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Rate of pachymeningeal failure following adjuvant WBRT vs SRS in patients with brain metastases

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ABSTRACT

Background: Stereotactic radiosurgery (SRS) has supplanted whole brain radiotherapy (WBRT) as standard-of-care adjuvant treatment following surgery for brain metastasis (BrM). Concomitant with the adoption of adjuvant SRS, a new pattern of failure termed "Pachymeningeal failure" (PMF) has emerged.

Methods: We reviewed a prospective registry of 264 BrM patients; 145 and 119 were treated adjuvantly with WBRT and SRS, respectively. The Cox proportional hazards model was used to identify variables correlating to outcomes. Outcomes were calculated using the cumulative incidence (CI) method. Univariate (UVA) and multivariate analyses (MVA) were done to identify factors associated with PMF.

Results: CI of PMF was 2 % and 18 % at 12 months, and 2 % and 23 % at 24 months for WRBT and SRS, respectively ($p < 0.001$). The CI of classic leptomeningeal disease (LMD) was 3 % and 4 % at 12 months, and 6 % and 6 % at 24 months for WBRT and SRS, respectively ($P = 0.67$). On UVA, adjuvant SRS [HR 9.75 (3.43–27.68) ($P < 0.001$)]; preoperative dural contact (PDC) [HR 6.78 (1.64–28.10) ($P = 0.008$)]; GPA score [HR 1.64 (1.11–2.42) ($P = 0.012$)]; and lung EGFR/ALK status [HR 3.11 (1.02–9.45) ($P = 0.045$)]; were associated with PMF risk. On MVA, adjuvant SRS [HR 8.15 (2.69–24.7) ($P < 0.001$)]; and PDC [HR 6.28 (1.51–26.1) ($P = 0.012$)] remained associated with PMF.

Conclusions: Preoperative dural contact and adjuvant SRS instead of adjuvant WBRT were associated with an increased risk of PMF. Strategies to improve pachymeningeal radiation coverage to sterilize at risk pachymeninges should be investigated.

Introduction

Approximately 20–40 % of cancer patients develop BrM [1,2]. Upfront surgery is generally indicated for several reasons: 1) for large lesions causing symptoms due to a mass effect; 2) need for histological diagnosis, and; 3) as part of primary treatment for patients with good performance status [3–5]. Surgery alone is associated with high rates of local failure (LF) [6,7] and the main adjuvant treatment options for resected brain metastasis include whole-brain radiation (WBRT) or focal radiation such as stereotactic radiosurgery (SRS) [8,9]. Adjuvant SRS results in lower rates of cognitive toxicity without compromising overall survival (OS) compared to WBRT, which led to increased adoption of this technique, despite it also resulting in lower rates of distant brain control [9]. Concurrent with increased use of adjuvant SRS, a new pattern of recurrence called pachymeningeal failure (PMF) (Fig. 1), also referred to as nodular leptomeningeal, has emerged, which appears to be specific to surgical BrM patients and has unique prognostic implications compared to the classic leptomeningeal disease (LMD) [10–12]. Among patients treated adjuvantly, we aimed to compare and analyze the incidence of PMF, along with LMD, local failure (LF), and distant failure

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(DF) to determine if PMF was specific to patients treated with SRS vs WBRT.

Materials and methods

From a prospective database of BrM patients, we identified 274 consecutively treated patients, 18 years or older, treated with upfront surgery followed by WBRT or SRS between January 2008 and June 2020. Patients who had had prior neurosurgical procedures were excluded. This study was approved by our local institutional Research Ethics Board at University Health Network 18–5741.

