

The threefold value of surgery in previously irradiated brain metastases

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Research Article

Keywords: Brain metastases, Radiation necrosis, Tumor recurrence, Salvage surgery, Stereotactic radiosurgery, Histopathology

Posted Date: June 28th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10064351/v1>

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Additional Declarations: No competing interests reported.

Version of Record: A version of this preprint was published at Journal of Neuro-Oncology on July 22nd, 2026. See the published version at <https://doi.org/10.1007/s11060-026-05723-z>.

Abstract

Purpose

Differentiating radiation necrosis (RN) from tumor recurrence (TR) in previously irradiated brain metastases (BM) remains a challenge. Imaging techniques lack sufficient diagnostic reliability, while therapeutic implications differ between both entities. This study aims to evaluate the diagnostic, therapeutic, and prognostic value of surgery in patients with progressive irradiated BM.

Methods

We studied patients who underwent surgical resection for progressive BM after prior irradiation. Histopathological diagnosis was classified as pure RN or TR. Clinical, radiological, surgical, and survival outcomes were analyzed.

Results

In 73 lesions, histopathology demonstrated TR in 68.5% of lesions. Among TR, 84.0% showed mixed pathological features combining viable tumor cells and radionecrotic patterns. Patients initially treated by irradiation alone were significantly more likely to present TR, whereas surgery followed by postoperative irradiation was significantly associated with RN. Median interval between radiation and surgery was significantly longer in the RN group and breast cancer seemed related to RN. Postoperative clinical improvement occurred in 80.4% of symptomatic patients and corticosteroid discontinuation within one month occurred in 72.3% of patients, without significant difference between RN and TR. Median overall survival was longer in patients with RN (39 vs 19 months, $p = 0.025$).

Conclusion

Surgery provides diagnostic, therapeutic, and prognostic value in patients with progressive irradiated BM. Beyond diagnostic clarification, surgery provides significant symptomatic improvement and corticosteroid withdrawal regardless of final pathology. Histopathological diagnosis influences survival outcomes and subsequent oncological management.

Introduction

Brain metastases (BM) are the most common intracranial tumors in adults, occurring in up to 20% of patients with systemic cancer, and their incidence is rising as systemic therapies prolong survival [1, 2]. Their management combines surgery, radiation therapy and systemic treatments: when feasible, surgery is followed by irradiation of the surgical cavity, otherwise stereotactic radiotherapy becomes the main treatment, so nearly all such lesions ultimately receive radiation [3].

Despite progress in irradiation techniques, some lesions evolve into progressive contrast-enhancing lesions within irradiated areas. These may represent tumor recurrence (TR), from persistent viable tumor cells, or radiation necrosis (RN), a delayed complication of radiation-induced vascular and inflammatory injury influenced by dose, fractionation, irradiated volume and systemic therapies [4–10].

Differentiating RN from TR remains a major challenge in neuro-oncology. Conventional MRI is frequently indistinguishable, both showing contrast enhancement with surrounding edema, although serial imaging may help orient the diagnosis [11, 12]. Advanced modalities such as perfusion MRI and MR spectroscopy aim to improve accuracy, but their performance is inconsistent across studies and none can reliably replace histopathology [13–17]. This uncertainty carries major therapeutic consequences: TR may require repeat surgery, systemic therapy or re-irradiation, whereas RN is managed with corticosteroids or bevacizumab, which is often insufficient [18–20].

In this context, surgery plays an increasingly important role: beyond definitive histopathological diagnosis, resection may relieve mass effect, improve symptoms, facilitate corticosteroid discontinuation and guide subsequent oncological management [21, 22], though it remains challenging in irradiated tissue. RN and TR are increasingly viewed not as distinct entities but as two extremes of a biological continuum, with mixed lesions frequently encountered and survival correlating inversely with the proportion of viable tumor [23–28]. Available evidence remains limited, as most studies are retrospective, monocentric and based on small heterogeneous cohorts [29, 30].

The aim of the present study is therefore to evaluate the diagnostic, therapeutic, and prognostic value of surgery in patients with previously irradiated progressive BM.

Materials and Methods

Study Design and Patient Population

We conducted a retrospective monocentric study at the CHU de Caen (Normandy, France) including consecutive patients who underwent surgical resection for progressive brain lesions arising after previous radiation therapy for BM between January 2010 and December 2025.

Inclusion criteria were previous radiation therapy for one or more BM, either stereotactic radiosurgery, postoperative cavity irradiation or whole brain radiotherapy. Radiological progression was characterized by enlargement of a previously treated lesion or appearance of a new contrast-enhancing lesion within a previously irradiated area on conventional magnetic resonance imaging. Availability of histopathological analysis following surgical resection was the cornerstone of the screening.

Patients treated exclusively by stereotactic biopsy were excluded because the primary objective of the study was to evaluate the diagnostic, therapeutic, and prognostic value of surgical resection.

The study was approved by the Institutional Review Board of the French College of Neurosurgery (Collège de Neurochirurgie IRB #1; IRB00011687; reference 2026/23; favourable opinion 1 April 2026) and conducted in accordance with the principles of the Declaration of Helsinki. As this was a retrospective study, the requirement for informed consent was waived by the committee.

Data Collection

Clinical, radiological, surgical, histopathological, and follow-up data were retrospectively collected from electronic medical records by the first author. They included demographic and clinical characteristics, histology, extracranial metastatic disease, radiation treatment modality, delay between radiation therapy and surgery, systemic therapies before surgery, radiological characteristics of the lesions, and perioperative and postoperative outcomes and complications.

Radiological Assessment

All preoperative magnetic resonance imaging examinations were retrospectively reviewed and the volumetric measures were all made by the first author.

Radiological variables included contrast-enhancing lesion volume if measurable, perilesional edema volume if present and measurable, cystic component and spontaneous intralesional hemorrhage.

