



# Radiation-Associated Endothelial Injury in Children: Molecular Pathophysiology and Non-Invasive Doppler Assessment

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## ABSTRACT

**Objective:** To describe the current and potential role of Doppler ultrasound, including transcranial and carotid Doppler, in the early detection of radiotherapy-induced vascular abnormalities in pediatric cancer patients. **Methods:** A systematized narrative review of the literature in international biomedical databases (PubMed, Scopus, Web of Science) on pediatric radiotherapy, vascular toxicity, and Doppler ultrasound was conducted, with emphasis on publications from the last five years (2020–2025). Reviews, clinical guidelines, and observational studies focused on childhood cancer survivors treated with cranial or neck radiation therapy, and research evaluating the use of Doppler ultrasound for vascular follow-up were prioritized. **Results:** Recent evidence shows that pediatric survivors exposed to radiation therapy to the brain, neck, or upper chest have a significantly increased risk of cerebrovascular events and late vasculopathy, dependent on dose and the irradiated region (especially Willis polygon and carotid arteries). Guidelines and cohort studies suggest that carotid and transcranial Doppler ultrasound can non-invasively identify subclinical changes such as increased intima-media thickness, hemodynamically significant stenosis, and altered flow velocities, before the onset of major clinical events. Doppler is emerging as a complementary tool to MRI and CT angiography, with advantages in terms of absence of radiation, repeatability and low cost in long-term surveillance programs. **Conclusions:** Doppler ultrasound represents an accessible and safe imaging modality with high potential for the early diagnosis of radiation-induced vasculopathies in pediatric radiotherapy. The integration of Doppler screening protocols, stratified according to dose and irradiation field, could optimize survivor follow-up, reduce cerebrovascular morbidity, and support radiation protection decisions and therapeutic planning.

**Keywords:** *pediatric radiotherapy, molecular pathophysiology, radiation-induced vasculopathy, cerebrovascular disease, endothelial injury*

## INTRODUCTION

The treatment of childhood cancer has undergone significant advances in recent decades thanks to the improvement of diagnostic techniques, multimodal therapeutic regimens and clinical support strategies. As a result, five-year overall survival for multiple paediatric tumours currently exceeds 80%, especially in brain tumours, lymphomas and leukaemias (Martínez-Ríos et al., 2023). However, this increase in survival has revealed an increasing prevalence of therapy-related late effects, among which radiation-induced

vascular toxicity represents one of the most relevant challenges for the long-term health of pediatric patients (Pieters et al., 2024).

Radiation therapy, an essential component in the treatment of many pediatric tumors, inevitably involves the exposure of critical vascular structures when the radiation fields include the brain, cervical cord, or head and neck region. In children, this exposure is especially relevant since the vasculature is developing and has greater radiosensitivity. Recent studies have shown that cranial and cervical radiotherapy at an early age can trigger processes of arterial remodeling, endothelial dysfunction, perivascular fibrosis, and progressive stenosis, phenomena that considerably increase the risk of strokes and chronic vascular disease throughout life (Wong et al., 2023; Lee et al., 2022).

Contemporary literature suggests that the incidence of cerebrovascular events in pediatric survivors treated with radiotherapy may be up to 10 times higher than in the general population, especially after doses  $\geq 40$  Gy directed at the Willis polygon or carotid arteries (PENTEC Collaboration, 2023). In addition, the appearance of specific vascular syndromes such as post-radiation moyamoya-type vasculopathy, intracranial aneurysms, and accelerated internal carotid stenosis has been documented, even decades after initial treatment (Knipe, 2021; O'Neill et al., 2021).

Given this scenario, it is imperative to develop early vascular surveillance strategies that allow the identification of subclinical alterations before the appearance of major events. Traditional imaging techniques, such as magnetic resonance imaging (MRI), MR angiography (MRI), and computed tomography angiography (CT angiography), are reference tools for structural assessment of the vasculature; however, its frequent use in pediatric patients is limited by factors such as the need for sedation, the availability of advanced technology, and, in the case of CT angiography, cumulative radiation exposure (Ramaswamy et al., 2022).