Treatments

All patients were treated with upfront surgical resection followed by adjuvant Gamma Knife Radiosurgery Unit (Elekta AB) targeting the surgical cavity vs. WBRT. Our center primarily treated patients with adjuvant WBRT as opposed to SRS, with the exception of patients enrolled on NCIC CEC.3 [13], until 2015. Hence forward, we have primarily used adjuvant SRS delivered to the cavity in 1–3 fractions per institutional policies and at the discretion of the staff radiation oncologist. For single-fraction (SF-SRS) we prescribed $\leq$ 4 cc/21 Gy, 4–10 cc /18 Gy, and $>$ 10 cc/15 Gy. When fractionated SRS (F-SRS) was implemented at our center in 2017 using the ICON frameless system, we implemented the following dosing regimen: 4-<10 cc 27 Gy/3, 10-< 20 cc 24 Gy/3, and $>$ 20 cc 21 Gy/3. Our SRS treatment procedure has been previously published [14,15]; briefly, a magnetic resonance imaging (MRI) with gadolinium-based contrast T1 and T2-weighted sequences and a computed tomography (CT) scan is obtained in a supine position and fused to define the treatment volumes. GTV not applicable for cavities, CTV: cavity + 1 mm, PTV 1 mm expansion on CTV. Since 2019, we have implemented the contouring guidelines for cavity SRS by Soliman et al. [16], which recommendedincluding the surgical tract (in addition to the surgical cavity) and a CTV expansion of 1–10 mm along the dura based on preoperative tumor contact with venous sinus or dura. All treatments were prescribed to a median isodose line of 50 % (range 40–65) with a CTV coverage $>$ 98 %. Each SRS treatment plan is reviewed and approved by two physicists, a radiation oncologist, and a neurosurgeon.

Surveillance

Each patient was followed every 8–12 weeks after WBRT or SRS with an MRI brain examination during the first year and then every 3–4 months for the second year unless additional imaging out of this schedule was clinically indicated.

Outcomes

For every patient, an agreement diagnosis of LF, DF, LMD, and PMF based on MRI was made during our multidisciplinary BrM conference by neurosurgeons and radiation oncologists. Moreover, for the purpose of this study, the presurgical brain MRI, MRI simulation, including treatment volumes (CTV, PTV, OARs), SRS isodose lines, and, if indicated, the brain MRI at the date of recurrence, were imported and fused into Raystation.

Sites of failures were contoured and classified by two radiation oncologists and one neurosurgeon, according to Turner et al. [17]. Briefly, the failures were classified as LF (new nodular growth within the cavity), DF (new brain metastasis), LMD (cranial nerve enhancement, or sugar-coating pattern) PMF was characterized as an enhancing nodule (or nodules) arising from the pachymeninges (dura) oralong the tentorium or ventricles with no involvement of the skull, $>$ /=1 cm beyond the surgical cavity [12,17].

Statistical methods

Each variable was summarized as frequencies and percentages (categorical) or as median and range (continuous). Associations between variables and patient or tumor characteristics were analyzed using Fisher's exact test for categorical variables and the Mann-Whitney *U* test for continuous variables. Overall survival (OS) was calculated from the radiotherapy (SRS or WBRT) date to the date of death or to the last visit. Survival percentages were calculated using the Kaplan-Meier method, and differences between groups were measured using Log-rank test. Associations between variables with OS were evaluated using univariate (UVA) and multivariate (MVA) Cox proportional hazards models. Additional outcomes (e.g., PMF, LMD, and DF) were estimated utilizing the cumulative incidence method with endpoint determined as the first MRI that first definitively identified that process based on consensus opinion. Cumulative incidence functions between groups were compared using the Fine-Gray method. Factors associated with PMF were assessed using univariate and multivariate competing risk models. Selected variables in multivariate models were determined based on significant results from univariate assessments. Kaplan-Meier curves and Cumulative incidence plots were provided to display group differences. Propensity-score matching between groups was performed using the nearest neighbor matching algorithm with ratio of 1:1. Matched variables were determined based on significant results of Cox proportional hazards model in OS. After matching, the balance of matched variables was assessed using the Mann-Whitney *U* test or chi-square test. The percentages of patients treated by different radiotherapies over accrual time were presented using bar plots. P values less than 0.05 were