When available, dynamic susceptibility contrast perfusion magnetic resonance imaging was analyzed. Hyperperfusion patterns were considered suggestive of TR.

Postoperative magnetic resonance imaging was reviewed to assess extent of resection based on residual contrast-enhancing tissue.

Histopathological Analysis

All surgical specimens were reviewed by specialized neuropathologists.

Lesions were classified into two histopathological categories: RN, defined by the complete absence of viable tumor cells, and TR, defined by the presence of viable tumor tissue with or without associated radionecrotic changes.

For statistical analyses, histopathological diagnosis was treated as a binary variable (RN versus TR). Mixed lesions containing both viable tumor cells and radionecrotic tissue were descriptively analyzed.

Outcome Measures

Outcome Measures

The primary diagnostic endpoint was final postoperative histopathological diagnosis.

Therapeutic outcomes included postoperative clinical improvement, corticosteroid discontinuation within one month after surgery, postoperative complications, 30-day mortality, and need for repeat surgery. Clinical improvement was evaluated separately for each preoperative neurological symptom.

Prognostic endpoints included overall survival, defined as the interval between surgery and death from any cause, and local progression-free survival, defined as absence of recurrence at the surgical site.

Statistical Analysis

Continuous variables were expressed as median and interquartile range (IQR) and compared using the Mann–Whitney U test. Categorical variables were expressed as counts and percentages and compared using Fisher's exact test. Missing data were transparently reported for each variable, and percentages were calculated based on available data.

Multivariate logistic regression analysis was performed to identify independent predictors of RN. The predefined primary model included initial treatment modality (stereotactic radiosurgery alone versus surgery followed by postoperative irradiation) and breast cancer primary tumor. Model discrimination was evaluated using the area under the curve, with 95% confidence intervals estimated by nonparametric bootstrap resampling using 2,000 iterations. Calibration was assessed by comparing observed and predicted probabilities of RN. Sensitivity analyses were performed using an extended model including extracranial metastatic disease, interval between radiation therapy and surgery and enhancing lesion volume. Missing data were handled using multiple imputation by chained equations ($m = 20$ imputations), with estimates pooled according to Rubin's rules.

The diagnostic performance of perfusion magnetic resonance imaging was assessed using histopathology as the reference standard. Sensitivity, specificity, positive predictive value, negative predictive value, and overall concordance were calculated.

Survival analyses were performed using the Kaplan–Meier method, with comparisons between groups using the log-rank test.

All statistical analyses were two-sided, and p values < 0.05 were considered statistically significant. No adjustment for multiple comparisons was performed because of the exploratory nature of the study. Statistical analyses were conducted using Python 3.12 with the SciPy, statsmodels, scikit-learn, and lifelines libraries.

Results

Patient Characteristics

A total of 73 previously irradiated progressive brain lesions in 71 patients were included in the study (Table 1). Median age at the time of surgery was 62 years (IQR 53–69), and 49.3% of patients were male. The most common primary tumor was lung cancer (57.5%), followed by breast cancer (17.8%) and gastrointestinal malignancies (9.6%). Extracranial metastatic disease was present in 43.8% of patients.

Regarding the initial management of BM, 72.6% of lesions had been treated with stereotactic radiosurgery alone, whereas 27.4% underwent surgical resection followed by postoperative cavity irradiation. Median interval between radiation therapy and salvage surgery was 13.5 months (IQR 8.8–25).

Most patients were symptomatic at the time of surgery (76.7%). The most frequent symptoms included headaches (35.6%), motor deficits (23.3%), visual disturbances (23.3%), and language disorders (20.5%). Preoperative corticosteroids were administered in 66.7% of patients, with a median equivalent prednisolone dose of 40 mg/day.

Table 1

Patient, lesion, treatment, imaging and outcome characteristics according to histological diagnosis (N = 73 lesions in 71 patients)

Characteristic	All lesions (N = 73)	Radiation necrosis (n = 23)	Tumor recurrence (n = 50)	p-value
Demographics				
Age at surgery, years — median [IQR]	62.0 [53.0–69.0]	63.0 [55.5–67.0]	61.5 [53.0–70.0]	0.673
Male sex — n (%)	36 (49.3)	11 (47.8)	25 (50.0)	1.000
Primary tumor — n (%)				
Lung	42 (57.5)	12 (52.2)	30 (60.0)	0.613
Breast	13 (17.8)	7 (30.4)	6 (12.0)	0.096
Digestive	7 (9.6)	2 (8.7)	4 (8.0)	1.000
Melanoma	6 (8.2)	1 (4.3)	4 (8.0)	1.000
Kidney	3 (4.1)	0 (0.0)	3 (6.0)	0.547
Other	6 (8.2)	1 (4.3)	3 (6.0)	1.000
Oncological context				
Systemic metastases — n (%)	32 (43.8)	8 (34.8)	24 (48.0)	0.321
Number of BM — median [IQR]	2 [1–2]	2 [1–2]	2 [1–2]	0.673
Ongoing systemic therapy at surgery — n (%)				
Chemotherapy	6 (8.2)	2 (8.7)	4 (8.0)	1.000
Hormone therapy	5 (6.8)	2 (8.7)	3 (6.0)	0.629
Targeted therapy	8 (11.0)	3 (13.0)	5 (10.0)	0.686
Radiation therapy — initial treatment, n (%)				
Stereotactic radiosurgery alone	53 (72.6)	10 (43.5)	43 (86.0)	< 0.001
Surgery + radiation therapy	20 (27.4)	13 (56.5)	7 (14.0)	< 0.001
Total radiation dose, Gy — median [IQR]	36.0 [30.0–61.5]	36.0 [30.0–60.0]	36.0 [30.0–66.0]	0.737
Number of fractions — median [IQR]	6 [3–10]	6 [3–8]	6 [3–10]	0.359