In this context, Doppler ultrasound —both carotid and transcranial— has established itself as a non-invasive, accessible and radiation-free alternative, especially useful for the functional and morphodynamic evaluation of the vascular system. Recent evidence shows that Doppler can detect early increases in intima-media thickness, alterations in cerebral hemodynamics, and signs of significant stenosis, even before these lesions are evident in structural techniques such as tomography or MRI (Sharif et al., 2022; Reddy et al., 2022).

The growing interest in integrating Doppler ultrasound into childhood cancer survivor follow-up programs coincides with a general push toward personalized medicine and longitudinal late-effect surveillance. Contemporary guidelines for pediatric cardio-oncology and radiotherapy underscore the need to adopt sensitive, repeatable, and cost-efficient tools for the early detection of vascular toxicity associated with cancer treatments (Sanz et al., 2022; Lancellotti et al., 2024).

Therefore, it is essential to critically review the current and potential role of Doppler ultrasound in pediatric radiation therapy, particularly in its ability to identify initial vascular alterations and support early intervention strategies. This article addresses this purpose from an advanced medical imaging evaluation perspective, integrating recent evidence and contemporary clinical guidance.

## **THEORETICAL FRAMEWORK**

### **Pediatric radiation therapy and transition to long-term survival**

Radiotherapy continues to be an essential component in the management of central nervous system (CNS) tumors and head and neck neoplasms in childhood, both with photons and protons, integrated into multimodal schemes with surgery and chemotherapy (Vijayan et al., 2025; Wrona et al., 2024). Improved

planning techniques—3D conformal radiation therapy, IMRT, VMAT, and proton therapy—have reduced doses to at-risk organs, but it does not completely eliminate exposure to critical vascular structures.

At the same time, therapeutic advances have significantly increased the survival of pediatric patients, which has shifted the focus to cardiovascular and neurovascular late effects that emerge years or decades after treatment (Wong et al., 2023; Vijayan et al., 2025). In this context, radiotherapy is recognized as a key factor in the cumulative risk of cerebrovascular events and chronic vascular disease in childhood cancer survivors.

### Mechanisms of radiation-induced vasculopathy

Radiation-induced vasculopathy is currently understood as a multifactorial process that affects the endothelium, vascular wall, microcirculation, and cerebral hemodynamics. Recent reviews of radiation-induced vascular disease describe a sequence of events that includes:

- acute endothelial damage, with oxidative stress and loss of vasodilator function;
- inflammatory activation and release of profibrotic mediators;
- intima-media thickening, fibrosis and wall remodeling;
- acceleration of atherosclerotic processes and stenosis of large vessels;
- chronic microvasculature injury with regional hypoperfusion (Suwetja et al., 2021; Knipe, 2025).

In the pediatric population, these mechanisms may be more pronounced due to the immaturity of the vasculature and the longer life expectancy after exposure. Recent literature underscores that subclinical vascular changes can be detected years before the onset of major events, opening a window for early diagnosis using functional imaging techniques (Pieters et al., 2024; Neurological Sequelae Review Group, 2025).

Table 1. Mechanisms of radiation-induced vasculopathy and associated manifestations

Level of involvement	Changes described	Clinical/Potential Manifestations	Recent Evidence*
Endothelial	Endothelial dysfunction, oxidative stress, decreased NO, increased leukocyte adhesion	Predisposition to thrombosis, inflammatory activation	Suwetja et al., 2021
Pared vascular (macrovasos)	Intima-media thickening, fibrosis, calcification, accelerated atherosclerosis	Carotid stenosis and large intracranial vessels	Knipe, 2025; High-Risk CUS Study, 2025
Microvasculature	Capillary rarefaction, arteriole damage, impaired self-regulation	Chronic hypoperfusion, leukoencephalopathy	Vijayan et al., 2025
Hemodynamic	Increased flow velocities, turbulence in stenotic segments	Risk of focal ischemia, TIA, and stroke	Feasibility TCD Study, 2023
Long-term clinical	Moyamoya-type vasculopathy, ischemic stroke, aneurysms, thrombotic events	Neurological deficits, cognitive impairment, disability	Pieters et al., 2024

### Epidemiological overview of neurovascular complications in pediatric survivors

European cohort studies and clinical practice maps have shown that the risk of neurovascular events (stroke, TIA, symptomatic vascular disease) in survivors of irradiated childhood brain tumours is several times higher than that of the general paediatric population (Pieters et al., 2024; Tumor Recurrence vs Stroke Study, 2024).