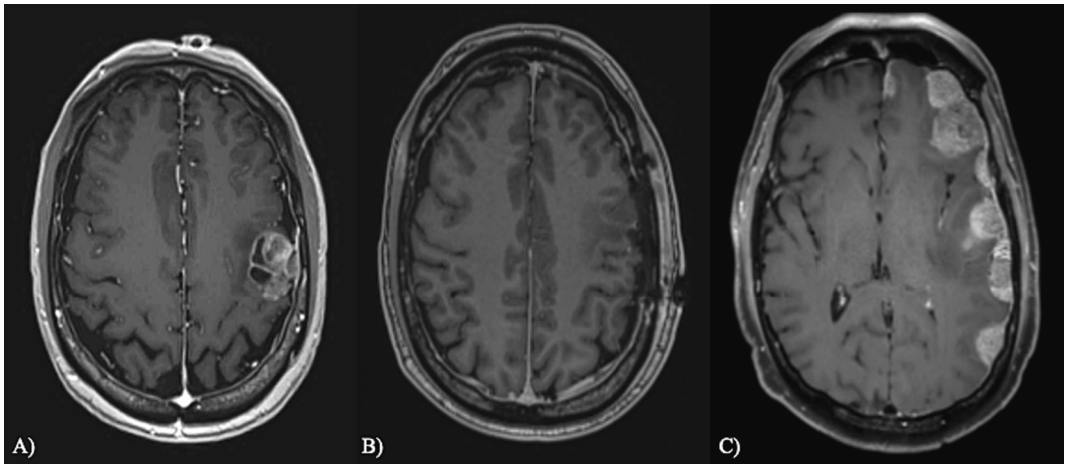

Fig. 1. A, B, C: Representative images of a patient with PMF.

considered to indicate statistically significant differences. Statistical analysis was performed using R, version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient and Treatment Information

We identified 264 patients who underwent adjuvant RT following surgical resection of brain metastases during the study period (Table 1). The median age at the time of surgery was 61 years (range: 22 to 90). There were 156 female patients (59 %) and 108 male patients (41 %). The most common primary tumors of origin were lung (39 %), breast (18 %), melanoma (15 %), and gastrointestinal (GI) (11 %). Of the entire cohort, 145 patients (54.92 %) received WBRT and 119 (45.08 %) received SRS following surgical resection.

On preoperative MRI, 181 patients (70 %) had brain metastases in contact with the dura. The median Graded Prognostic Assessment (GPA) score was 2.5 (0.5, 4) for the entire cohort, 2 (0.5, 4) for the WBRT group, and 2.5 (0.5, 4) for the SRS group. The SRS group, which exhibited a significantly higher GPA, also had lower number of brain metastases and better performance scores. The median number of BrM was 1 (1–14) in the SRS group and 1 (1–19) in the WBRT group. The dosing regimens for adjuvant SRS, including both single-fraction and fractionated regimens, are reported in Supplementary content, along with fractionations used for WBRT. After 2019, 39 patients were treated as per contouring guidelines by Soliman et al. [16].

Events: PMF, LMD, LF, DF

The mean and median follow-up time for all patients was 66.8 and 57.9 months (36.1–136.7), respectively. There was a significantly higher incidence of PMF in patients treated with adjuvant SRS compared to WBRT (Fig. 2A); 1-year2% vs. 18 %; 2-year 2 vs 23 %, ($p < 0.001$). On univariate analysis, SRS ($p < 0.001$), preoperative dural contact (PDC) ($p = 0.008$), GPA score ($p = 0.012$) and lung EGFR/ALK status ($P = 0.045$) were associated with a higher risk of PMF (Table 2). Multivariate analysis suggested that SRS ($p < 0.001$) and PDC ($p = 0.012$) were independently associated with PMF risk (Table 3). In contrast, the incidence of classic LMD was not significantly different among patients treated with adjuvant SRS vs. WBRT Among the entire cohort, 4 % experienced LMD at one year, including 3 % from the WBRT group and 4 % of the SRS group; 6 % sustained LMD at two-year, including among 6 % of the WBRT and 6 % of the SRS group (Fig. 2B).

Similarly, there was not a significant difference in the incidence of local failure among patients treated with SRS vs WBRT; 1-year 12 vs. 20 %; 2-year 26. vs 24 % ($p = 0.88$, Fig. 3A). As expected, we observed higher rates of distant intracranial failure among patients treated with adjuvant SRS vs. WBRT; 1-year 35 % vs. 17 % and 2-year 49 % vs 25 %. ($p = 0.001$, Fig. 3B). The absolute number of events for OS, PMF, LMD, LF, and DF, along with Grade 3 radiation necrosis (requiring surgery), were also calculated (Supplementary Fig. 1). Of 264 patients, 32 patients had evidence of PMF, resulting in an incidence of 12.1 %; 4 of those 32 patients underwent adjuvant WBRT and 28 underwent adjuvant SRS.

