INTERNATIONAL JOURNAL OF
RADIATION ONCOLOGY • BIOLOGY • PHYSICS
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CLINICAL INVESTIGATION

Radiation-Induced Cerebral Contrast Enhancements Strongly Share Ischemic Stroke Risk Factors

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Received Jul 16, 2023; Accepted for publication Dec 31, 2023

Purpose: Radiation-induced cerebral contrast enhancements (RICE) are frequent after photon and particularly proton radiation therapy and are associated with a significant risk for neurologic morbidity. Nevertheless, risk factors are poorly understood. A more robust understanding of RICE risk factors is crucial to improve management and offer adaptive therapy at the outset and during follow-up.

Methods and Materials: We analyzed the comorbidities in detail of 190 consecutive adult patients treated at a single European national comprehensive cancer center with proton radiation therapy (54 Gy relative biological effectiveness) for LGG from 2010 to 2020 who were followed with serial clinical examinations and magnetic resonance imaging for a median 5.6 years.

Results: Classical vascular risk factors including age (≥50 vs <50 years: 1.6-fold; $P = .0024$), hypertension (2.7-fold; $P = .00012$), and diabetes (11.7-fold; $P = .0066$) were observed more frequently in the cohort that developed RICE. Dyslipidemia (2.1-fold),

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DOI of original article: http://dx.doi.org/10.1016/j.ijrobp.2024.01.007.

Disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest for the submitted work. T. E. is funded by the Clinician-Scientist Fellowship of the Heidelberg Research College for Neurooncology of Heidelberg University, Herbert Kienzle Foundation, and Else Kröner-Fresenius Foundation and received travel reimbursement from Bristol-Myers Squibb outside the submitted work. J.H.-R. received speaker fees from ViewRay Inc and Pfizer Inc and research grants from IntraOP Medical and Varian Medical Systems outside the submitted work. L.K. reports grants from Ruprecht-Karls Universität Heidelberg during the conduct of the study and personal fees from Accuray Inc and Novocure GmbH outside the submitted work. J.D. reports grants from CRI The Clinical Research Institute, ViewRay Inc, Accuray International, Accuray Incorporated, RaySearch Laboratories AB, Vision RT Ltd, Merck Serono GmbH, Astellas Pharma GmbH, AstraZeneca GmbH, Siemens Healthcare GmbH, Solution Akademie GmbH, Eromed PLC Surrey Research Park, Quintiles GmbH, Pharmaceutical Research Associates GmbH, Boehringer Ingelheim Pharma GmbH Co, PTW-Frieburg Dr Pychlau GmbH, and Nanobiotix A.a. outside the submitted work. All authors acknowledge financial support by Deutsche Forschungsgemeinschaft within the funding program for Open Access Publishing, by the Baden-Württemberg Ministry of Science, Research, and the Arts, and by Ruprecht-Karls-Universität Heidelberg.

Data Sharing Statement: The data sets generated for this study will not be made publicly available because national legislation and the terms of study ethics approval do not allow data set sharing outside of the institutions participating in the analysis.

Acknowledgments—T.E. acknowledges generous support from the Herbert Kienzle Foundation and the Else Kröner-Fresenius Foundation.

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ijrobp.2023.12.044.

https://doi.org/10.1016/j.ijrobp.2023.12.044

being overweight (2.0-fold), and smoking (2.6-fold), as well as history of previous stroke (1.7-fold), were also more frequently observed in the RICE cohort, although these factors did not reach the threshold for significance. Multivariable regression modeling supported the influence of age ($P = .05$), arterial hypertension ($P = .01$), and potentially male sex ($P = .02$), diabetes ($P = .0008$), and smoking ($P = .001$) on RICE occurrence over time, independent of each other and further vascular risk factors. If RICE occurred, bevacizumab treatment was 2-fold more frequently needed in the cohort with vascular risk factors, but RICE long-term prognosis did not differ between the RICE subcohorts with and without vascular risk factors.

Conclusions: This is the first report in the literature demonstrating that RICE strongly shares vascular risk factors with ischemic stroke, which further enhances the nebulous understanding of the multifactorial pathophysiology of RICE. Classical vascular risk factors, especially age, hypertension, and diabetes, clearly correlated independently with RICE risk. Risk-adapted screening and management for RICE can be directly derived from these data to assist in clinical management.

Introduction

Radiation-induced cerebral contrast enhancements (RICE) as an entity has risen into the consciousness of the radiation oncology community in the modern era, with an incidence ranging from 5% to as high as 31%.[1-7] Several publications in the literature have shown an association between RICE and particle therapy.[8] There is in vitro evidence of a (locally) higher radiobiological effectiveness (RBE) of protons than the world-wide accepted constant factor of 1.1,[9] which can lead to uncertainties in dose calculation and may lead to excess radiobiological dose deposition. One manifestation of this hitherto unrealized elevation in RBE is the risk of RICE, especially when proton therapy is combined with chemotherapy.[10-12] Data focusing on proton therapy for low-grade glioma report an incidence of RICE of 21% during a median observation period of 3 years.[13] However, RICE is not specific to particle therapy and can also occur with x-ray−based therapies.[14] A recent publication reports a RICE rate of 23% after photon radiation therapy for grade 2 gliomas.[15]

As nomenclature in the literature is heterogenous, "RICE" is often used as an umbrella term for findings that can be characterized by radiation-induced contrast-enhancements and may include radiation necrosis, pseudoprogression, and radiation-induced blood-brain barrier disruption.[16] The pathophysiology of RICE appears to be the result of transient blood-brain barrier disruptions.[17] Corticosteroids and anti−vascular endothelial growth factor (VEGF) agents like bevacizumab have been demonstrated to be effective in clinical management.[18,19] The occurrence of RICE can greatly confound the diagnosis of tumor progression, as both may present with new contrast enhancement and edema in the treated region. In an attempt to differentiate the 2 entities, the Response Assessment in Neuro-Oncology Working Group (RANO) recommends the diagnosis of tumor progression not be made within the first 3 months after radiation therapy.[20-22] Recommendations for differentiation between RICE and tumor progression are available in the literature.[16,19]

Our institution has attempted to assist clinicians in tackling the challenges of RICE. Thus, in previous articles we reported our analysis of the patient-, tumor-, and treatment-related risk factors for RICE.[8,19,23] We demonstrated treatment-related factors including chemotherapy and reirradiation characteristics to be associated with an elevated risk of RICE.[19] RICE risk also depends on inherent tumor characteristics such as World Health Organization (WHO) grading.[8,23] Anatomically, the highest rates are noted in tumors located near the periventricular region or when simultaneous chemotherapies are used.[1-7,19] In addition, the rise in RICE incidence may have paralleled the increased use of particle beam therapy in the treatment of central nervous system (CNS) malignancies; thus, some data posit a causal relationship between the two.[6,10-12] Children, who are more commonly offered proton therapy in an effort to minimize integral radiation dose exposure, are at a much lower risk for RICE relative to adults, and as such RICE risk increases with age.[8,23] Intrinsically, there is a clear biological change with time between children and adults that appears to be independent of tumor and treatment factors. In the present study, we explore known vascular risk factors associated with the development of ischemic stroke and their association with the evolution of RICE.

