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Original Article

Patterns and risk factors of intracranial recurrence after surgical resection of brain metastases from malignant tumors

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Abstract: Background: The incidence of brain metastases is increasing, and surgical resection remains a key treatment modality. However, postoperative intracranial recurrence - including local recurrence (LR), distant brain recurrence (DBR), and leptomeningeal disease (LMD) - significantly impacts patient prognosis. Previous studies have predominantly focused on single tumor types and lacked systematic analyses of recurrence patterns and risk factors. Objectives: This study aimed to investigate the incidence, temporal distribution, and independent risk factors associated with distinct postoperative recurrence patterns. Methods: Demographic, imaging, surgical, pathological, and post-treatment data from 198 patients who underwent resection of brain metastases were retrospectively analyzed. Kaplan-Meier and Fine-Gray models were used to evaluate recurrence timing, and a multinomial logistic regression model (using the non-recurrence group as reference) was applied to identify risk factors. A cause-specific Cox proportional hazards model was further employed to analyze recurrence timing while considering death as a competing risk. Results: Intracranial recurrence occurred in 119 patients (60.1%). LR was the most frequent type (47.1%), whereas LMD developed latest (median 14.6 *vs.* 9.1 months for LR, $P<0.05$). Independent risk factors for LR included tumor size >3 cm, proximity to the ventricle or dura mater, intraoperative tumor rupture, and omission of cavity radiotherapy. DBR was associated with ≥3 brain metastases, extracranial metastases, and lack of whole-brain radiotherapy. LMD was linked to primary breast cancer, intraoperative rupture, meningeal invasion, and delayed radiotherapy (≥4 weeks). The areas under the curve (AUCs) of predictive models were 0.78 for LR, 0.74 for DBR, and 0.81 for LMD. Stratified analysis by tumor type revealed that lung cancer most commonly exhibited LR (30.0%), followed by DBR (21.7%), with LMD being least frequent (5.8%); breast cancer demonstrated the highest incidence of LMD (21.4%). Multivariable analysis identified tumor size >3 cm and ventricular/dural proximity as independent risk factors for LR in lung cancer, while ≥3 metastases predicted DBR. In breast cancer, human epidermal growth factor receptor 2 positivity and delayed radiotherapy (≥4 weeks) were associated with LMD. Predictive model AUCs ranged from 0.65 to 0.83, indicating that recurrence patterns and risk factors are tumor type-specific. Conclusion: Postoperative intracranial recurrence after surgical resection of brain metastasis demonstrates distinct incidence rates, temporal profiles, and independent risk factors. These recurrence patterns and associated risks are highly dependent on the tumor type.

Keywords: Brain metastasis, postoperative recurrence, local recurrence, distant brain recurrence, leptomeningeal disease

Introduction

With advances in systemic anticancer therapies and the consequent prolongation of patient survival, the incidence of brain metastases - the most common form of distant metastasis to the central nervous system - has continued to rise, now affecting approximately 40% of all cancer patients [1]. Lung cancer, breast cancer, and melanoma are the predominant primary tumors, with non-small cell lung cancer (NSCLC) and breast cancer accounting for the majority of cases [2, 3]. Surgical resection remains an essential treatment modality, particularly for patients with solitary or limited (≤4) resectable lesions accompanied by intra-

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cranial symptoms [4]. Despite providing effective symptomatic relief, postoperative intracranial recurrence continues to adversely affect both prognosis and quality of life.