Characteristic	All lesions (N = 73)	Radiation necrosis (n = 23)	Tumor recurrence (n = 50)	p- value
Demographics				
Radiation-to-surgery interval, months — median [IQR]	13.5 [8.8–25.0]	18.0 [12.5–30.5]	11.0 [7.0–20.8]	0.033
Clinical presentation at surgery				
Symptomatic — n (%)	56 (76.7)	17 (73.9)	39 (78.0)	0.769
Headache	26 (35.6)	11 (47.8)	15 (30.0)	0.189
Motor deficit	17 (23.3)	4 (17.4)	13 (26.0)	0.556
Language disorder	15 (20.5)	3 (13.0)	12 (24.0)	0.361
Visual deficit	17 (23.3)	6 (26.1)	11 (22.0)	0.769
Epilepsy	12 (16.4)	4 (17.4)	8 (16.0)	1.000
Cognitive decline	2 (2.7)	0 (0.0)	2 (4.0)	1.000
Preoperative corticosteroids — n (%)	48 (66.7)	14 (63.6)	34 (68.0)	0.789
Daily dose, mg prednisolone-equivalent — median [IQR]	40 [20–60]	50 [32–75]	40 [20–60]	0.112
Lesion location — n (%)				
Frontal	29 (39.7)	7 (30.4)	22 (44.0)	0.313
Temporal	8 (11.0)	4 (17.4)	4 (8.0)	0.251
Parietal	7 (9.6)	4 (17.4)	3 (6.0)	0.196
Occipital	18 (24.7)	5 (21.7)	13 (26.0)	0.777
Cerebellar	11 (15.1)	3 (13.0)	8 (16.0)	1.000
Conventional MRI				
Contrast enhancement — n (%)	70 (100.0)	22 (100.0)	48 (100.0)	—
Enhancing lesion volume, cm ³ — median [IQR]	8.62 [4.02–16.90]	6.36 [3.79–13.85]	9.21 [4.78–17.35]	0.418
Perilesional edema (FLAIR) — n (%)	69 (98.6)	22 (100.0)	47 (97.9)	1.000
Spontaneous bleeding (T2*) — n (%)	22 (37.3)	8 (38.1)	14 (36.8)	1.000
Cystic component — n (%)	9 (13.6)	2 (9.1)	7 (15.9)	0.706

Characteristic	All lesions (N = 73)	Radiation necrosis (n = 23)	Tumor recurrence (n = 50)	p- value
Demographics				
Advanced imaging				
Perfusion MRI performed – n (%)	11 (15.1)	4 (17.4)	7 (14.0)	—
Hyperperfusion pattern – n (%)	7 (63.6)	4 (100.0)	3 (42.9)	0.194
Surgical outcomes				
Complete resection (T1-Gd) – n (%)	20 (54.1)	6 (40.0)	14 (63.6)	0.193
Any complication – n (%)	13 (17.8)	3 (13.0)	10 (20.0)	0.743
Infection	7 (9.6)	2 (8.7)	5 (10.0)	1.000
Cerebrospinal fluid leak	4 (5.5)	1 (4.3)	3 (6.0)	1.000
New neurological deficit	3 (4.1)	1 (4.3)	2 (4.0)	1.000
30-day mortality	2 (2.7)	0 (0.0)	2 (4.0)	1.000
Other complication	3 (4.1)	1 (4.3)	2 (4.0)	1.000
Reoperation – n (%)	16 (22.2)	3 (13.0)	13 (26.5)	0.239
Functional outcomes				
Overall symptom improvement – n (%)	45 (80.4)	14 (82.4)	31 (79.5)	1.000
Headache	24 (92.3)	10 (90.9)	14 (93.3)	1.000
Motor deficit	13 (76.5)	2 (50.0)	11 (84.6)	0.219
Language disorder	15 (100.0)	3 (100.0)	12 (100.0)	—
Visual deficit	9 (52.9)	3 (50.0)	6 (54.5)	1.000
Epilepsy	1 (8.3)	0 (0.0)	1 (12.5)	1.000
Cognitive decline	2 (100.0)	0 (0.0)	2 (100.0)	—
Steroid weaning – n (%)	34 (72.3)	9 (69.2)	25 (73.5)	1.000
Oncological follow-up				
Postoperative radiation therapy – n (%)	24 (34.8)	4 (18.2)	20 (42.6)	0.060

Characteristic	All lesions (N = 73)	Radiation necrosis (n = 23)	Tumor recurrence (n = 50)	p-value
Demographics				
Local recurrence at operated site – n (%)	13 (19.1)	1 (4.3)	12 (26.7)	0.047

BM, brain metastasis; FLAIR, fluid-attenuated inversion recovery; IQR, interquartile range; MRI, magnetic resonance imaging; RN, radiation necrosis; SRS, stereotactic radiosurgery; TR, tumor recurrence. Percentages are calculated on available data; denominators therefore vary according to the number of lesions with documented information. No patient was receiving immunotherapy or bevacizumab at the time of surgery, and no insular lesion was present in the cohort. Perfusion MRI data relate to the 11 lesions in which perfusion MRI was performed. Overall symptom improvement is defined as improvement in at least one preoperative neurological deficit among symptomatic patients, and per-symptom improvement is calculated among patients presenting with that deficit preoperatively. Steroid weaning denotes corticosteroid discontinuation within one month after surgery among patients receiving preoperative corticosteroids. Continuous variables were compared using the Mann–Whitney U test and categorical variables using Fisher's exact test. Statistically significant p-values (< 0.05) are shown in bold.