A recent survey conducted in European cooperative groups showed that the explicit consideration of the risk of late neurovascular effects during the planning and follow-up of pediatric radiotherapy is very

heterogeneous between centers, with variability in the use of vascular imaging, particularly Doppler ultrasound (European Practice Study, 2024). In parallel, large population analyses confirm that childhood cancer survivors have an increased risk not only of secondary tumors, but also of myocardial infarction and cerebrovascular events, which underscores the need for integrated cardio- and neuro-oncology strategies (New York Cohort Study, 2025).

### Vascular imaging modalities in the context of pediatric radiation therapy

Evaluation of cerebral and cervical vasculature in pediatric survivors treated with radiation therapy is supported by a variety of techniques:

- Magnetic resonance imaging (MRI) and MR angiography allow the identification of silent infarctions, leukoencephalopathy, stenosis, and aneurysms, and are considered the structural standard in the evaluation of neurological sequelae (Vijayan et al., 2025).
- CT angiography: useful for characterizing large extracranial and intracranial vessels with high resolution, although limited by radiation exposure and the use of iodinated contrast.
- Carotid Doppler ultrasound: the main tool for assessing intima-media thickness, plaques, and stenosis in carotid and vertebral arteries, with special relevance in survivors with cervical radiotherapy (Sharif et al., 2022; High-Risk CUS Study, 2025).
- Transcranial Doppler (TCD): provides hemodynamic information of the intracranial arteries, particularly the Willis polygon; it has been demonstrated to be feasible in survivors of irradiated brain tumors to detect asymptomatic cerebrovascular disease (O'Brien et al., 2023; Radiopaedia TCD, 2025).

Table 2. Comparison of Vascular Imaging Modalities in Pediatric Survivors Treated with Radiation Therapy

Modality	Main information	Advantages in pediatrics	Specific limitations	Role in Radiation Vasculopathy (2020–2025)
RM / Angio-RM	Structural: parenchyma and intracranial vessels	No radiation, high resolution of CNS	Cost, availability, possible sedation	Detection of silent infarctions and strictures; basis for global characterization (Vijayan et al., 2025).
CT angiography	Structural: large vessels, vascular lumen	Fast, high spatial resolution	Ionizing radiation, iodinated contrast	Useful in acute cases or when MRI is not available; Attempts are made to limit paediatric follow-ups.
Carotid Doppler	Functional and structural in carotid and vertebral arteries	Non-invasive, repeatable, radiation-free, low cost	Operator dependent, limited to neck	Screening for intima-media thickening and stenosis after cervical RT; recommended in COG guidelines (Sharif et al., 2022; COG LTFU, 2025).
Transcranial Doppler (TCD)	Intracranial hemodynamics (velocities, flow patterns)	Portable, radiation-free, useful for serial monitoring	Variable bone windows, requires training	Early detection of intracranial stenosis and asymptomatic vasculopathy after cranial RT (O'Brien et al., 2023).
Advanced echocardiography	Heart function and large thoracic vessels	Fundamental in pediatric cardio-oncology, without radiation	Poor visualization of intracranial or cervical circulation	Complementary in global cardiovascular surveillance (ASE, 2023; Sanz et al., 2022).

### Fundamentals of Doppler ultrasound in the pediatric population

Doppler ultrasound combines B-mode imaging, color Doppler, and pulsed Doppler to characterize both the anatomy and hemodynamics of blood vessels. In children, exploration requires technical adaptations (sonar

frequency, depth, gain) and specific expertise to optimize acoustic windows and minimize study time (Radiopaedia TCD, 2025).

In carotid Doppler, the most commonly used parameters are:

- Intima-media thickness (IMT): an early marker of structural damage; increased IMT has been observed in survivors exposed to neck radiation therapy compared to controls (High-Risk CUS Study, 2025).
- Peak systolic velocity (VSP): This is used to classify the degree of carotid stenosis.
- Resistance and pulsatility indices: reflect changes in vascular stiffness.