Previous studies have shown that postoperative intracranial recurrence primarily comprises local recurrence (LR) [5], distant brain recurrence (DBR) [6], and leptomeningeal disease (LMD) [7]. These recurrence patterns differ significantly in biological behaviour, treatment response, and prognosis. LR is closely related to the completeness of en bloc resection and the adequacy of cavity radiotherapy, whereas DBR is influenced by tumor biology, micrometastatic potential, and the efficacy of systemic therapies [8]. However, most existing studies have focused on single variables or specific primary tumors such as NSCLC, evaluating factors like serum carcinoembryonic antigen levels or tumor size. Systematic comparisons of recurrence patterns across multiple primary tumor types remain limited [9]. Moreover, the impact of postoperative radiotherapy - including whole-brain radiotherapy (WBRT), focal radiotherapy, sequential therapy, and targeted immunotherapy - on recurrence patterns is complex. The 2025 American Society of Clinical Oncology (ASCO) report indicated that focal radiotherapy following surgical resection of cerebellar metastases reduced the risk of LMD, although variations in target volume design could increase the likelihood of marginal recurrence [10]. While prior studies have independently examined LR, DBR, or LMD, few have systematically classified postoperative recurrence patterns across diverse primary tumors in conjunction with multivariable risk-factor analysis. Consequently, accurate predictive models remain lacking, and clinical decision-making continues to rely largely on empirical judgment, leading to considerable interindividual variability.

Therefore, this study was designed to systematically classify postoperative intracranial recurrence patterns using a real-world, multicentre, large-sample retrospective cohort. It comprehensively analyzed multidimensional variables - including surgical techniques, tumor characteristics, preoperative imaging parameters, and adjuvant treatment strategies - with the aim of developing risk prediction models for each recurrence type. These models are intended to provide evidence-based guidance for postoperative management and adjuvant therapeutic decision-making.

Research methods

Study design and data sources

Patients who underwent surgical resection for intracranial metastases at Tianjin Medical University Cancer Institute and Hospital between January 1, 2022 and December 31, 2024, were retrospectively enrolled. All procedures were performed by the neurosurgical team, and standardized postoperative follow-up and adjuvant therapies were provided under the guidance of a multidisciplinary tumor board (MDT) [11]. The flowchart for patient selection is presented in Figure S1. Of the 285 initially screened cases, 17 with extradural invasion or skull involvement, 9 with preoperative meningeal dissemination, 6 perioperative deaths, and 55 with incomplete data were excluded, resulting in 198 patients being included in the final analysis. The standardized follow-up protocol consisted of contrast-enhanced brain magnetic resonance imaging (MRI) every 3 months during the first 2 years postoperatively, followed by every 6 months until death or the data cutoff (June 30, 2025). Comprehensive clinical, imaging, and follow-up data were ensured. Demographic characteristics, tumor features, surgical parameters, and adjuvant treatment details were jointly extracted from the electronic medical record, the Picture Archiving and Communication System, and the radiotherapy and oncology databases. This study was approved by the Ethics Committee of Tianjin Medical University Cancer Institute and Hospital. Given its retrospective design, the requirement for informed consent was waived. The primary outcome was the cumulative incidence of the three postoperative intracranial recurrence patterns (LR, DBR, LMD). Secondary outcomes included recurrence-free survival (RFS), median time to each recurrence type, and identification of independent risk factors.

Inclusion criteria were as follows: (1) age ≥18 years; (2) presence of an intracranial space-occupying lesion on imaging with postoperative pathological confirmation of metastasis; (3) a definite primary tumor type; (4) at least one postoperative brain imaging follow-up and a follow-up duration ≥6 months or a documented recurrence event; and (5) complete preop-

erative and postoperative treatment information. Exclusion criteria were as follows: (1) lesions penetrating the dura mater or involving the extradural space or skull; (2) radiological or pathological evidence of meningeal dissemination before surgery; (3) perioperative death (within 30 days after surgery); and (4) missing data, incomplete follow-up, or duplicate inclusion.

A total of 198 eligible patients was ultimately enrolled. All data were independently entered by two investigators and cross-verified, while key variables were re-examined by a third investigator.

Variable definition and data collection

Classification of recurrence patterns: Recurrence patterns were categorized based on the first radiologically confirmed event and were mutually exclusive (LR, DBR, LMD). If the initial recurrence simultaneously met the criteria for multiple patterns, the case was reviewed by the MDT; however, no such cases were identified in this study cohort.

LR: Appearance of new or recurrent enhancing lesions within the surgical cavity or within 1 cm of its margin.