Overall survival

Patients treated with adjuvant SRS lived longer compared to those who received WBRT. The 1- and 2-year rates of OS were 47 % and 28 % in the WBRT cohort compared to 70 % and 44 % in the SRS cohort ($p < 0.001$, Fig. 3c). There was a shift in our institutional practice from WBRT to SRS over the time of study accrual (Supplementary Fig. 2). Treatment type (SRS), the pre-surgical volume of the resected lesion, ECOG, GPA, LMD/PMF and extracranial disease status correlated to OS (Supplementary Table 1). Multivariate analyses indicate that treatment type (SRS vs. WBRT), and LMD/PMF status remained significantly correlated to OS (Supplementary Table 2). Propensity score matched (PSM) analysis according to tumor volume, ECOG, GPA, and extracranial disease status also suggested an association between SRS and improved survival (Supplementary Table 3). Salvage radiation therapy was administered to 68 % of patients following PMF, (WBRT in 50 % of patients and focal/partial radiation therapy in 18 % of patients), the median time to salvage treatment was 8.1 (1.6–57.8) months. Neurologic death was observed in 78 % of patients who developed PMF (Supplementary Table 4).

Table 1
Patients, tumor and treatment characteristics.

	Full Sample (n = 264)	WBRT (n = 145)	SRS (n = 119)	p-value
Age				0.85
Mean (sd)	59.9 (12.4)	59.8 (11.8)	60.1 (13.1)	
Median (Min,Max)	61 (22, 90)	61 (22, 84)	61 (23, 90)	
Gender				**0.049**
F	156 (59)	94 (65)	62 (52)	
M	108 (41)	51 (35)	57 (48)	
Number of BrM				**0.022**
Mean (sd)	2.1 (2.2)	2.4 (2.6)	1.7 (1.6)	
Median (Min,Max)	1 (1, 19)	1 (1, 19)	1 (1, 14)	
Volume calculated of the index lesion				0.087
Mean (sd)	38.9 (36.1)	42.9 (40.1)	34.1 (30.0)	
Median (Min,Max)	29 (1, 189)	30.9 (1.0, 189.0)	24.0 (1.7, 132.0)	
Missing	4	4	0	
Preoperative dural contact				0.31
0	76 (30)	45 (33)	31 (26)	
1	181 (70)	93 (67)	88 (74)	
Missing	7	7	0	
ECOG				**0.029**
0	55 (21)	27 (19)	28 (24)	
1	144 (55)	85 (59)	59 (50)	
2	48 (18)	21 (14)	27 (23)	
3	15 (6)	12 (8)	3 (3)	
4	2 (1)	0 (0)	2 (2)	
Total GPA Score				**<0.001**
Mean (sd)	2.4 (0.8)	2.3 (0.8)	2.6 (0.7)	
Median (Min,Max)	2.5 (0.5, 4.0)	2.0 (0.5, 4.0)	2.5 (0.5, 4.0)	
Type				**0.015**
Breast	48 (18)	32 (22)	16 (13)	
GI	30 (11)	16 (11)	14 (12)	
GU	13 (5)	4 (3)	9 (8)	
GYN	10 (4)	4 (3)	6 (5)	
Lung	104 (39)	57 (39)	47 (39)	
Melanoma	40 (15)	17 (12)	23 (19)	
Other	13 (5)	12 (8)	1 (1)	
Sarcoma	6 (2)	3 (2)	3 (3)	
Extracranial Control pre RT				**<0.001**
Controlled	113 (50)	53 (40)	60 (67)	
Uncontrolled	111 (50)	81 (60)	30 (33)	
Missing	40	11	29	
Lung EGFR/ALK				0.82
No	84 (81)	47 (82)	37 (79)	
Yes	20 (19)	10 (18)	10 (21)	
Missing	160	88	72	
HER2 neu				1.00
No	33 (66)	23 (66)	10 (67)	
Yes	17 (34)	12 (34)	5 (33)	
Missing	214	110	104	
Melanoma BRAF				0.19
No	17 (47)	10 (62)	7 (35)	
Yes	19 (53)	6 (38)	13 (65)	
Missing	228	129	99	

Table 1. Table Showing the demographic characteristic of the patients, tumors and treatments.
Abbreviations: BrM, Brain Metastases; ECOG, Eastern Cooperative Oncology Group; GPA, Graded Prognostis Assessment; RT, Radiotherapy.