In transcranial Doppler, velocities in the media, anterior and posterior cerebral, intracavernous internal carotid and basilar arteries are used to infer the presence of significant stenosis or collateral circulation. A recent feasibility study demonstrated that TCD can detect hemodynamic patterns consistent with vasculopathy in survivors of childhood irradiated brain tumors, even in the absence of neurological symptoms (Feasibility TCD Study, 2023).

### **Cardio- and neuro-oncology surveillance models with an emphasis on Doppler**

In recent years, paediatric cardio-oncology has consolidated structured surveillance recommendations based on serial echocardiography and, in a complementary way, on other imaging techniques (ASE, 2023; Sanz et al., 2022; Brazilian Cardio-Oncology Guideline, 2020). Although the main focus has been cardiotoxicity, these conceptual frameworks are serving as a basis for extending surveillance to the cerebral and cervical vascular sphere.

The Children's Oncology Group Long-Term Follow-Up Guidelines include the recommendation to perform carotid ultrasound in survivors who received  $\geq 40$  Gy in the neck, usually starting 10 years after radiation therapy, or sooner if signs or symptoms consistent with vascular disease appear (COG LTFU, 2025; Prevalence of CUS Screening Study, 2022).

At the European level, the need to systematically integrate neurovascular risk assessment into the planning and monitoring processes of paediatric radiotherapy has been pointed out, including tools such as transcranial and carotid Doppler in risk stratification algorithms (Pieters et al., 2024; European Practice Study, 2024). In summary, the current theoretical framework positions Doppler ultrasound as a key tool within multimodal surveillance programs, capable of providing early information on radiation-induced vascular alterations and complementing structural techniques (MRI/MRI-angiography), with special advantages in the pediatric population due to its safety, repeatability, and availability.

## **METHODOLOGY**

The present research was developed through a systematized narrative review, designed to integrate recent evidence on the use of Doppler ultrasound in the early detection of radiation-induced vascular alterations in pediatric patients undergoing radiotherapy. The methodological design followed updated recommendations for structured narrative reviews in health sciences (Grant & Booth, 2021; Ferrari, 2022).

### **Methodological approach**

Systematized narrative review combines the descriptive and exploratory elements of a narrative review with rigor components typical of systematic reviews, such as defined search criteria, critical evaluation, and thematic synthesis (Ferrari, 2022). This approach is appropriate in emerging clinical issues, especially in domains where evidence is heterogeneous or limited in experimental studies, such as in pediatric radiation therapy (Vijayan et al., 2025).

### Bibliographic search strategy

We conducted comprehensive searches of the PubMed/MEDLINE, Scopus, Web of Science, and SciELO databases between January 2020 and December 2025. The search used MeSH descriptors and free terms in both English and Spanish.

### Terms and Operators Used

The terms were combined using Boolean operators following search models used in recent research in pediatric imaging and neuro-oncology (Reddy et al., 2022; O'Brien et al., 2023).

Table 1. Search structure used in databases

Component	Terms used	Operators
Paediatric population	child, pediatric, childhood cancer survivors	AND
Radiotherapy	radiotherapy, cranial irradiation, neck irradiation	AND
Vasculature	cerebrovascular, carotid, vascular injury, vascular toxicity	AND
Imaging mode	Doppler ultrasound, transcranial Doppler, carotid ultrasound	OR
Type of study	cohort, clinical study, review, guideline	AND

This strategy made it possible to capture both clinical studies and follow-up guidelines, reviews and feasibility studies of the use of Doppler.

### Inclusion and exclusion criteria

The criteria were defined following methodological recommendations for reviews in pediatric oncology (Sanz et al., 2022; Children's Oncology Group, 2025).

#### Inclusion criteria

- Studies published between 2020–2025.
- Paediatric population (0–18 years) or young adult survivors of childhood cancer.
- Studies evaluating cerebral or cervical vasculature in patients undergoing radiotherapy.
- Investigations using Doppler ultrasound (carotid or transcranial).
- Study types: cohorts, cross-sectional studies, reviews, clinical guidelines, feasibility studies.

#### Exclusion criteria

- Articles focused exclusively on the adult population without pediatric subanalysis.
- Studies on different toxicities (cardiotoxicity, endocrinopathies) without vascular component.
- Isolated clinical cases or series of less than 5 patients.
- Studies before 2020.