DBR: Appearance of new metastatic lesions outside the surgical cavity, located in the ipsilateral or contralateral cerebral hemisphere, cerebellum, or brainstem [12].

LMD: Radiological evidence of enhancement along the cerebral sulci, or ventricular margins, or positive cerebrospinal fluid cytology findings [13].

Independent variables: Demographic and baseline characteristics: sex, age, Karnofsky Performance Status (KPS) score [14], primary tumor type, and the presence or absence of extracranial metastases. Only extracranial metastases newly identified after the diagnosis of brain metastases were included, whereas those present before the diagnosis of brain metastases were excluded. A history of chemotherapy, targeted therapy, or immunotherapy administered within three months prior to surgery was also recorded.

Imaging parameters included the number of brain metastases (solitary, oligometastatic, or multiple), maximum tumor diameter, lesion location (cerebral hemisphere, cerebellum, or brainstem), presence of peritumoral edema (>1 cm), adjacency to the ventricle or dura mater, and evidence of intratumoral haemorrhage.

Surgical information included the operative approach (en bloc vs. piecemeal resection), completeness of resection (no residual tumor on postoperative MRI), intraoperative tumor rupture, intraoperative blood loss (>100 mL), and postoperative complications (haemorrhage, infection, or epilepsy).

Pathological and molecular markers included histological subtype, Ki-67 proliferation index (<10%, 10-30%, or >30%), vascular invasion, meningeal invasion, and immunohistochemical markers (epidermal growth factor receptor [EGFR], human epidermal growth factor receptor 2 [HER2], and programmed death-ligand 1 [PD-L1]). EGFR positivity was defined as an immunohistochemistry (IHC) score of ≥1+ or the presence of a sensitizing mutation detected by next-generation sequencing [15]. HER2 positivity was defined as IHC 3+ or fluorescence in situ hybridization amplification [16]. PD-L1 positivity was defined as a tumor proportion score of ≥1% [17].

Postoperative management strategies included the radiotherapy modality, the timing of its initiation, and the use of systemic therapy. Radiotherapy modalities comprised no radiotherapy, WBRT (30 Gy in 10 fractions) [18], stereotactic radiosurgery (18-24 Gy in a single fractio) [19], or cavity radiotherapy (40-50 Gy in 25 fractions) [20], all administered in accordance with contemporary treatment guidelines. Additional variables included the interval between surgery and radiotherapy initiation (<4 weeks vs. ≥4 weeks) and the administration of postoperative systemic therapies, including targeted therapy, immunotherapy, or hormonal therapy. All systemic treatments were administered according to current standards for the primary tumor type - for example, EGFR tyrosine kinase inhibitors for NSCLC and anti-HER2 therapy for breast cancer.

Imaging recurrence assessment

Postoperative intracranial recurrence was jointly evaluated by two senior neuroradiologists

and one neurosurgeon under double-blind conditions, following the international Response Assessment in Neuro-Oncology Brain Metastases [21, 22] and the European Association of Neuro-Oncology-European Society for Medical Oncology criteria [23]. Contrast-enhanced MRI sequences, including T1-weighted imaging, T2-weighted imaging/fluid-attenuated inversion recovery, diffusion-weighted imaging, and perfusion sequences, were primarily analyzed. Computed tomography or spinal MRI was performed when necessary to exclude distant dissemination. The time to first recurrence was defined as the date on which new or progressive lesions were first detected on imaging. LR: new or recurrent enhancing lesions within the surgical cavity or within 1 cm of its margin. DBR: new metastatic lesions outside the surgical cavity, located in the ipsilateral or contralateral cerebral hemisphere, cerebellum, or brainstem. LMD: radiological evidence of enhancement along the cerebral sulci, cisterns, or ventricular margins, or positive cerebrospinal fluid cytology. When cytology was negative, cases were classified as probable LMD by consensus of an expert panel. Discrepancies in diagnosis were resolved by a third-party MDT. To ensure consistency, 10% of the cases were randomly re-evaluated, yielding a Kappa coefficient ≥0.8. MRI follow-up was conducted every 2-3 months postoperatively according to protocol, ensuring accurate detection of intracranial recurrence.