Methods and Materials

All analyses were performed following institutional guidelines and the Declaration of Helsinki of 1975 in its most recent version. Ethics approval for the study was granted by the Heidelberg University ethics committee (#S-494/2021). Patient confidentiality was maintained by anonymizing patient data to remove any identifying information.

Patient characteristics

In the present study, we analyzed 190 consecutive adult (age ≥21 years) patients with low-grade glioma who underwent proton radiation therapy between 2010 and 2020 at a single national comprehensive cancer center. Patient and treatment data were obtained from a single institutional database and included a detailed review of clinical records. Analysis was performed in retrospective fashion and longitudinally over the entire follow-up period using routine clinical examinations and follow-up magnetic resonance imaging (MRI). More

detailed oncological data on a significantly overlapping mixed pediatric and adult cohort were previously published.[8] Vascular risk factors were identified in detail for all patients and included the following: age, sex, arterial hypertension, diabetes mellitus, dyslipidemia, being overweight, and smoking. Information was gathered by all available medical records, patient questionnaires, and interviews. Arterial hypertension was based on European Society for Cardiology guidelines of 2018 defined by a blood pressure >140/90 mm Hg. The used European definition is less strict compared with the American definition in the American College of Cardiology/American Heart Association guidelines, which define arterial hypertension by a blood pressure >130/80 mm Hg. Diagnosis of diabetes mellitus was made based on WHO and American Diabetes Association definitions, which consider blood glucose and HbA1c values. Diagnosis of dyslipidemia was made based on 2019 European Society for Cardiology and European Atherosclerosis Society guidelines. Guidelines for the management of dyslipidemias are quite complex. The guidelines recommend not only a review of total cholesterol, triglycerides, LDL cholesterol, non-HDL cholesterol, and HDL cholesterol but also a consideration of the overall cardiovascular risk of the patients. Apolipoprotein B and lipoprotein (a) analyses could also be used. "Overweight" was defined by body mass index (based on height and weight) ≥25. Smoking history was defined by the abuse of inhalable tobacco products on a regular basis in the past or present. Lifetime smoking status (yes/no) and overall abuse (pack-years, calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person has smoked) were assessed. In addition, we reviewed medical records and patient questionnaires or interviews for manifestation of (cardio-)vascular diseases (VD), including history of stroke, myocardial infarctions, thromboembolism, coronary artery disease, peripheral artery disease, and chronic kidney disease. Finally, patient medication history (medications used at the time of radiation therapy start) was reviewed with focus on antihypertensives, antidiabetics, antiarrhythmics, cholesterol lowering agents, anticoagulants, and platelet aggregation inhibitors. Dosage of medications was not considered for the present analysis. Tumor control and survival data were previously published.[8]

Diagnosis of RICE

We defined RICE as new non-tumor-related posttreatment contrast enhancement on cMRI in surrounding brain tissue within the 80% isodose region, analogous to RANO criteria.[24] Every retrospectively suspected RICE case was (re-) presented at an interdisciplinary tumor board conference. Tumor board members reviewed comprehensive data sets on each patient. These imaging data sets included a current MRI with ≤1-mm slice thickness and contrast-enhanced T1 and T2, FLAIR, and diffusion sequences. Imaging was compared with all previous MRIs and to the radiation therapy treatment plan within the radiation therapy planning software, as previously published.[8,19,23] Additionally, clinical data on patients' state of health, medications, potential surgeries, and systemic therapies were reviewed. Equivocal cases underwent secondary biopsy for evaluation of tumor progression versus RICE. If multidisciplinary tumor board members had discordant or suspicious opinions, cases were excluded from this analysis. Only cases that were ultimately confirmed to be RICE by the tumor board conference were included in this analysis. As this is a retrospective analysis, we were also able to adjust the diagnosis over time, which dramatically reduced diagnostic uncertainties. Previously published recommendations for diagnosis of RICE were used.[19] In the evaluation of RICE course over time, 3-dimensional longitudinal volumetric analysis of RICE was conducted. Two example cases of RICE adjacent to the corresponding radiation therapy plans are shown in Figure 1.

Endpoint definition

The primary endpoint of the study was RICE occurrence or, for time-to-event analysis, freedom from RICE over time. Secondary endpoints were time to RICE occurrence, RICE severity (documented by Common Terminology Criteria for Adverse Events grading), RICE treatment, and RICE outcome.

Statistical analysis

Descriptive statistics for baseline variables (Tables 1 and 2) and for endpoints (Tables 3 and 4) included means (SD) and/or median (IQR and range, as appropriate) for continuous variables, and absolute and relative frequencies for categorical variables. For time-to-event endpoints like freedom from RICE (Figs. 2 and E1), Kaplan-Meier estimates were calculated including CIs, *P* values, and a corresponding table with the number at risk for each time point. Linear multivariable regression modeling was used for time latency from radiation therapy to first occurrence of RICE as a continuous endpoint to assess for RICE risk factors (Table 5). All vascular risk factors were included in the multivariable regression model: age, sex, arterial hypertension, diabetes mellitus, dyslipidemia, body mass index, being overweight, and smoking. Given this is an exploratory data analysis, *P* values are of a descriptive nature. A P value <.05 was considered statistically significant. Statistical analyses were performed with the software R version 4.0.2 (r-project.org).

Results

Comparison of clinical and dosimetric risk factors in patients who developed RICE (RICE cohort) with those without RICE (non-RICE cohort)

The subcohort that developed RICE during the follow-up period was compared with the subcohort that did not develop RICE during follow-up (Tables 1 and 2). RICE and