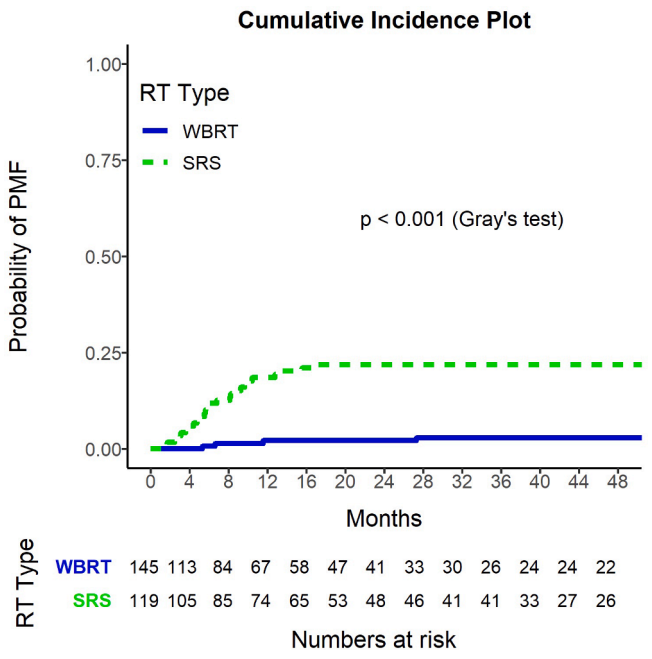

Fig. 2A. Cumulative incidence of Paquimeningeal failure (PMF) in patients receiving whole brain radiotherapy (WBRT) vs stereotactic radiosurgery (SRS).

Table 2
Risk of PMF Univariate.

	HR(95 %CI)	p-value
RT Type		**<0.001**
WBRT	Reference	
SRS	9.75 (3.43, 27.68)	
Age	1.00 (0.96, 1.03)	0.81
Gender		0.13
F	Reference	
M	0.55 (0.26, 1.18)	
Number of BrM	0.73 (0.48, 1.13)	0.16
Volume calculated of the index lesion	1.01 (1.00, 1.01)	0.17
Preoperative dural contact		**0.008**
0	Reference	
1	6.78 (1.64, 28.10)	
days from surgery to RT	0.99 (0.96, 1.02)	0.51
ECOG		0.73
0	Reference	
1	1.52 (0.57, 4.09)	0.40
2	1.41 (0.43, 4.69)	0.57
3/4	0.64 (0.07, 5.64)	0.69
Total GPA Score	1.64 (1.11, 2.42)	**0.012**
Type		0.78
Lung	Reference	
Other	1.11 (0.54, 2.25)	
Extracranial Control pre RT		0.33
Controlled	Reference	
Uncontrolled	0.67 (0.30, 1.50)	
Lung EGFR/ALK		**0.045**
No	Reference	
Yes	3.11 (1.02, 9.45)	
HER2 neu		0.37
No	Reference	
Yes	2.03 (0.43, 9.73)	
Melanoma BRAF		0.64
No	Reference	
Yes	1.75 (0.16, 18.75)	

Table 2. Univariate Analysis risk of Pachymeningeal Failure (PMF). Abbreviations: BrM, Brain Metastases; ECOG, Eastern Cooperative Oncology Group; GPA, Graded Prognostic Assessment; RT, Radiotherapy.

Table 3
Risk of PMF Multivariate.

	HR(95 % CI)	p-value
RT Type		
WBRT	Reference	
SRS	8.15 (2.69, 24.7)	**<0.001**
Preoperative dural contact		
0	Reference	
1	6.28 (1.51, 26.1)	**0.012**
Total GPA Score	1.32 (0.81, 2.15)	0.3

Table 3. Multivariate Analysis of Pachymeningeal Failure (PMF) Abbreviations: RT, Radiotherapy; GPA, Graded Prognostic Assessment.