Statistical analysis

All statistical analyses were performed using R software (version 4.2.2) and SPSS (version 26.0). Continuous variables were expressed as mean ± standard deviation or median interquartile range (IQR), depending on the data distribution, whereas categorical variables were summarized as frequencies and percentages. Intergroup comparisons of categorical variables were conducted using the χ^2 test or Fisher's exact test, while continuous variables were compared using one-way analysis of variance or the Kruskal-Wallis test, followed by post hoc pairwise comparisons when appropriate. Survival analyses were performed using the Kaplan-Meier method to estimate RFS curves, and group differences were assessed with the log-rank test. The Fine-Gray competing risk model was applied to account for competing events such as death, and cumulative incidence function curves were generated. To address the biological heterogeneity among different primary tumor types, patients were stratified into three major groups: lung cancer, breast cancer, others. Within each stratum, the incidence rates of LR, DBR, and LMD were evaluated, and independent risk factors for each recurrence pattern were identified using multivariable logistic regression models. Risk prediction models were subsequently constructed and their performance assessed within each tumor-type stratum. Multivariable analyses were also performed using a multinomial logistic regression model, with the no-recurrence group as the reference category, to determine factors associated with each recurrence pattern (LR/DBR/LMD). This model was chosen because the recurrence patterns were mutually exclusive, allowing for direct comparison with the no-recurrence reference group and providing interpretable odds ratios (ORs).

Cause-specific Cox proportional hazards models were applied to analyze the time to occurrence of each recurrence type, treating death and other recurrence types as competing risks. Variables with $P<0.05$ in univariate analyses were entered into stepwise regression to identify significant risk factors. Given the limited number of LMD events (n=24), the multivariable model strictly adhered to the events-per-variable ≥10 principle. Accordingly, the number of covariates was restricted to ≤2 (intraoperative tumor rupture and meningeal invasion), with priority assigned to variables that were significant in univariate analysis or considered clinically essential. Risk prediction models for each recurrence type were subsequently developed, and internal validation was performed using receiver operating characteristic curves, AUCs, and the bootstrap method. All statistical tests were two-sided, and $P<0.05$ was considered statistically significant.

Results

Overall intracranial recurrence and distribution of recurrence patterns

A total of 198 patients were analyzed, with a median postoperative follow-up duration of 14.8 months (IQR: 10.6-21.3). By the end of follow-up, 119 patients (60.1%) had experienced a first documented intracranial recurrence. Among these, 56 (28.3%) were classified

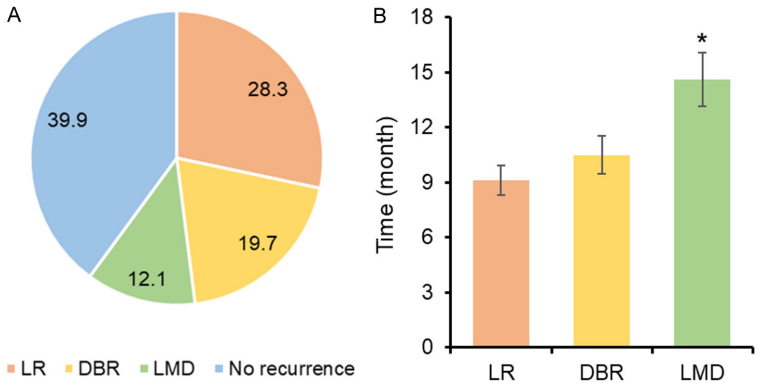

Figure 1. Distribution of first recurrence patterns and their time of occurrence in all patients. A: Recurrence patterns; B: Median time to first recurrence; *P<0.05; DBR, distant brain recurrence; LR, local recurrence; LMD, leptomeningeal disease.