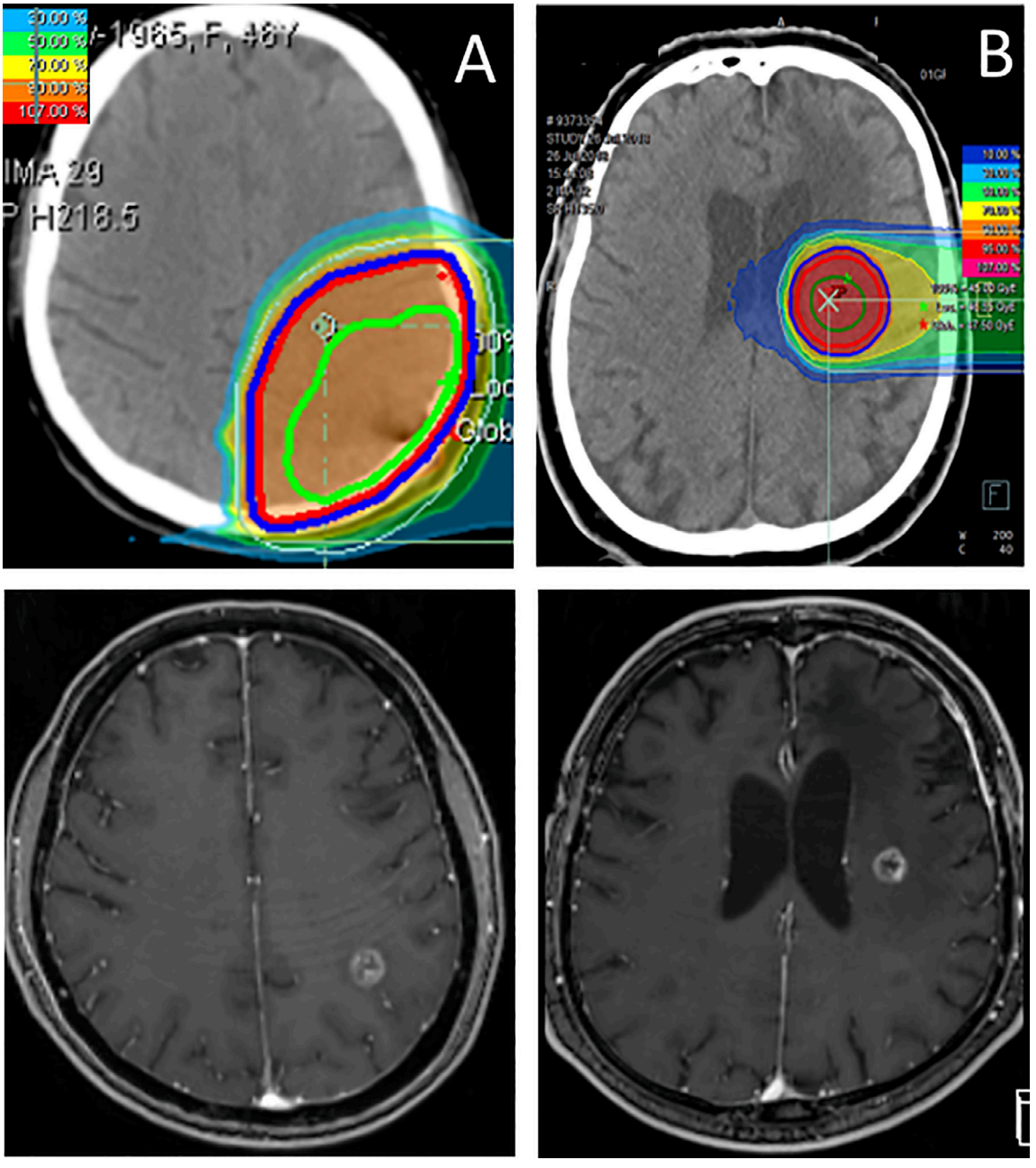


Fig. 1. Two typical examples of periventricular radiation-induced contrast enhancements in patients with significant vascular risk factors adjacent to the corresponding radiation therapy plan. The patient in example case A was a 46-year-old woman with a notable diabetes history and World Health Organization grade 2 astrocytoma who underwent definitive radiation therapy (54 Gy [relative biological effectiveness] in 27-fraction protons). The patient in example case B was a 64-year-old man with World Health Organization grade 2 oligodendroglioma who underwent definitive radiation therapy (54 Gy [relative biological effectiveness] in 27-fraction protons). The patient was overweight (body mass index 33.5 kg/m^2) and had arterial hypertension. Colored isodose lines demonstrate relative dose (%) of prescription dose (Gy).

non-RICE subcohorts did not significantly differ in sex, Karnofsky performance status, and tumor histology in the present analysis but did differ in age (older age in RICE cohort) and tumor grading (more WHO 2 in RICE cohort). Surgical resection data were comparable in the RICE and non-RICE cohorts. A review of radiation therapy dose characteristics demonstrated a 1.5-fold higher RICE rate with 2.0 Gy (RBE) per fraction compared with 1.8 Gy (RBE) per fraction. Absence of chemotherapy was associated with a RICE risk reduction of one-third (no chemotherapy in 12.2% of RICE cohort vs 37.6% of non-RICE cohort), while chemotherapy delivery increased RICE risk (higher rates with

Table 1 Baseline characteristics of patients

Patients	Overall cohort n = 190 [%]	RICE n = 49 [%]	No RICE n = 141 [%]
Gender			
Female	80 [42.1%]	21 [42.9%]	59 [41.8%]
Male	110 [57.9%]	28 [57.1%]	82 [58.2%]
Age at radiation therapy			
Median	39.9	45.1	37.4
Minimum to maximum	21.0-76.3	27.5-76.3	21.0-71.2
Karnofsky performance status	n = 161 [%]	n = 42 [%]	n = 119 [%]
≤70	20 [12.4%]	7 [16.7]	13 [10.9%]
80	23 [14.3%]	3 [7.1%]	20 [16.8%]
90	66 [41.0%]	17 [40.5%]	49 [41.2%]
100	52 [32.3%]	15 [35.7%]	37 [31.1%]
Diagnosis	n = 190 [%]	n = 49 [%]	n = 141 [%]
Astrocytoma	126 [66.3%]	34 [69.4%]	92 [65.2%]
WHO 1	16 [12.7%]	0 [0%]	16 [17.4%]
WHO 2	110 [87.3%]	34 [100%]	76 [82.6%]
Oligodendroglioma	44 [23.2%]	11 [22.5%]	33 [23.4%]
WHO 1	5 [11.4%]	1 [9.1%]	4 [12.1%]
WHO 2	36 [81.8%]	9 [81.8%]	27 [87.9%]
Other/mixed glioma	20 [10.5%]	4 [8.1%]	16 [11.3%]
WHO 1	4 [20.0%]	0 [0%]	4 [25.0%]
WHO 2	16 [80.0%]	4 [100%]	12 [75.0%]
Past surgery	n = 180 [%]	n = 43 [%]	n = 137 [%]
No surgery	2 [1.1%]	1 [2.3%]	1 [0.7%]
Biopsy	77 [42.8%]	17 [39.5%]	60 [43.8%]
Subtotal resection	53 [29.4%]	13 [30.2%]	40 [29.2%]
Total resection	48 [26.7%]	12 [27.9%]	36 [26.3%]
Chemotherapy	n = 190 [%]	n = 49 [%]	n = 141 [%]
None	59 [31.1%]	6 [12.2%]	53 [37.6%]
PCV	41 [21.6%]	13 [26.5%]	28 [19.9%]
Temozolomide	75 [39.5%]	22 [44.9%]	53 [37.6%]
Other	15 [7.9%]	8 [16.3%]	7 [4.9%]

Abbreviations: PCV = procarbazine/lomustine/vincristine regimen; RICE = radiation-induced contrast enhancement; WHO = World Health Organization.

procarbazine/lomustine/vincristine [PCV] regimen compared with temozolomide). Based on results of our previous research, which similarly demonstrated that chemotherapy profoundly influences RICE prognosis,[19] analysis of RICE outcome after additional chemotherapy was also conducted (Table E1). No relevant outcome differences were found in patients with RICE who did not undergo chemotherapy. However, the subgroup of patients with RICE that did not undergo chemotherapy was too small (n = 6) to conduct reliable comparison analyses, including statistical testing for differences.