Histopathological Findings

Histopathological analysis demonstrated TR in 50 lesions (68.5%) and pure RN in 23 lesions (31.5%). Among recurrent tumors with available histopathological assessment, 84.0% demonstrated mixed pathological features combining viable tumor cells and radionecrotic areas, supporting the concept of a histopathological continuum between RN and TR (Fig. 1c).

The proportion of RN varied according to primary tumor histology. RN occurred more frequently in breast cancer metastases compared with other primary tumors (53.8% versus 26.7%), although this difference did not reach statistical significance ($p = 0.096$) (Fig. 1b). No pure RN was observed among renal cell carcinoma metastases (Fig. 1a).

Patients initially treated with stereotactic radiosurgery alone were significantly more likely to present TR (86.0% versus 43.5%, $p < 0.001$), whereas lesions initially managed with surgery followed by cavity irradiation more frequently developed RN (56.5% versus 14.0%, $p < 0.001$). The interval between radiation therapy and surgery was significantly longer in the RN group compared with the TR group (18 versus 11 months, $p = 0.033$).

Perfusion Magnetic Resonance Imaging Analysis

Perfusion magnetic resonance imaging was available in 11 patients (15.1%). Hyperperfusion was observed in 63.6% of examinations. Overall concordance between perfusion magnetic resonance imaging findings and final histopathological diagnosis was only 27.3% (Table 1).

Using hyperperfusion as a criterion suggestive of TR, sensitivity was 42.9%, specificity 0%, positive predictive value 42.9%, and negative predictive value 0%. Notably, all RN cases evaluated with perfusion magnetic resonance imaging also demonstrated hyperperfusion patterns, which would have incorrectly suggested TR. No conventional magnetic resonance imaging characteristic significantly differentiated RN from TR, including enhancing lesion volume (median 6.4 vs 9.2 cm³, $p = 0.418$), perilesional edema ($p = 1.000$), cystic component ($p = 0.706$), or spontaneous hemorrhage ($p = 1.000$).

Predictive Factors Associated with RN

Multivariate analysis identified initial treatment modality as the only independent predictor associated with final histopathological diagnosis. Initial stereotactic radiosurgery alone was associated with a significantly higher likelihood of TR compared with RN (OR 0.14, 95% CI 0.04–0.46, $p = 0.001$). Breast cancer primary showed a non-significant trend toward radiation necrosis (OR 1.98, 95% CI 0.49–7.95, $p = 0.336$) (Fig. 2a).

The radiation-to-surgery interval, although significantly longer in RN on univariate comparison, was not entered in the pre-specified parsimonious model given the limited number of events (23 RN), which constrained the model to two variables. When tested in the extended model adjusting for initial treatment modality, the interval no longer reached independent significance, suggesting its univariate association is largely mediated by treatment modality.

A simple predictive model combining initial treatment modality and breast cancer primary tumor achieved an area under the curve of 0.737 (95% CI 0.605–0.848) with excellent calibration, predicted and observed probabilities of RN differing by less than 4% across strata (Fig. 2b, 2c). A sensitivity analysis using the extended model with multiple imputation confirmed this association (pooled OR 0.10, $p = 0.001$; AUC 0.771).

Outcomes

Surgical, functional and follow-up outcomes are presented in Table 1. The overall 30-day postoperative complication rate was 17.8%. Main complications included surgical site infection (9.6%), cerebrospinal fluid leakage (5.5%) and new neurological deficits (4.1%). 30-day postoperative mortality was 2.7%. No significant difference was observed between histological groups.

Among symptomatic patients, postoperative clinical improvement occurred in 80.4% of cases, without significant difference between RN and TR groups (82.4% versus 79.5%, $p = 1.000$).

The highest improvement rates were observed for language disorders (100%), cognitive dysfunction (100%) and headaches (92.3%). Motor deficits improved in 76.5% of patients, whereas visual symptoms and seizures showed lower improvement rates (52.9% and 8.3%, respectively) (Fig. 3a).

Among patients receiving corticosteroids preoperatively, discontinuation within one month after surgery was achieved in 72.3% of cases, with no difference between RN and TR groups (Fig. 3b).

After a median follow-up of 19 months (IQR 9–35), 48 patients had died, corresponding to an overall mortality rate of 65.8%. Follow-up duration was significantly longer in the RN group compared with the TR group (27 versus 17 months, $p = 0.031$). Median overall survival after surgery was significantly longer in patients with RN than in those with TR (39 versus 19 months, $p = 0.025$) (Fig. 4a).

Local progression-free survival was also significantly longer in the RN group ($p = 0.013$) (Fig. 4b). Local recurrence at the surgical site occurred in only 4.3% of RN cases compared with 26.7% of TR cases ($p = 0.047$). Postoperative additional radiation therapy was more frequently administered in the TR group (42.6% versus 18.2%), although this difference did not reach statistical significance ($p = 0.060$).

Discussion

In this retrospective study of 73 surgically treated previously irradiated progressive BM, surgery provided substantial diagnostic, therapeutic and prognostic value.

TR predominated among operated lesions (68.5%), whereas pure RN represented 31.5%. This likely reflects selection bias, as patients referred for surgery present with progression, more often associated with TR than with stable or medically managed RN; for most of the study period, lesions were operated for suspected recurrence, surgery for suspected RN becoming frequent only recently. In this context, the finding that 31.5% of these lesions ultimately proved to be pure RN illustrates the limited accuracy of integrated clinico-radiological judgment and underscores the diagnostic value of resection. This figure does not represent a formal diagnostic specificity, as the cohort lacks a comparator arm operated under a presumptive diagnosis of RN. Importantly, most recurrent tumors (84.0%) contained radionecrotic changes, reinforcing the RN–TR continuum hypothesis.

