survivors treated with radiotherapy. *Radiother Oncol* 2013; **110:** 448-54. doi: 10.1016/j.radonc.2013.10.029

12. Hull MC, Morris CG, Pepine CJ, Mendenhall NP. Valvular dysfunction and carotid, subclavian, and coronary artery disease in survivors of Hodgkin lymphoma treated with radiation therapy. *JAMA* 2003; **290:** 2831-7. doi: 10.1001/jama.290.21.2831

13. Meeske KA, Nelson MD, Lavey RS, Gee S, Nelson MB, Bernstein L, et al. Premature carotid artery disease in long-term survivors of childhood cancer treated with neck irradiation: Five case reports. *J Pediatr Hematol Oncol* 2007; **29:** 480-4. doi: 10.1097/MPH.0b013e3180601029

14. King LJ, Hasnain SN, Webb JA, Kingston JE, Shafford EA, Lister TA, et al. Asymptomatic carotid arterial disease in young patients following neck radiation therapy for Hodgkin lymphoma. *Radiology* 1999; **213:** 167-72. doi: 10.1148/radiology.213.1.r99oc07167

15. Meeske KA, Siegel ES, Gilsanz V, Bernstein L, Nelson MB, Sposto R, et al. Premature carotid artery disease in pediatric cancer survivors treated with neck irradiation. *Pediatr Blood Cancer* 2009; **53:** 615-21. doi: 10.1002/pbc.22111

16. Brouwer CAJ, Postma A, Hooimeijer HLH, Smit AJ, Vonk JM, van Roon AM, et al. Endothelial damage in long-term survivors of childhood cancer. *J Clin Oncol* 2013; **31:** 3906-13. doi: 10.1200/JCO.2012.46.6086

17. Vatanen A, Sarkola T, Ojala TH, Turanlahti M, Jahnukainen T, Saarinen-Pihkala UM. Radiotherapy related premature arterial aging in young adult and adolescent. Long-term survivors of high-risk neuroblastoma. *Pediatr Blood Cancer* 2015; **62:** 2000-6. doi: 10.1002/pbc.25616

18. Krystal JI, Reppucci M, Mayr T, Fish JD, Sethna C. Arterial stiffness in childhood cancer survivors. *Pediatr Blood Cancer* 2015; **62:** 1832-7. doi: 10.1002/pbc. 25547

19. Meinders JM, Hoeks APG. Simultaneous assessment of diameter and pressure waveforms in the carotid artery. *Ultrasound Med Biol* 2004; **30:** 147-54. doi: 10.1016/j.ultrasmedbio.2003.10.014

20. Rhee MY, Lee HY, Park YB. Measurements of arterial stiffness: Methodological aspects. *Korean Circ J* 2008; **38:** 343-50. doi: 10.4070/kcj.2008.38.7.343

21. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J* 2006; **27:** 2588-605. doi: 10.1093/eurheartj/ehl254

22. Jaroch J, Łoboz Grudzień K, Bociąga Z, Kowalska A, Kruszyńska E, Wilczyńska M, et al. The relationship of carotid arterial stiffness to left ventricular diastolic dysfunction in untreated hypertension. *Kardiol Pol* 2012; **70:** 223-31.

23. Krawczuk-Rybak M, Tomczuk-Ostapczuk M, Panasiuk A, Goscik E. Carotid intima-media thickness in young survivors of childhood cancer. *J Med Imaging Radiat Oncol* 2017; **61:** 85-92. doi: 10.1111/1754-9485.12510

24. Sadurska E, Brodzisz A, Zaucha-Prażmo A, Kowalczyk J. The estimation of intima-media thickness and cardiovascular risk factors in young survivors of childhood cancer. *J Pediatr Hematol Oncol* 2016; **38:** 549-54. doi: 10.1097/MPH. 0000000000000513

25. Silverberg GD, Britt RH, Goffinet DR. Radiation-induced carotid artery disease. *Cancer* 1978; **41:** 130-7. doi: 10.1002/1097-0142(197801)41:1<130::AID-CNCR 2820410121>3.0.CO;2-X

26. Chow AY, Chin C, Dahl G, Rosenthal DN. Anthracyclines cause endothelial injury in pediatric cancer patients: a pilot study. *J Clin Oncol* 2006; **24:** 925-8. doi: 10.1200/JCO.2005.03.5956

27. Kalabova H, Melichar B, Ungermann L, Doležal J, Krčmova L, Kašparova M. Intima-media thickness, myocardial perfusion and laboratory risk factors of atherosclerosis in patients with breast cancer treated with anthracycline-based chemotherapy. *Med Oncol* 2011; **28:** 1281-7. doi: 10.1007/s12032-010-9593-1