Known vascular risk factors are prognostic for the development of RICE

Analysis of vascular risk factors for RICE occurrence demonstrated age to be an important risk factor, with patients ≥50 years relative to patients <50 years being at 2-fold risk for RICE ($P = .024$). Arterial hypertension and diabetes mellitus were associated with a 2.7-fold risk for RICE ($P = .00012$) and an 11.7-fold risk for RICE ($P = .0066$), respectively, and were the 2 most important vascular risk factors for RICE development. Other vascular risk factors

Table 2 Baseline characteristics of radiation therapy

Radiation therapy	Overall cohort n = 227 [%]	RICE n = 49 [%]	No RICE n = 141 [%]
Radiation therapy total dose			
Median dose (range) [Gy RBE]	54 (50.4-60)	54 (50.4-60)	54 (50.4-60)
<54 Gy RBE	28 [12.3%]	10 [20.4%]	18 [12.8%]
Radiation therapy dose per fraction (Gy RBE)			
1.8 Gy RBE	104 [56.2%]	21 [45.7%]	85 [60.3%]
2 Gy RBE	81 [43.8%]	25 [54.3%]	56 [39.7%]
Macroscopic tumor volume (GTV) (mL)			
Median	54	66	40.5
Minimum to maximum	4-589	12-309	4-589

If not otherwise visible, absolute and relative frequencies are shown. Relative frequencies are based on the available data and exclude missings.
Abbreviations: GTV = gross tumor volume; RBE = relative biologic effectiveness; RICE = radiation-induced contrast enhancement.

Table 3 Vascular risk factors and medications

Risk factors and medications	Overall cohort n = 190 [%]	RICE n = 49 [%]	No RICE n = 141 [%]	*P* value
Vascular risk factors				
Age at radiation therapy ≥50 y	36 [18.9%]	13 [26.5%]	23 [16.3%]	**.024**
Male sex	106 [55.8%]	28 [57.1%]	78 [55.3%]	.56
Arterial hypertension	37 [21.0%]	18 [36.7%]	19 [13.5%]	**.00012**
Diabetes mellitus	5 [2.8%]	4 [8.2%]	1 [0.7%]	**.0066**
Dyslipidemia	14 [8.0%]	6 [12.2%]	8 [5.7%]	.17
Overweight (BMI ≥25)	52 [46.0%]	18 [48.7%]	34 [24.1%]	.36
Smoking	27 [31.4%]	8 [34.8%]	19 [13.5%]	.53
Manifest vascular diseases				
History of stroke	16 [9.1%]	6 [12.2%]	10 [7.1%]	.24
History of myocardial infarction	1 [0.6%]	0 [0%]	1 [0.7%]	.58
History of any thromboembolism	22 [12.5%]	8 [16.3%]	14 [9.9%]	.3
Coronary artery disease	2 [1.1%]	0 [0%]	2 [1.4%]	.44
Peripheral artery disease	2 [1.1%]	2 [4.1%]	0 [0%]	**.024**
Chronic kidney disease	20 [11.4%]	8 [16.3%]	12 [8.5%]	.23
(Cardio-)vascular medications				
Antihypertensives	30 [17.1%]	15 [31.3%]	15 [10.6%]	**.00041**
Antidiabetics	6 [2.8%]	4 [8.3%]	2 [1.2%]	**.0063**
Antiarrhythmics	11 [6.3%]	6 [12.5%]	5 [3.1%]	**.034**
Cholesterol lowering agents	14 [8.0%]	6 [12.5%]	8 [4.9%]	.16
Anticoagulants	10 [5.7%]	3 [6.3%]	7 [4.9%]	.57
Platelet aggregation inhibition	8 [4.6%]	3 [6.3%]	5 [3.1%]	.55

If not otherwise visible, absolute and relative frequencies are shown. *P* values ≤.05 are in boldface.
Abbreviations: BMI = body mass index; RICE = radiation-induced contrast enhancement.

including dyslipidemia (2.1-fold), being overweight (2.0-fold), smoking (2.6-fold), and history of any manifestation of VD also demonstrated a higher rate of RICE, but threshold for significance was not reached for the descriptive group difference. For manifestations of VD, history of stroke as well as history of any thromboembolism, peripheral artery disease, and chronic kidney disease were 1.6- to 1.9-fold found in the RICE subcohort compared with the

Table 4 RICE outcomes in the cohort

Outcome of RICE cases	Overall cohort n = 49	VRF/VD n = 32	No VRF/VD n = 17
Time from radiation therapy end to first occurrence of RICE (mo)			
Median	16.9	16.9	17.0
Minimum to maximum	1.7-40.9	2.8-33.8	1.7-40.9
RICE CTCAE grading			
Grade 0	21 [44.7%]	16 [50.0%]	5 [29.4%]
Grade 1	12 [25.5%]	6 [18.8%]	6 [35.3%]
Grade 2*	0 [0%]*	0 [0%]*	0 [0%]*
Grade 3	13 [27.7%]	8 [25.0%]	5 [29.4%]
Grade >3	0 [0%]†	0 [0%]†	0 [0%]†
RICE treatment needed			
No treatment needed	34 [72.3%]	22 [68.8%]	12 [70.6%]
Treatment needed	13 [26.5%]	8 [25.0%]	5 [29.4%]
Steroids only	4 [8.5%]	2 [6.3%]	2 [11.7%]
Bevacizumab (anti-VEGF antibody)	9 [19.2%]	6 [18.8%]	3 [17.6%]
Outcome			
Complete RICE remission at the end of FU	0 [0%]	0 [0%]	0 [0%]
Partial RICE remission at the end of FU	3 [61.2%]	2 [6.3%]	1 [5.9%]
Stable RICE at the end of FU	42 [85.7%]	27 [84.4%]	15 [88.2%]
Progressive RICE at the end of FU	4 [8.1%]	2 [6.3%]	2 [11.8%]

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; FU = follow-up; RICE = radiation-induced contrast enhancement; VD = vascular diseases; VEGF = vascular endothelial growth factor; VRF = vascular risk factors.

* In cases of moderate symptoms, treatment was administered according to in-house standards. Need for treatment was defined as CTCAE version 3 in our analysis; therefore, there is no patient with moderate symptoms but no RICE treatment.

† One patient had RICE shortly before death. The patient was, however, asymptomatic, and after careful assessment of available data RICE was classified as unlikely to be related.

non-RICE subcohort, but only peripheral artery disease reached the threshold for significance ($P = .024$). Detailed analysis of vascular risk factors associated with RICE development is illustrated in Table 3. RICE-free survival was calculated for all vascular risk factors and demonstrated RICE to be more frequent and to occur earlier in patients with vascular risk factors. The plots are shown in Figures 1 and E2. Use of (cardio-)vascular medications at the time of radiation therapy start was also analyzed, and all were more frequent in the RICE subcohort relative to the non-RICE subcohort (Table 3). Antihypertensives (3.0-fold, $P = .00041$), antidiabetics (6.9-fold, $P = .0063$), antiarrhythmics (4.0-fold, $P = .034$), cholesterol-lowering agents (2.6-fold, not significant), anticoagulants (1.3-fold, not significant), and platelet aggregation inhibitors (2.0-fold, not significant) represented underlying vascular risk factors and VDs and were more frequent in the RICE cohort. In event time analysis for RICE-free survival, the relevance of antihypertensives, antidiabetics, and antiarrhythmics were factors associated with higher rates of RICE and shorter time latency for RICE occurrence (Fig. E2).