A major finding concerns the limited reliability of perfusion MRI in real-world practice: concordance with histopathology was only 27.3%, and all RN lesions evaluated demonstrated hyperperfusion patterns usually suggestive of TR. Radiation-induced inflammation, vascular permeability and reactive neoangiogenesis can mimic active tumor vascularization, and was performed in only a minority (15.1%) of patients, mainly equivocal cases. Our analysis did not include amino-acid positron emission tomography (PET), which has become a cornerstone of the non-invasive work-up of irradiated BM [31]. Tracers such as 18F-FDOPA and 18F-FET outperform perfusion MRI, with pooled sensitivity and specificity of approximately 82% and 84% [32, 33], and are now incorporated into international recommendations [34]. The absence of systematic PET data is therefore a limitation, and our findings pertain to perfusion MRI alone rather than to advanced imaging as a whole. Nevertheless, even multimodal imaging retains a non-negligible error rate, and surgery remains the only means of obtaining a definitive diagnosis when these modalities are discordant or equivocal.

Initial treatment modality was the strongest predictor: surgery plus cavity irradiation more often led to RN, whereas stereotactic radiosurgery alone was associated with TR. Cavity irradiation exposes a larger volume of normal brain to injury, increasing the risk of delayed necrosis, whereas initial cytoreduction reduces residual tumor burden and hence local persistence. Breast cancer was also more frequently

associated with RN, though non-significantly, consistent with reports of increased susceptibility under newer systemic therapies acting synergistically with radiation [35, 36]. Finally, the radiation-to-surgery interval was longer in RN than in TR, a finding already well described in the literature [37].

Surgery provided substantial symptomatic benefit regardless of histology: over 80% of symptomatic patients improved and steroids were withdrawn in nearly three-quarters of those taking them [38, 39]. The comparable benefit in RN and TR suggests that symptom relief relates more to decompression of mass effect and edema than to histology. Steroid weaning matters, as prolonged corticosteroid exposure carries substantial morbidity, impairs quality of life, and may blunt the efficacy of immunotherapy and negatively affect survival [40, 41]. These benefits should be weighed against the alternatives for symptomatic RN: first-line corticosteroids and, in refractory cases, bevacizumab, whose response is frequently partial or transient and whose use is constrained by cost and vascular contraindications [18–20]. By providing immediate, durable decompression together with a definitive tissue diagnosis, surgery achieves what medical therapies cannot, particularly when steroids cannot be safely tapered or immunotherapy is planned.

The highest improvement rates were observed for language disorders, cognitive dysfunction, and headaches, whereas seizure control improved less frequently, which may reflect the difficulty of assessing seizure activity in patients on long-standing antiepileptic therapy. Postoperative morbidity and 30-day mortality remained acceptable (17.8% and 2.7%, respectively) and comparable with published series; although surgery in previously irradiated tissue may be technically challenging, our findings support its safety when performed in experienced centers [42].

Complete resection was achieved in 54.1% of lesions with available postoperative imaging and tended to be less frequent in the RN group (40.0% versus 63.6%, $p = 0.193$). These data should be interpreted with caution, as postoperative MRI was available in only about half of patients (49.3%). Lower resection rates in RN may reflect the non-oncological intent of surgery and radiation-altered tissue planes, without apparent effect on the postoperative benefit.

Histopathology also carried major prognostic significance, pure RN showing significantly longer overall survival (39 versus 19 months, log-rank $p = 0.025$) and better local control than TR [43], likely reflecting the absence of intracranial tumor burden and better systemic control in patients surviving long enough to develop delayed injury [44].

The study has several limitations: its retrospective monocentric design entails selection bias and limited generalizability; the few perfusion examinations preclude definitive imaging assessment; the predictive model requires external validation; and quality-of-life data are lacking [45]. Our main strength is the histological reference standard, with a clear cut-off for RN that excludes any malignant cell, together with a reproducible interval between the start of radiation therapy and the date of surgery.

Future prospective multicentre studies should better characterize the RN–TR continuum, evaluate amino-acid PET and assess quality of life. Standardized histological grading of mixed lesions may

further improve prognostic stratification.

Conclusion

The management of progressive brain lesions arising after radiation therapy for BM remains a major diagnostic and therapeutic challenge because of the difficulty in distinguishing RN from TR.

Our findings demonstrate that surgery provides major diagnostic, therapeutic, and prognostic value. Nearly one-third of surgically treated lesions corresponded to pure RN, whereas two-thirds represented TR. Histopathological analysis remains the reference standard for differentiating RN from TR when imaging findings are inconclusive, while prior surgery followed by cavity irradiation (and, to a lesser, non-significant extent, a breast cancer primary) may raise the pre-test probability of radiation necrosis. In addition, surgery leads to substantial symptomatic improvement and facilitates corticosteroid discontinuation regardless of final histopathological diagnosis. Finally, it carries valuable prognostic information, since both entities present very different evolutive trajectories and treatment modalities. Therefore, surgery should not be considered merely as a salvage diagnostic procedure but rather as a central component of multidisciplinary management for diagnostic, therapeutic, and prognostic purposes in selected patients with previously irradiated progressive BM.

Declarations

Competing interests

The authors have no relevant financial or non-financial interests to disclose.

Ethics approval

This retrospective study was approved by the Institutional Review Board of the French College of Neurosurgery (Collège de Neurochirurgie IRB #1; IRB00011687; reference 2026/23; favourable opinion 1 April 2026) and was performed in line with the principles of the Declaration of Helsinki.

Consent to participate

Given the retrospective design of the study, the requirement for informed consent to participate was waived by the ethics committee.

Consent to publish

Not applicable. The manuscript does not contain any individual person's identifying data, images or videos.

Funding

No funds, grants, or other support were received during the preparation of this manuscript.