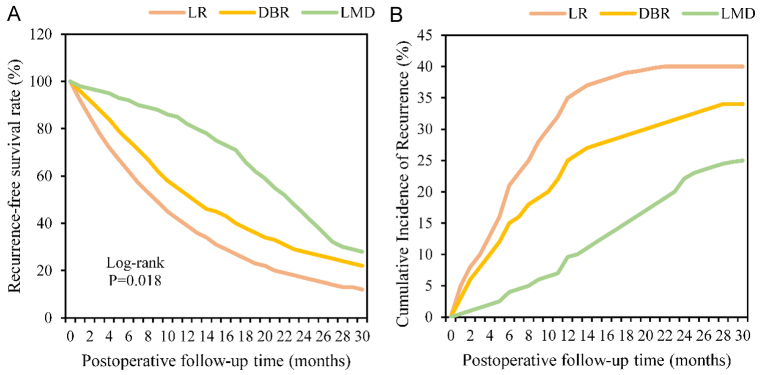

Figure 2. Comparison of postoperative RFS Kaplan-Meier curves and CIF curves for the different intracranial recurrence types. A: RFS curves for LR, DBR, and LMD patients; B: Cumulative incidence of each recurrence type depicted by the Fine-Gray competing risk model with death treated as a competing event; CIF, cumulative incidence function; DBR, distant brain recurrence; LR, local recurrence; LMD, leptomeningeal disease; RFS, recurrence-free survival.

as LR, 39 (19.7%) as DBR, and 24 (12.1%) as LMD. The remaining 79 patients (39.9%) showed no evidence of intracranial recurrence during follow-up. LR represented the most common recurrence pattern, accounting for 47.1% of all recurrences, followed by DBR (32.8%) and LMD (20.2%). The median time to first recurrence was significantly longer for LMD compared with LR and DBR (14.6 months [IQR: 10.9-19.3] vs. 9.1 months [IQR: 6.4-13.0] and 10.5 months [IQR: 7.2-14.8], respectively; both P<0.05) (**Figure 1**).

Postoperative intracranial recurrence: temporal patterns and distribution characteristics

Kaplan-Meier and Fine-Gray competing risk analyses were performed. The median RFS for the entire cohort of 198 patients was 10.2 months (95% confidence interval [CI]: 8.9-11.7), with 1-year and 2-year RFS rates of 41.7% and 21.4%, respectively. Stratified analysis showed that the longest median RFS was observed in patients with LMD (14.6 months), followed by DBR (10.5 months) and LR (9.1 months) (log-rank P=0.018). The Fine-Gray model demonstrated that the cumulative incidence of LR peaked at 6 months postoperatively (21.2%), significantly exceeding that of DBR (14.9%) and LMD (4.0%). At 12 months, the cumulative incidences of LR and DBR further increased to 34.7% and 25.2%, respectively, whereas LMD remained delayed at 9.6%. By 24 months, however, the incidence of LMD had risen markedly to 22.1% (**Figure 2**).

Comparison of data across recurrence patterns

Demographic and baseline characteristics: Among the 198 patients, no statistically significant difference was observed in sex distribution across recurrence groups. Although females were slightly more frequent in the LMD group (58.3%), this trend did not indicate a definitive sex-related association with meningeal metastasis. The mean age of patients with LMD was lower (53.7 years) than that of patients with LR (59.2 years) or DBR (57.8 years) (P=0.042). The median Karnofsky Performance Status (KPS) did not differ across groups. Primary tumor type varied markedly (P<0.001): breast cancer was most prevalent in the LMD group (37.5%), whereas lung cancer predominated in both the LR (65.2%) and DBR (66.7%) groups. The frequency of extracranial metastases was highest in the DBR group (76.9%), significantly exceeding that observed in the other groups (P= 0.027). Previous systemic treatments - including chemotherapy, targeted therapy, and immunotherapy - were similarly distributed among the three groups (**Table 1**).