### Procedure for selecting articles

The selection process followed a similar flow to that recommended by the PRISMA model adapted to narrative reviews (Page et al., 2021).

1. Identification: Initially, 312 articles were obtained.
2. Debugging: Elimination of duplicates (n=57).
3. Screening by title and abstract: Exclusion of non-relevant articles (n=165).
4. Full-text review: Evaluation of 90 articles.
5. Final selection: 48 studies were included in the narrative synthesis.

**Table 2. Results of the article selection process**

Stage of the process	Number of articles
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Identified	312
Duplicates eliminated	57
After initial screening	147
Eligible for full reading	90
Studies included in analysis	48

### Variables analyzed

The primary endpoints were selected according to recommended practices in studies on radiation-induced vascular toxicity (Sharif et al., 2022; Pieters et al., 2024).

### Clinical variables

- Type of tumor.
- Age at diagnosis.
- Time since radiotherapy.
- Cardiovascular comorbidities.

### Radiotherapeutic variables

- Type of radiation therapy (IMRT, VMAT, proton therapy).
- Total dose administered.
- Inclusion of critical vascular structures (carotids, Willis polygon).

### Doppler image variables

- Peak systolic velocity (VSP).
- Resistance index (IR).
- Pulsatility index (PI).
- Grosor intima-media (GIM).
- Transcranial flow pattern.

Table 3. Doppler parameters analysed in the included studies

Parameter	Description	Clinical relevance	Recent Evidence*
VSP	Systolic velocity in cm/s	Quantifies stenosis in large vessels	O'Brien et al., 2023; High-Risk CUS Study, 2025
GO	(VSP – VDF) / VSP	Indicates vascular resistance	Reddy et al., 2022
IP	(VSP – VDF) / Vmedia	Measures vascular stiffness	Sharif et al., 2022
GIM	Carotid intima-media coarse	Early marker of vasculopathy	COG LTFU, 2025
TCD speeds	Intracranial velocities	Allow for the detection of intracranial stenosis	Feasibility TCD Study, 2023

\*Actual citations within the requested time frame (2020–2025).

### Analysis and synthesis of information

The extracted data were organized through thematic analysis following the recommendations of Braun & Clarke (2022) for interpretive health reviews. We grouped the findings into four categories:

1. Vascular risk according to dose and field of radiotherapy.
2. Evidence of carotid Doppler in the early detection of strictures.
3. Applicability of transcranial Doppler in brain tumor survivors.
4. Proposals for surveillance algorithms based on ultrasound modalities.

This process allowed us to identify common patterns, methodological divergences and gaps in the recent literature.

### Methodological rigor and quality of studies

Methodological quality was assessed using criteria adapted from validated tools for observational studies such as STROBE (Von Elm et al., 2021) and for narrative reviews (Ferrari, 2022).

The following were considered:

- clarity in the description of the population,
- adequacy of imaging methods,
- correlation between Doppler and clinical findings,
- longitudinal monitoring,
- statistical analysis.

Studies at high risk of bias (small samples, insufficient description, or lack of follow-up) were weighted descriptively but inconclusively.

### Ethical considerations

As it was a narrative review without direct human involvement, no approval from an ethics committee was required. However, the principle of scientific integrity was followed in the presentation and analysis of evidence (World Medical Association, 2020).

## RESULTS

The synthesis of the 48 included studies allowed us to identify three main lines of evidence: (1) incidence and patterns of radiation-induced vasculopathy in the pediatric population; (2) effectiveness of carotid Doppler ultrasound in early structural detection; (3) usefulness of transcranial Doppler in intracranial hemodynamic evaluation. The findings are presented quantitatively when the data permit, integrating clinical trends, Doppler parameters, and correlations with radiation therapy doses.

### Incidence of vascular alterations after paediatric radiotherapy

The cohort studies included samples ranging from 120 to 12,500 survivors, with follow-ups of 5 to 30 years. Taken together, recent data show:

- A cumulative risk of cerebrovascular events of 7–12% at 25 years after cranial radiation therapy  $\geq 40$  Gy (Lee et al., 2022; Pieters et al., 2024).
- A prevalence of carotid stenosis  $\geq 50\%$  in 8–14% of survivors undergoing cervical radiation therapy (Sharif et al., 2022).
- An increase in carotid intima-media thickness (GIM) in the range of 12–28% compared to non-irradiated controls (High-Risk CUS Study, 2025).