Overall, RICE was mitigating and resulted in a relevant number of cases in need of therapy. Specifically, 27.7% of RICE cases went along with symptoms that made RICE-directed therapy (dexamethasone or bevacizumab) necessary (Common Terminology Criteria for Adverse Events version 3). In this cohort, complete RICE remission was not observed in any single patient during the follow-up period, which supports that RICE has long-lasting sequela. Nevertheless, despite the occurrence of RICE, prognosis was not found to depend on the presence of vascular risk factors. Analysis of the influence of vascular risk factors within the RICE subcohort did not demonstrate relevant differences between patients with known vascular risk factors versus patients without known vascular risk factors. By the time RICE occurs, the influence of vascular factors may decrease. However, this subgroup analysis might lack statistical power for reliable results. Details on RICE severity and outcome according to vascular risk factors subgroups can be found in Table 4.

Multivariable regression modeling was conducted to evaluate potential confounders, particularly age as a main confounder for vascular risk factors. Table 5 shows a multivariable linear regression model calculated for the endpoint time latency to RICE occurrence (in days) and including the vascular risk factors age (≥40 years, cutoff set based on

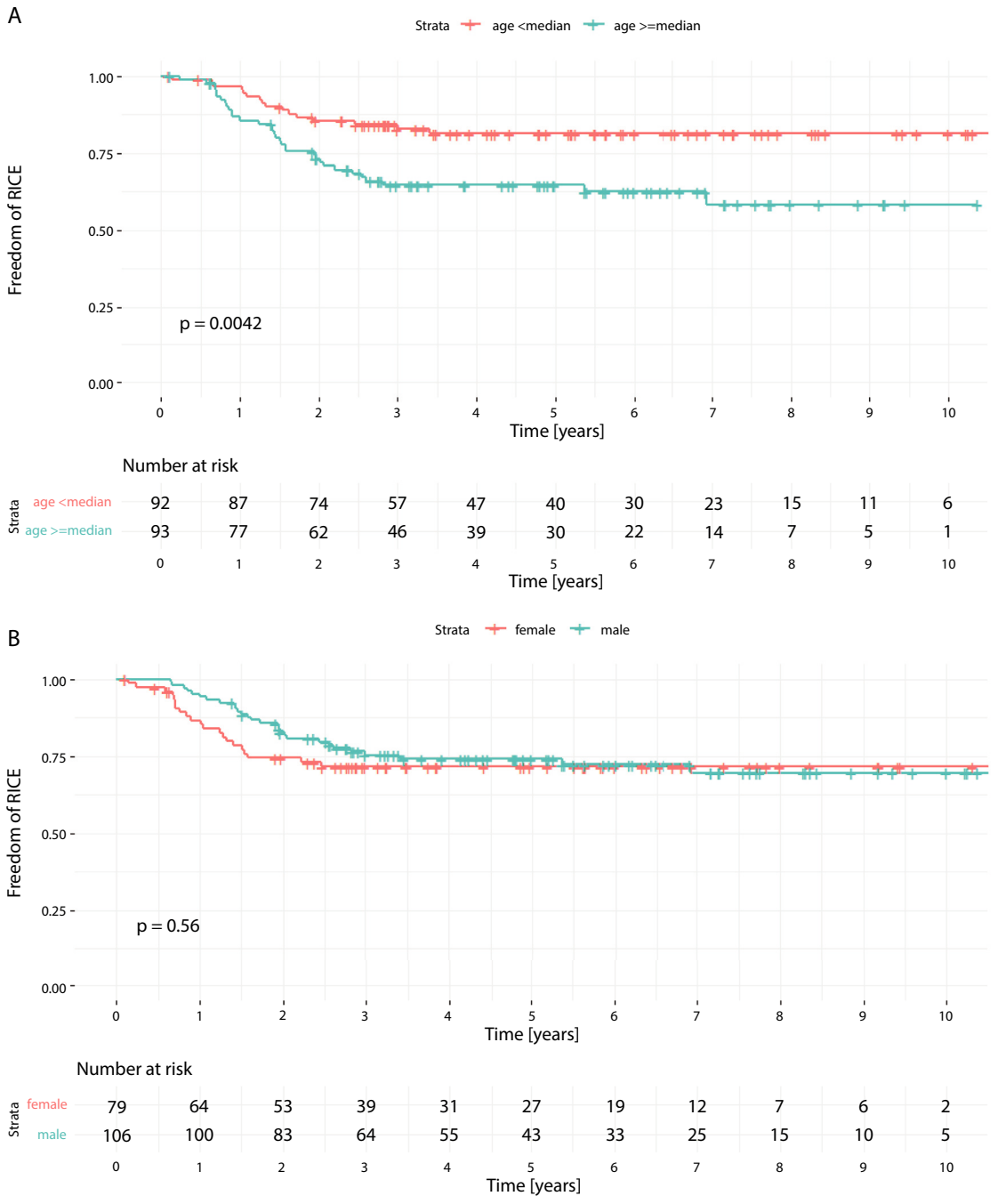


Fig. 2. Time-to-event analyses for radiation-induced contrast enhancement (RICE) occurrence stratified by vascular risk factors. (A) Age. Median age in this study cohort was 40 years. (B) Sex. (C) Hypertension. (D) Diabetes. (E) Dyslipidemia. (F) Overweight. *Overweight* was defined as body mass index ≥25. (G) Smoking.

median age in the cohort), sex, arterial hypertension, diabetes mellitus, dyslipidemia, being overweight, and smoking. The model demonstrated that male sex ($P = .02$), arterial hypertension ($P = .006$), diabetes mellitus ($P = .0008$), and smoking ($P = .001$) influence time latency from radiation therapy to RICE occurrence independently of each other and other vascular risk factors.