Author Contribution

All authors contributed to the study conception and design. Data collection was performed by J.M. and L.Y. The first draft of the manuscript was written by J.M., and the final and complete revision was performed by A.L. M.D., J.G., M.F., G.B., P.L., N.G., V.P., T.G. and E.E. critically reviewed and commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Acknowledgements

The authors thank the neuropathology teams of Caen University Hospital.

Data availability

The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

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Figures

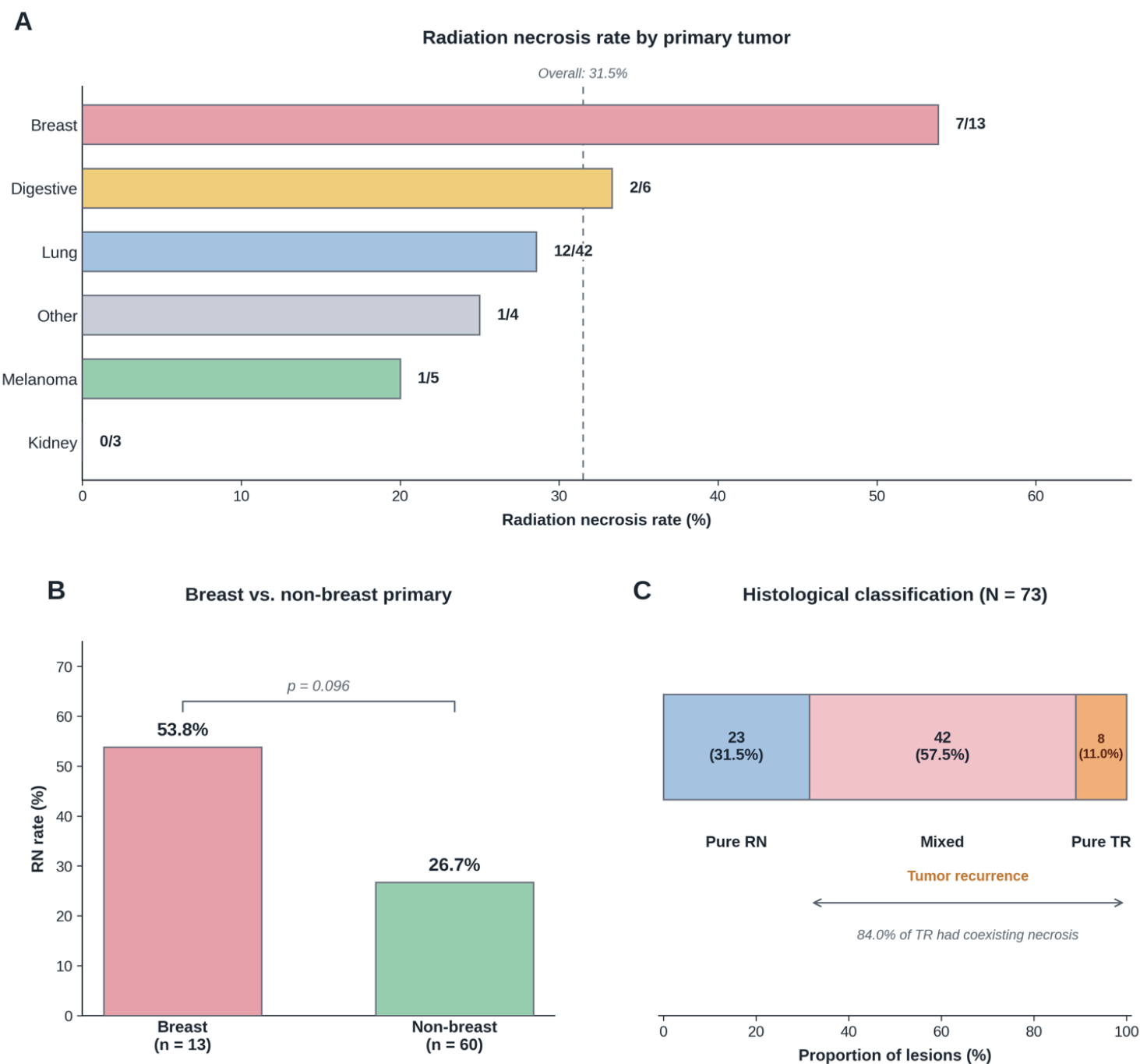


Figure 1

Histological findings and radiation necrosis rates by primary tumor (N = 73). (a) Radiation necrosis rate by primary tumor type; the dashed line indicates the overall rate of 31.5%. (b) Comparison of radiation necrosis rates between breast and non-breast primary tumors. (c) Histological classification of the 73

evaluable lesions, showing the proportions of pure radiation necrosis, tumor recurrence with coexisting necrosis, and tumor recurrence without necrosis.