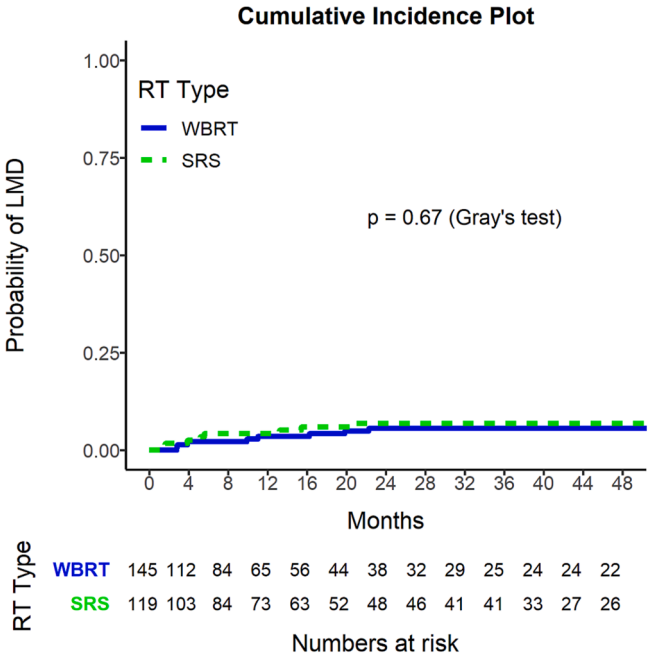

Fig. 2B. Cumulative incidence of leptomeningeal disease (LMD) in patients receiving whole brain radiotherapy (WBRT) vs stereotactic radiosurgery (SRS).

Discussion

In this report, the incidence of PMF was significantly higher in patients treated with adjuvant SRS compared to WBRT, suggesting that wider treatment fields from WBRT decreased PMF risk. Of note, contouring guideline consensus recommendations issued by Soliman et al aim at, in part, to reduce the risk of PMF and suggest up to 1 cm dural margins beyond the cavity in the setting of PDC. The ongoing ALLIANCE A071801 (CEC7) trial may provide insight into whether or not including meningeal surfaces adjacent to PDC reduces PMF as that approach was recommended in the contouring guidelines. PMF may result from tumor spillage during surgery and a plausible hypothesis based on our results is that WBRT sterilizes these microscopic deposits that are otherwise beyond the SRS target volume. Investigating the potential link between recurrence patterns, the margins used, and dose coverage in the dura surrounding the surgical cavity is essential. After 2019, 39 patients were treated following new contouring guidelines that recommended CTV expansion 1–10 mm along the dura. Our data set may not be adequate for in-depth exploratory insights into this matter; however it is worth noting that in our report, the incidence of local failure did not vary significantly between the WBRT and SRS groups. This finding could suggest that local failure is not a consistent precursor to PMF, supporting the prevailing hypothesis that surgical seeding is primarily responsible for this type of failure.

The incidence of PMF reported here, 12.1 %, is within the range of

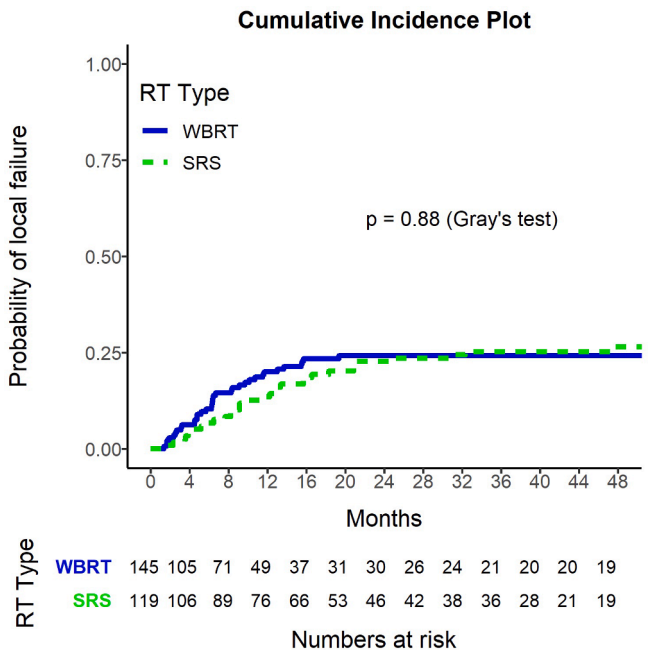

Fig. 3A. fCumulative incidence of local failure (LC) Patients receiving whole brain radiotherapy (WBRT) vs stereotactic radiosurgery (SRS).