Discussion

We report a strong association between classical vascular risk factors and RICE occurrence after proton beam radiation therapy for low-grade glioma. In our analysis, hypertension was the most important risk factor independent of age. Additionally, diabetes mellitus, dyslipidemia,

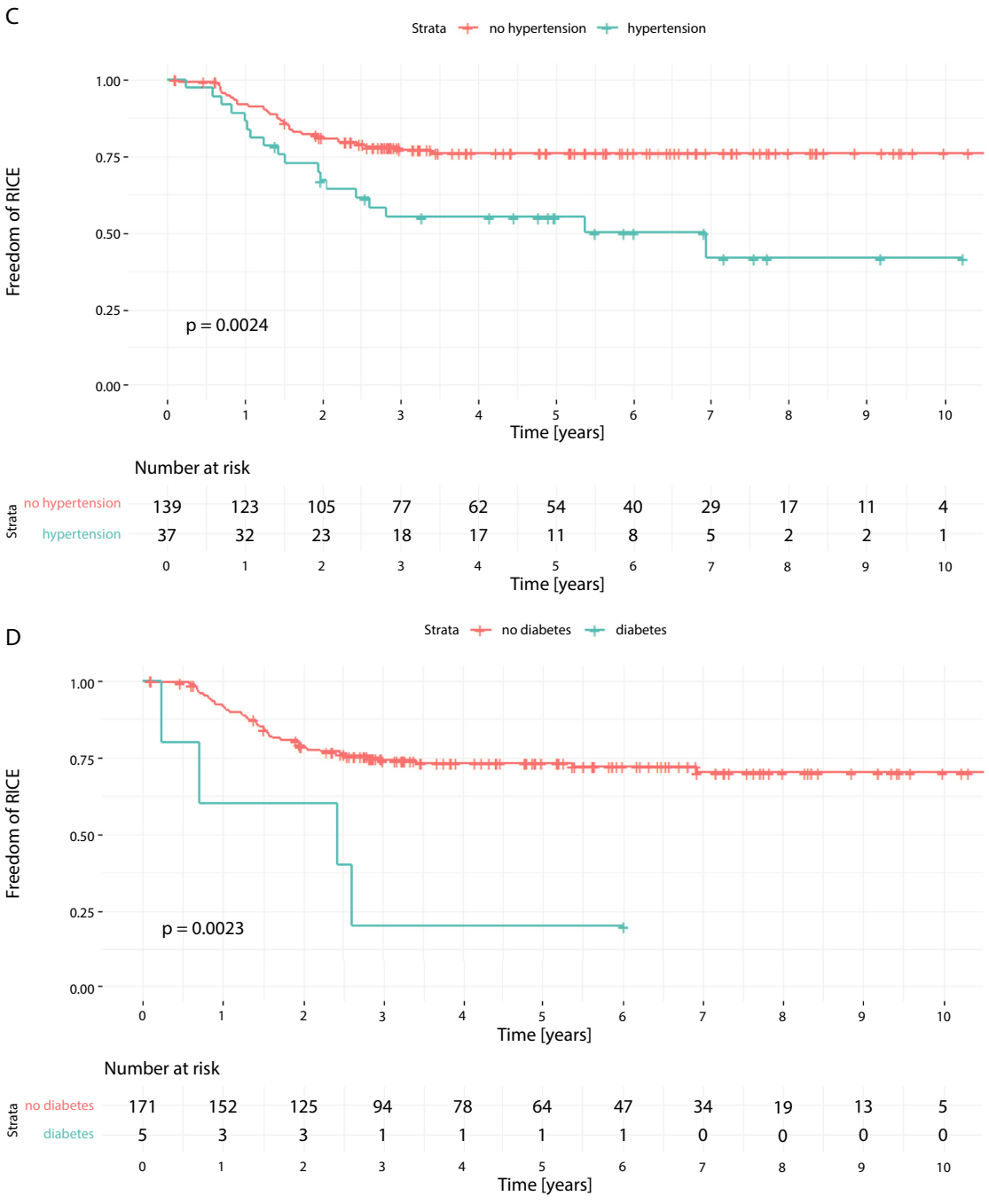


Fig. 2. Continued.

overweight status, smoking, and history of previous stroke were more frequently observed in patients who developed RICE.

Underlying vascular pathology as a risk factor for the development of radiation toxicity in the CNS has limited reports in the literature. The literature on brain stem tolerance to radiation therapy of skull base tumors reported similar findings, with a reduced tissue tolerability associated with vascular risk factors reported decades ago.[25] Beyond the CNS, cell studies demonstrated fibroblasts of patients with coronary artery disease to be more radiosensitive as controls.[26] In patients with breast cancer, it was shown that radiation dose to pre-existing calcified atherosclerotic plaques in the left anterior descending coronary artery was strongly associated with the development of acute coronary events. After cancer treatment, intimal thickening, lipid deposition, and adventitial fibrosis are found within the vascular system. It is possible the triggered effects of radiation