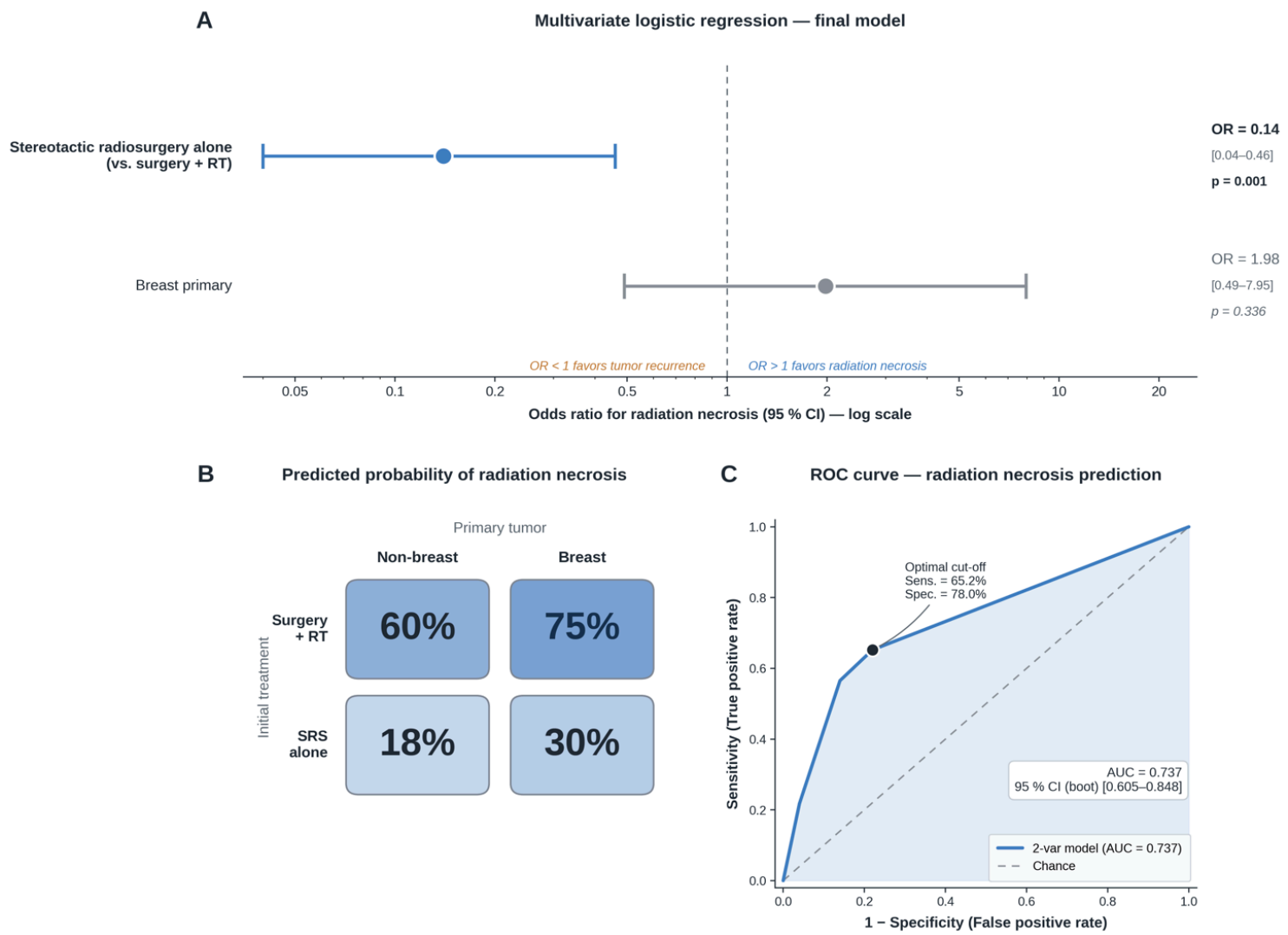


Figure 2

Multivariate predictive model for radiation necrosis. (a) Forest plot of odds ratios with 95% confidence intervals from the pre-defined two-variable logistic regression model; significant predictors are shown in bold. (b) Clinical decision matrix showing predicted and observed probabilities of radiation necrosis across the four combinations of initial treatment modality and breast cancer primary. (c) Receiver operating characteristic curve of the predictive model (AUC = 0.737; 95% CI 0.605–0.848).