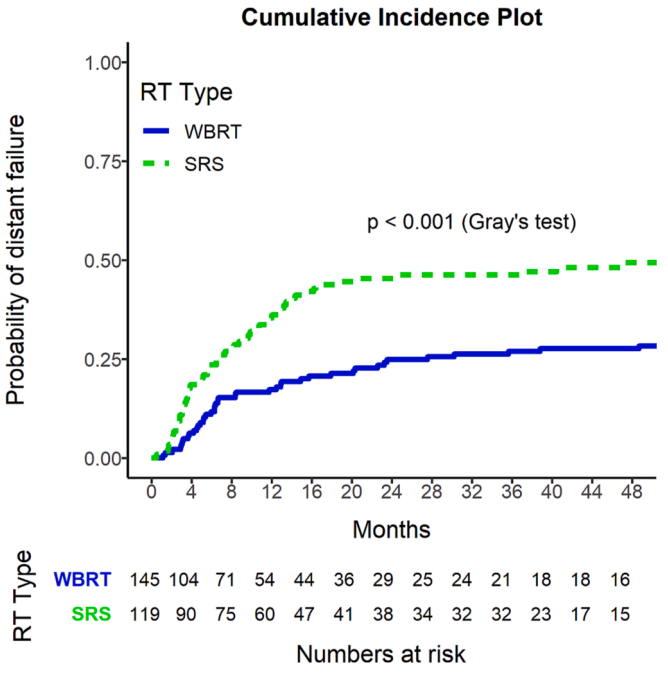

Fig. 3B. Cumulative incidence of distant failure (DF) in patients receiving whole brain radiotherapy (WBRT) vs stereotactic radiosurgery (SRS).

7.7 % to 21.5 % reported in other studies that included patients who underwent resection followed by adjuvant SRS [12,18–20]. It is worth noting that multiple studies have reported a correlation between PMF and extracranial disease control, which may reflect survival bias or other differences in the care of this sub-cohort. [12,18,19,21]. While systemic chemotherapy has not been shown to affect the development of PMF [18], one study found that the addition of immunotherapy to adjuvant SRS following resection of brain metastases significantly reduced the 12-month cumulative rates of LMD/PMF (22 % vs. 6 %)[22].

In the adjuvant setting, one group reported results using adjuvant

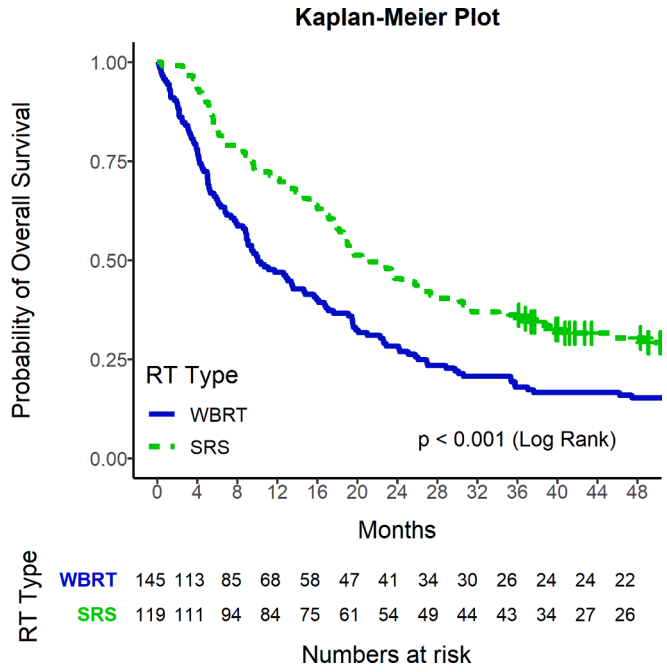

Fig. 3C. Overall survival in patients treated with adjuvant whole brain radiotherapy (WBRT) vs stereotactic radiosurgery (SRS).

fractionated partial brain radiotherapy, with 6- and 12-month freedom from local failure rates of 97.0 % and 88.2 % in 45 patients following 30–42 Gy in 3 Gy per fraction, presumably targeting a larger field than is typical for SRS [23]. Unfortunately, this study did not differentiate between the incidence of LMD and PMF.

Alternatively, neoadjuvant SRS, which is hypothesized to result in fewer viable tumour cells present at the time of resection, and therefore a decreased the risk of pachymeningeal seeding, may prove to be a superior technique with regard to PMF risk [24]. Supporting this, Prabhu et al. [25] reported on patients treated with preoperative SRS, noting that of the 242 patients, 19 (7.9 %) developed LMD. Among these, 13 patients (5.4 %) had cLMD, while only 6 patients (2.5 %) developed PMF. In other words, the incidence of PMF was lower than historical data, including ourshere, in patients managed with adjuvant SRS. Intraoperative radiotherapy (IORT), including brachytherapy and external beam techniques, is another therapeutic modality for managing BrM [26,27]. However, to the best of our knowledge, there is lack of data reporting its possible impact on PMF. In one recent prospective observational study including 35 patients who received IORT, the incidence of LMD was 5.7 %" [26].