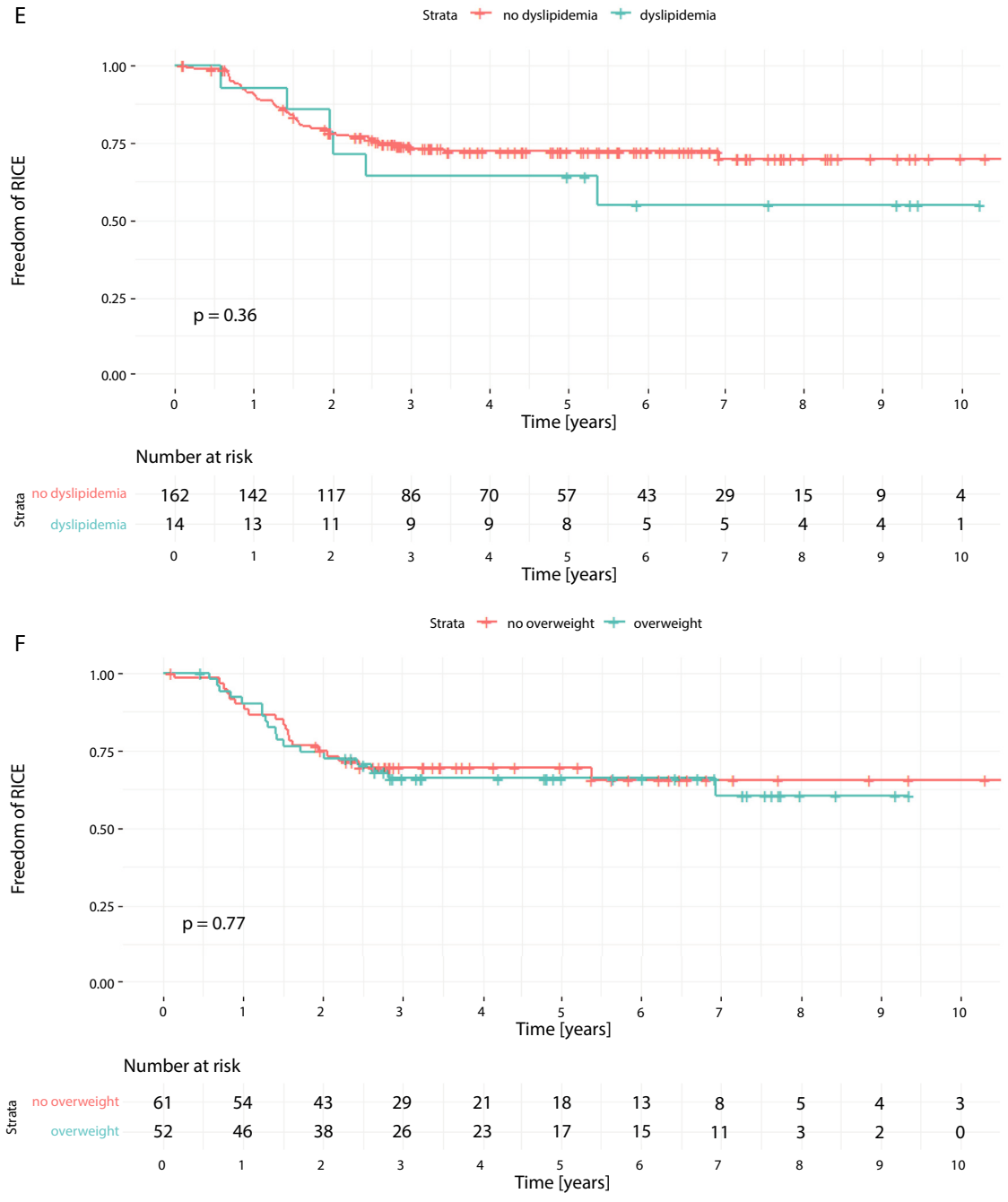


Fig. 2. Continued.

exposure to "healthy" nonatherosclerotic arteries take decades to develop, while in patients with atherosclerosis the progression is accelerated and may manifest sooner.[27-29]

We found hypertension, known as the most important risk factor for the development of primary stroke, to be the most important risk factor for RICE.[30] Furthermore, age, hypertension, diabetes, dyslipidemia, being overweight, smoking, and history of previous stroke were associated with an increased RICE risk, and again these are all well-known stroke risk factors.[31] Manifestations of cardiovascular diseases were also associated with higher RICE rates, but the group difference did not meet the threshold for significance. Sequela I of VD are rarer than the classical vascular risk factors; for example, history of stroke was found in 8% of all patients, which resulted in limited statistical power. The findings of this study support our hypothesis that the underlying vascular status, which is strongly influenced by atherosclerosis, plays a critical role in RICE development. The literature evaluating the effectiveness of bevacizumab identified radiation-induced vascular tissue damage as the causal etiology

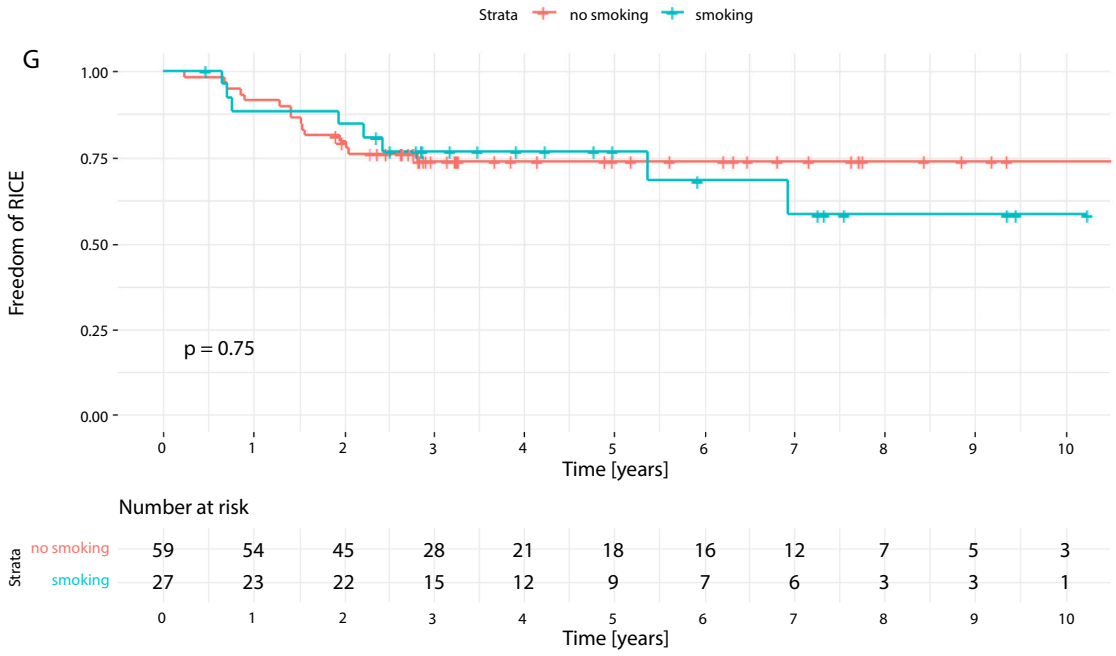


Fig. 2. Continued.

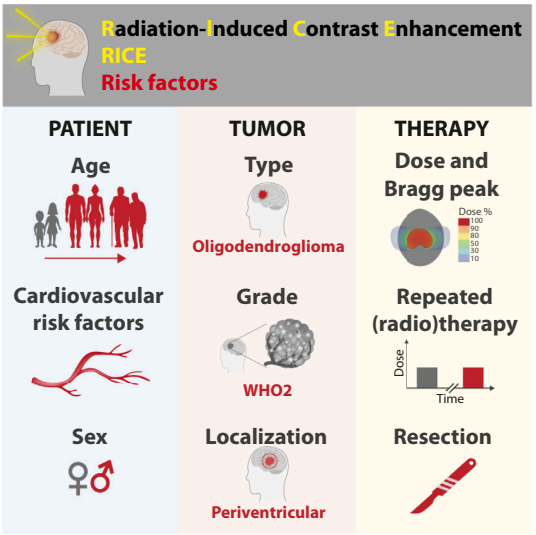
for RICE. As a consequence, local ischemia and hypoxia could be expected to directly result in tissue damage. Moreover, radiation-induced hypoxia-inducible factor 1α (HIF-1α) and VEGF neovascularization can increase vascular permeability resulting in brain edema visible on surveillance scans. As VEGF is known to be an integral part of the neovascularization cascade, extensive literature supports the effectiveness of bevacizumab via its anti-VEGF mechanism. Anti-VEGF agents may help to mitigate the increase in vascular permeability and therefore minimize ongoing edema, thus allowing local oxygen and nutrient supply and yielding improvement. Consequently, anti-VEGF agents are not expected to reverse existing cellular damage but are thought to interrupt the vicious circle of inflammation, edema, poor nutrient supply, and neovascularization, resulting in resolution of RICE.[32,33] The incremental role of neuroinflammation and edema for brain tissue damage associated with RICE is also supported by the effectiveness of corticosteroids in RICE.[18] Despite the very different inciting injuries with stroke, we do find similarities in the pathophysiology of this process. For example, HIF-1α has an extensive role as a sensitive regulator of oxygen homeostasis in stroke and its role includes neuronal survival, neuroinflammation, angiogenesis, glucose metabolism, and blood-brain barrier regulation.[34] The final pathway in RICE and stroke might be similar and result in tissue necrosis and neuronal damage if not remedied at an early stage. Nevertheless, the management is quite different; while dexamethasone has been tested for stroke edema with disappointing results,[35] bevacizumab is, in fact, contraindicated. The literature reports an increased risk

Table 5 Vascular risk factors influencing time latency (days) from radiation therapy to first occurrence of RICE

Model 2	Estimate	Error	*P* value
Age at radiation therapy ≥40 y	−401.4	250.7	.14
Male sex	443.4	169.0	**.02**
Arterial hypertension	576.3	172.6	**.006**
Diabetes mellitus	1313.3	296.1	**.0008**
Dyslipidemia	120.7	227.8	.61
Overweight (BMI ≥25)	229.3	147.5	.15
Smoking	799.2	191.0	**.001**
	$R^2 = 0.8314$	Adjusted $R^2 = 0.7331$	F-statistics for model: ***P* = .0008**

Multivariable linear regression modeling. Variables were scaled (Z-statistics) for comparability. *P* values ≤.05 are in boldface. Dependent variable is time latency from radiation therapy to first occurrence of RICE.