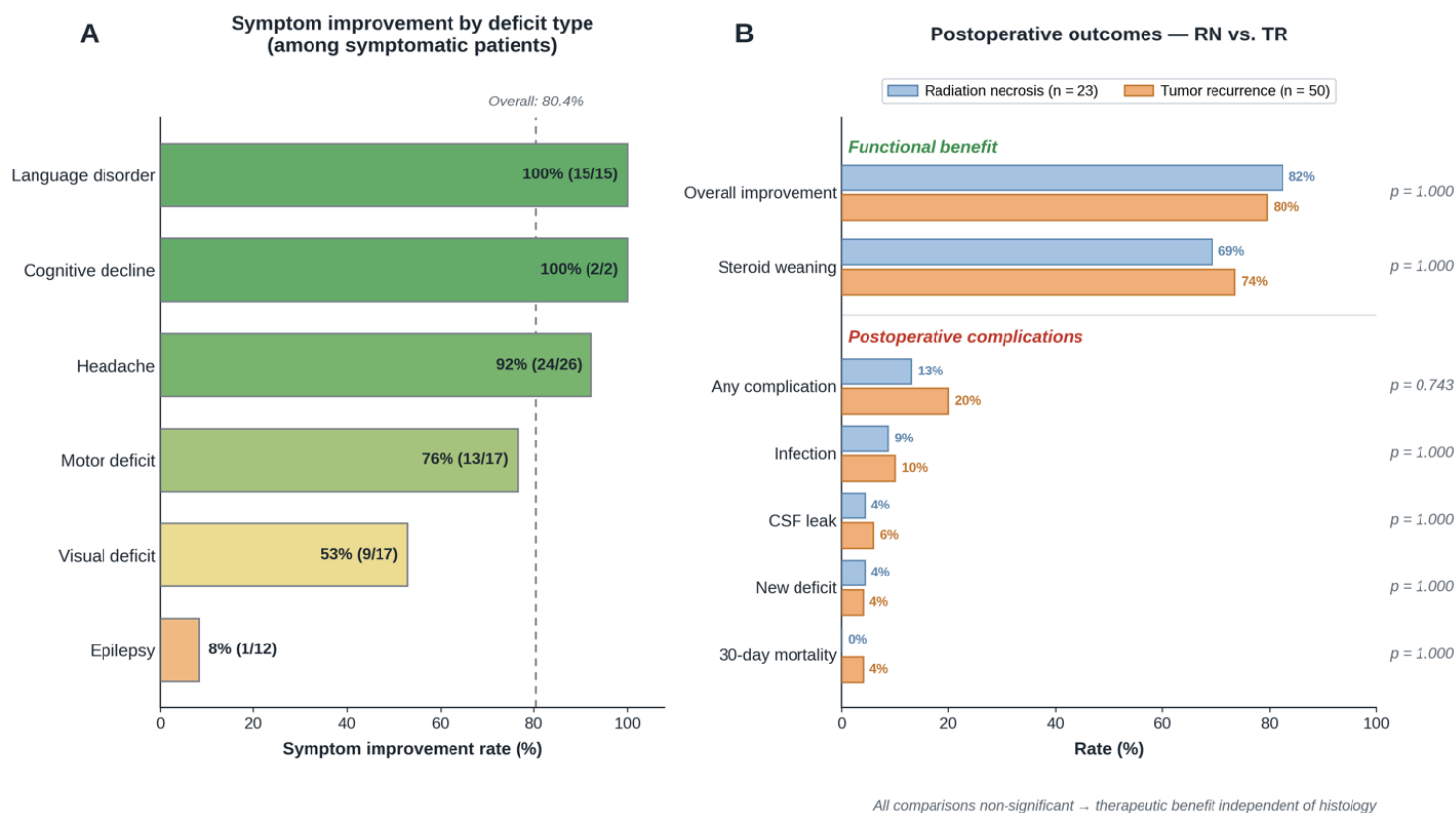


Figure 3

Functional outcomes after surgery. (a) Symptom improvement rates by preoperative deficit type among affected patients; the dashed line indicates the overall rate (80.4%). (b) Comparison of functional benefit and complication rates between the radiation necrosis and tumor recurrence groups (dumbbell plot with Fisher p-values).

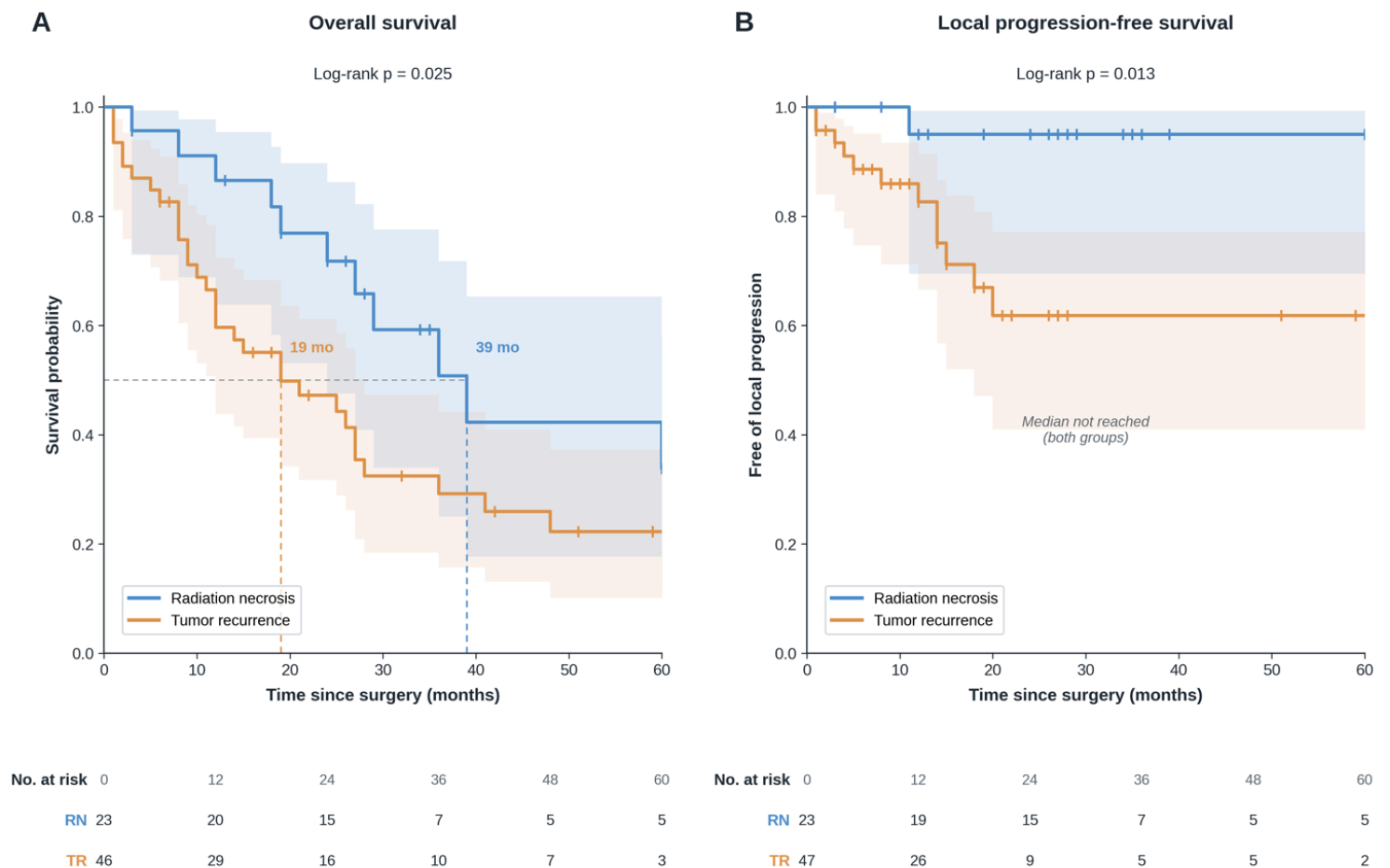


Figure 4

Survival analysis by histological group. (a) Overall survival and (b) local progression-free survival estimated using the Kaplan–Meier method. Blue: radiation necrosis; salmon: tumor recurrence. Shaded areas represent 95% confidence intervals; numbers at risk are displayed below each panel.

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