Other strategies to improve meningeal coverage with radiation to minimize the risk of PMF include using definitive F-SRS or staged SRS administered in 2–5 fractions [28,29]. Both are associated with favorable local control and OS rates for mid to large-sized BrM. However, these methods may not be ideal for patients presenting with significant neurological symptoms or those yet to be diagnosed with cancer. Additionally, systemic therapies, particularly immunotherapies and targeted therapies, have become increasingly significant in BrM management. For example, kinase inhibitors used to treat melanoma, namely vemurafenib and dabrafenib, have substantial central nervous system activity [30], while osimertinib for EGFRm-positive non-small-cell lung carcinoma has a central nervous system response rate (CNS RR) of 91 % [31]. Similarly, in HER2-positive breast cancer, therapies such as lapatinib combined with capecitabine, and tucatinib with capecitabine and trastuzumab, have substantial efficacy in controlling CNS disease [32,33]. These and other drugs offer a valuable alternative or adjunct to traditional local treatments for BrM. Integrating these systemic therapies with advanced radiotherapy techniques could also

potentially provide a more comprehensive approach to managing PMF.

Despite the risk of PMF in the adjuvant SRS setting, in our study, this cohort experienced improved OS compared to those who received adjuvant WBRT, including on PSM analysis. A *meta*-analysis by Sahgal et al. [34] comparing WBRT + SRS to SRS alone in patients with 1–4 brain metastases found that omission of WBRT resulted in favourable survival rates in patients younger than 50; however, randomized trials published since then comparing SRS to WBRT have not detected a survival difference comparing these techniques [35]. Our observation should be evaluated with caution as there are undoubtedly confounding variables underpinning that result. In particular, patients receiving WBRT were treated in an earlier era than patients managed with advances in supportive, radiotherapy and surgical management.

There has been significant progress in the development and application of immunotherapies and targeted therapies that demonstrate high intracranial response rates [30,31,33,36]. Additionally, radiation techniques have undergone considerable improvements, complemented by a deeper understanding of disease behavior [37,38] and the establishment of contouring guidelines and fractionation recommendations that have further optimized therapeutic ratio [16,39,40]. It is also worth noting that patients in the WBRT group had a higher number of metastases at the time of treatment; this variable was included in the propensity-matched analysis. Beyond these factors, during the era in which SRS became standard of care, there were concurrent advances in cancer care, including improved systemic therapies, non-CNS radiation techniques, and surgical treatments; better symptom management, rehabilitation services, and psychosocial support, all of which contributed to improved overall care. Finally, while PMF likely carries an improved prognosis compared to classical LMD, [21] it still represents a critical oncologic event; in the present study, 24 (75 %) of patients diagnosed with PMF suffered a neurologic death, which is similar to prior reports [12,21].

Future directions

PMF is a pattern of failure that occurs in post-operative BrM patients that is only sometimes salvageable with focal treatment modalities or WBRT [35]. Because surgery is a critical modality and is associated, in some studies, with improved survival for patients with large BrM [14], further research into potential mechanisms of PMF is needed to determine the surgical and radiation strategies that best minimize its risk [41]. This includes identifying the incidence of PMF following the implementation of concensus contouring guidelines [16], utilizing appropriate doses and fractionation for large cavities, and delivering adjuvant SRS in a timely fashion. Understanding PMF incidence in this context will provide a more accurate representation of its occurrence according tothe current standard of managing resected BrM. Future research should also focus on characterizing patterns of PMF, such as its proximity to the surgical cavity or confinement to specific compartments, which could aid in developing specific radiation guidelines. For instance, adjuvant posterior fossa radiation could be recommended for resected cerebellar metastases, particularly if PMF is confined in the infratentorial region. It's also important to investigate how the integration of immunotherapy and targeted agents, known for effective intracranial responses, impacts the incidence and evolution of PMF.

Conclusion

To the best of our knowledge, this is the first study to compare the incidence of pachymeningeal failure following adjuvant WBRT vs SRS. Our study suggests that PDC, and adjuvant SRS instead of WBRT correlate with an increased risk for PMF. Prospective studies are necessary in order to determine the optimal surgical and adjuvant radiation techniques to decrease the risk of PMF.

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Appendix A. Supplementary data

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