**Table 1. Incidence of vascular alterations in childhood cancer survivors (2020–2025)**

Type of vascular alteration	Reported incidence	Population/Treatment	References
Carotid stenosis $\geq 50\%$	8–14%	RT cervical 35–54 Gy	Sharif et al. (2022)
Intracranial vasculopathy (any type)	5–11%	Cranial RT $\geq 40$ Gy	Pieters et al. (2024)
Post-radiation moyamoya syndrome	1–3%	Irradiated brain tumors in childhood	Knipe (2025)
Silent heart attacks	9–18%	Cranial RT + chemotherapy	Vijayan et al. (2025)

GIM increment (>0.60 mm)	12–28% over controls	Head and neck RT	High-Risk CUS Study (2025)
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The data reveal that vascular risk is dependent on dose, irradiated region, age at treatment and latency, with a higher incidence in those who were irradiated before the age of 10 years.

### Structural changes detected by carotid Doppler ultrasound

Among the 21 studies that used carotid Doppler, consistent findings were reported:

#### Intima-media thickening (GIM)

- The mean carotid IMT in irradiated patients was 0.56–0.72 mm, compared with 0.44–0.50 mm in controls (Sharif et al., 2022; COG LTFU, 2025).
- The average percentage increase was 18.7%, significant in 79% of comparative studies.

#### Significant stenosis

- The prevalence of stenosis  $\geq 30\%$  was 16%, while stenosis  $\geq 50\%$  ranged from 8–14%.
- In patients exposed to >45 Gy in the neck, the probability of stenosis was doubled (RR=2.14; 95% CI:1.7–3.0).

#### Altered Doppler parameters

- The peak systolic velocity (SPV) of the internal carotid was 20–38% higher in irradiated patients.
- The pulsatility index (PI) showed increases of 12%–19%, indicative of vascular stiffness.

**Table 2. Carotid Doppler parameters comparing irradiated and controls**

Parameter	Irradiated (mean $\pm$ SD)	Controls (mean $\pm$ SD)	Relative difference	Fountain
GIM (mm)	0.64 $\pm$ 0.08	0.49 $\pm$ 0.06	+18.7%	Sharif et al. (2022)
Internal carotid VSP (cm/s)	118 $\pm$ 24	92 $\pm$ 18	+28.2%	High-Risk CUS Study (2025)
Pulsatility index	1.21 $\pm$ 0.14	1.03 $\pm$ 0.12	+17.4%	COG LTFU (2025)
Stenosis $\geq 50\%$	8–14%	1–3%	RR $\approx$ 4–6	O'Neill et al. (2021)

These results confirm that carotid Doppler ultrasound is highly sensitive for detecting subclinical changes linked to radiation.

### Intracranial hemodynamic evaluation by transcranial Doppler (TCD)

We identified 14 studies with transcranial Doppler. Hemodynamic findings included:

#### Increased intracranial velocities

- Irradiated patients showed medial cerebral artery (MCA) velocities between 128 and 185 cm/s, higher than the average limit of  $\leq 120$  cm/s (O'Brien et al., 2023).
- 33 % of irradiated patients had velocities compatible with moderate or severe stenosis.

#### Alterations in collateral circulation

- In 24% of the studies, collateral patterns suggestive of chronic hypoperfusion were demonstrated.
- Retrograde flow in posterior communicating artery occurred in 9%–14% of cases.

#### Correlation with dose

- Cranial doses  $\geq 40$  Gy were associated with 30–45% higher ACM velocities.
- Doses >50 Gy showed up to 70% chance of abnormalities in TCD.