Abbreviations: BMI = body mass index; RICE = radiation-induced contrast enhancement.



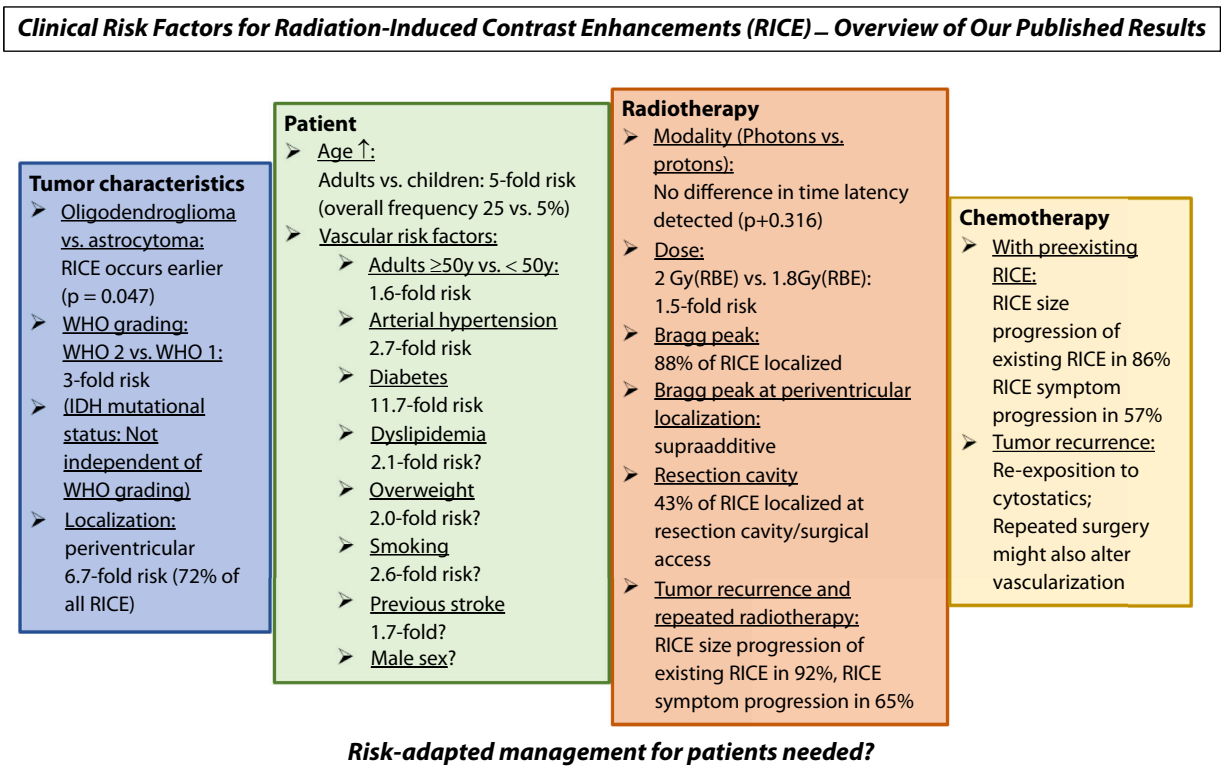


Fig. 3. (A) Overview of clinical risk factors for radiation-induced contrast enhancement (RICE). (B) Description of clinical risk factors for RICE that we found in our recent research. Risk factors that failed the threshold for significance in this work are marked by "?" even if some of them met the threshold for significance in multivariable regression modeling (see Table 5). Sources in addition to the current data: references 8, 19, and 23.

for stroke with bevacizumab. Even if the pathophysiology behind it is not completely understood, this may be a result of hypertension (as a common side effect of bevacizumab) or impaired neovascularization in an atherosclerotic situation with increased need for that.[36,37]

Cytostatic chemotherapies like PCV or temozolomide also seem to be an important risk factor for RICE.[19] This is of special relevance as most patients with low-grade glioma do undergo chemotherapy after radiation therapy when brain tissue is at its most vulnerable. The present data demonstrate that a PCV regimen may be more toxic than temozolomide from a RICE standpoint. However, given the lack of statistical power in the present data set, detailed conclusions remain out of reach.

What lessons can be learned from these new findings? On the one hand, a better understanding of RICE risk factors helps to identify patients at increased risk for RICE development; thus, the pretest probability for RICE occurrence can

be adjusted and early intervention can be undertaken. Even before therapy initiation, radiation oncologists can take special care to reduce controllable risk factors if possible, and more rigorous follow-up schedules may allow for early detection and treatment. As proton radiation therapy is a limited resource with certain advantages (eg, sparing of vulnerable tissue or critical structures, higher RBE, fewer secondary malignancies in the long run), understanding the association of RICE and its risk factors may assist in better triaging of patients with a wider therapeutic window for particle therapy. A better understanding of RICE development may also open doors for prophylactic therapeutic interventions. For multiple reasons, a patient's vascular risk factors should be aggressively managed in a multidisciplinary approach for improvement in the patient's global health beyond a risk of RICE. To date, it is unknown if aggressive use of antihypertensives and other agents in controlling vascular risk factors could be helpful in prevention or treatment of RICE in patients with these specific vascular risk factors. From a mechanistic point of view, we need to evaluate the molecular targets that can be addressed in the RICE pathophysiology, for example the HIF-1α pathway. For ischemic stroke, this pathway is already under investigation as a mechanism to escape the vicious circle of neuronal injury and neuroinflammation.[34,38,39] In summary, understanding the pathophysiology and clinical management of RICE is in its infancy, and our analysis provides important knowledge regarding RICE risk factors and a hypothetical pathophysiology mechanism that may directly affect everyday patient care. An overview of clinical risk factors for RICE discovered at our institution is illustrated in Figure 3. It served to provide a streamlined approach for the clinician to evaluate RICE risk in daily clinical care.

Conclusion

This is the first publication demonstrating that the risk of RICE development is strongly linked to risk factors associated with ischemic stroke. The data further enhance our vague understanding of multifactorial pathophysiology and opportunities for tackling RICE in the clinical setting. Classical vascular risk factors, specifically age, hypertension, and diabetes, correlated the strongest with RICE risk. Risk-adapted screening and therapy can be derived from these data.

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