Table 1. Comparison of demographic and baseline characteristics among the 198 patients across different recurrence patterns

Variable	LR (n=56)	DBR (n=39)	LMD (n=24)	No-recurrence (n=79)	*P*
Gender (male) (%)	33 (58.9)	22 (56.4)	10 (41.7)	49 (62.0)	0.274
Age (years)	59.2±9.6	57.8±10.2	53.7±11.1	57.3±9.8	0.042*
KPS	85 (80-90)	80 (70-90)	85 (80-90)	85 (80-90)	0.368
Primary tumor type (%)					<0.001*
Lung cancer	36 (65.2)	26 (66.7)	7 (29.2)	51 (64.6)	
Breast cancer	10 (17.9)	6 (15.4)	9 (37.5)	17 (21.5)	
Others	10 (16.9)	7 (17.9)	8 (33.3)	11 (13.9)	
Extracranial metastases (present) (%)	30 (53.6)	30 (76.9)	11 (45.8)	26 (40.5)	0.027*
Prior chemotherapy (yes) (%)	35 (62.5)	22 (56.4)	13 (54.2)	48 (60.8)	0.683
Prior targeted therapy (yes) (%)	14 (25.0)	11 (28.2)	7 (29.2)	24 (30.4)	0.911
Prior immunotherapy (yes) (%)	9 (16.1)	5 (12.8)	4 (16.7)	15 (19.0)	0.859

Note: *P<0.05; DBR, distant brain recurrence; KPS, Karnofsky Performance Status; LR, local recurrence; LMD, leptomeningeal disease.

Comparison of imaging parameters: A significant difference in the number of brain metastases was observed among the groups (*P*<0.001). In the LR group, solitary lesions predominated, accounting for 53.6% of cases, whereas oligometastatic and multiple lesions constituted 28.6% and 17.9%, respectively. The highest proportions of multiple lesions were observed in the DBR (61.5%) group. The mean maximum lesion diameter in the LR group (3.2±1.0 cm) was significantly larger than in the DBR (2.5± 0.7 cm), LMD (2.7±0.8 cm), and no-recurrence groups (2.8±0.9 cm) (*P*=0.021). A significant difference in lesion location distribution was also detected (*P*=0.034). Lesions in the cerebral hemisphere were the most common overall; however, the proportion observed in the LR group (76.8%) was markedly higher than in the DBR (66.7%), LMD (62.5%), and non-recurrent groups (67.1%). The proportion of lesions adjacent to the ventricle or dura mater differed significantly among recurrence patterns (*P*= 0.009); the LR group exhibited the highest rate (67.9%), whereas the LMD group showed the lowest (33.3%). No significant differences were found in the presence of marked edema (>1 cm) or preoperative hemorrhage among the groups (both *P*>0.05) (**Table 2**).

Comparison of surgery-related characteristics: The surgical characteristics of recurrent patients were analyzed and it was found that en bloc resection was most frequently performed in the LR group (67.9%), whereas piecemeal resection was more common in the LMD group (62.5%) (*P*=0.037). The rate of gross total resection, as evaluated by postoperative MRI, was highest in the LR group (79.6%) and lowest in the LMD group (54.2%) (*P*=0.014). It should be noted that the en bloc resection rate (69.6%) and gross total resection rate (88.6%) in the non-recurrent group were higher than those in all recurrent groups. Intraoperative tumor rupture occurred most frequently in the LMD group (41.7%), which was significantly higher than in the LR (21.4%) and DBR (18.0%) groups (*P*=0.004). No significant differences in intraoperative massive hemorrhage (>100 mL) or postoperative complication rates were observed among the recurrence patterns (both *P*> 0.05) (**Table 3**).