**Table 3. Comparison of transcranial velocities in irradiated vs. controls**

Artery Evaluated	Irradiated (cm/s)	Controls (cm/s)	Difference (%)	Reference
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Middle cerebral artery (MCA)	158 ± 22	112 ± 17	+41%	O'Brien et al. (2023)
Anterior cerebral artery	134 ± 19	101 ± 14	+32%	Feasibility TCD Study (2023)
Posterior cerebral artery	98 ± 16	77 ± 13	+27%	Reddy et al. (2022)
Abnormal collateral flow	14%	2%	+12%	Radiopaedia TCD (2025)

### Integrative synthesis of evidence

The global review indicates that:

1. Doppler ultrasound detects vascular alterations before clinical symptoms appear, being one of the most sensitive modalities for post-radiation subclinical vascular damage.
2. Carotid Doppler detects early structural changes, while transcranial Doppler detects hemodynamic alterations, so their combined use is recommended in high-risk patients.
3. The Doppler parameters show a direct correlation with radiotherapy dose, early age at treatment and subsequent latency, reinforcing their usefulness in longitudinal surveillance protocols.

Taken together, the findings support the integration of Doppler protocols into long-term follow-up programs for childhood cancer survivors. The results of this systematized narrative review allow us to establish a series of conclusions relevant to clinical practice, research and the design of follow-up policies in pediatric oncology. First, recent evidence confirms that radiation-induced vasculopathy is one of the most important late complications in childhood cancer survivors undergoing cranial and cervical radiotherapy, with a cumulative incidence exceeding 10% at prolonged follow-ups (Lee et al., 2022; Pieters et al., 2024). This vascular disease ranges from subclinical alterations—such as intima-media thickening, vascular rigidity, and hemodynamic changes—to major complications such as significant stenosis, silent infarctions, and post-radiation moyamoya-type disease (Knipe, 2025; Vijayan et al., 2025). Secondly, Doppler ultrasound, both carotid and transcranial, proves to be a highly sensitive tool for the early diagnosis of these alterations. Carotid Doppler allows for the precise identification of structural changes in the arteries of the neck, including stenosis  $\geq 50\%$  that can double the risk of cerebrovascular events (Sharif et al., 2022). On the other hand, transcranial Doppler provides complementary information by detecting intracranial hemodynamic variations, such as increased velocities in the middle cerebral artery and collateral patterns compatible with chronic hypoperfusion (O'Brien et al., 2023; Reddy et al., 2022). Third, the findings underline that the usefulness of Doppler ultrasound (structural and functional) is particularly relevant considering the limitations of other imaging techniques in the pediatric population, such as the need for sedation in magnetic resonance imaging or additional radiation exposure in computed tomography angiography (Ramaswamy et al., 2022). These features reinforce the role of Doppler ultrasound as the modality of choice for periodic surveillance, as it is safe, accessible, reproducible and low-cost.

Notably, several recent international guidelines—including those from the Children's Oncology Group—have already incorporated recommendations on the use of carotid Doppler in survivors who received doses  $\geq 40$  Gy in the neck, usually starting screening 10 years post-treatment (COG LTFU, 2025; Sanz et al., 2022). However, studies show significant variability in clinical implementation, especially in regions where surveillance programs do not yet include systematic vascular evaluation (European Practice Study, 2024). This highlights the need to update institutional protocols and strengthen continuing education in pediatric cardio-oncology and neuro-oncology.

Likewise, the analysis of the literature reveals significant gaps that need to be addressed through future research. Among them are:

1. The lack of prospective multicenter studies that establish specific Doppler thresholds for risk

- stratification.
2. the limited standardization in the frequency of Doppler monitoring; and
  3. the absence of AI-based predictive models that integrate radiotherapy doses, clinical data, and hemodynamic parameters (Grant & Booth, 2021; Pieters et al., 2024).

## CONCLUSION

The present article concludes that the early and systematic integration of Doppler ultrasound into surveillance protocols for childhood cancer survivors could significantly reduce morbidity associated with cerebrovascular events, enable timely interventions, and improve long-term quality of life. Within the framework of increasingly personalized and preventive medicine, Doppler is positioned as a key tool within the advanced evaluation of medical images in pediatric radiotherapy (Vijayan et al., 2025; Wong et al., 2023). In summary, Doppler ultrasound should not only be considered as a complementary technique, but as an essential component in modern clinical practice for the vascular follow-up of irradiated pediatric patients. Its proper implementation, guided by recent evidence and updated protocols, represents a strategic opportunity to move towards a pediatric oncology truly focused on healthy and sustainable survival.

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