Comparison of pathological and molecular markers: A significant difference in histological subtype was observed among recurrence patterns (*P*<0.001). Patients with breast cancer were predominantly concentrated in the LMD group, whereas lung cancer accounted for the majority of cases in the LR and DBR groups. A high Ki-67 proliferation index (>30%) was more frequently observed in the LR and LMD groups (46.4% and 50.0%, respectively) and was slightly lower in the DBR group (35.9%) (*P*= 0.058). Vascular invasion and meningeal invasion were markedly more common in LMD, with both invasion rates reaching 54.2% (*P*=0.036 and *P*<0.001, respectively). Among immunohistochemical markers, HER2 positivity was

Table 2. Comparison of imaging parameters among patients with different recurrence patterns

Parameters	LR (n=56)	DBR (n=39)	LMD (n=24)	No-recurrence (n=79)	*P*
Number of metastatic lesions (%)					<0.001*
Solitary	30 (53.6)	8 (20.5)	7 (29.2)	36 (45.6)	
Oligometastatic (2-3 lesions)	16 (28.6)	7 (17.9)	6 (25.0)	38 (48.1)	
Multiple (≥4 lesions)	10 (17.9)	24 (61.5)	11 (45.8)	5 (6.3)	
Maximum lesion diameter (cm)	3.2±1.0	2.5±0.7	2.7±0.8	2.8±0.9	0.021*
Lesion location (%)					0.034*
Cerebral hemisphere	43 (76.8)	26 (66.7)	15 (62.5)	53 (67.1)	
Cerebellum	8 (14.3)	8 (21.1)	5 (20.8)	20 (25.3)	
Brainstem	5 (8.9)	2 (5.3)	2 (8.3)	11 (13.9)	
Marked edema (>1 cm)	30 (53.6)	16 (41.0)	8 (33.3)	35 (44.3)	0.152
Adjacency to ventricle or dura mater (%)	38 (67.9)	21 (53.8)	8 (33.3)	46 (58.2)	0.009*
Preoperative imaging evidence of hemorrhage (%)	11 (19.6)	9 (23.1)	4 (16.7)	21 (26.6)	0.394

Note: *P<0.05; DBR, distant brain recurrence; LR, local recurrence; LMD, leptomeningeal disease.

Table 3. Comparison of surgery-related information among patients with different recurrence patterns

Variable	LR (n=56)	DBR (n=39)	LMD (n=24)	No-recurrence (n=79)	*P*
Surgical approach (%)					0.037*
En bloc	38 (67.9)	21 (53.8)	9 (37.5)	55 (69.6)	
Piecemeal	18 (32.1)	18 (46.2)	15 (62.5)	24 (30.4)	
Postoperative gross total resection rate (%)					0.014*
Achieved	45 (79.6)	26 (66.7)	13 (54.2)	70 (88.6)	
Not achieved	11 (20.4)	13 (33.3)	11 (45.8)	9 (11.4)	
Intraoperative tumor rupture (%)	12 (21.4)	7 (18.0)	10 (41.7)	9 (11.4)	0.004*
Intraoperative blood loss >100 mL (%)	9 (16.1)	6 (15.4)	5 (20.8)	11 (13.9)	0.782
Postoperative complications (%)	6 (10.7)	5 (12.8)	3 (12.5)	6 (7.6)	0.771

Note: *P<0.05; DBR, distant brain recurrence; LR, local recurrence; LMD, leptomeningeal disease.

significantly higher in LMD (P=0.041), whereas no significant differences were detected in EGFR positivity or PD-L1 expression among the recurrence patterns (both P>0.05) (**Table 4**).

Comparison of postoperative treatment strategies: A significant difference in postoperative radiotherapy modality was observed among the recurrence groups (P=0.011). Cavity radiotherapy was most frequently administered in the LR group (82.1%), whereas WBRT was delivered most often in the LMD group (58.3%). Delayed initiation of radiotherapy (≥4 weeks) was more common in the LMD group (45.8%), markedly higher than the LR group (19.6%) (P=0.019). No statistically significant differences were observed in the administration rates of postoperative targeted therapy or immunotherapy among the recurrence groups, whereas hormonal therapy was more frequently used in breast cancer patients with LMD (P=0.042) (**Table 5**).

Independent risk factors for different intracranial recurrence patterns

A multinomial logistic regression model, using the no-recurrence group as the reference, was applied to identify factors associated with each recurrence pattern (LR/DBR/LMD). In addition, cause-specific Cox proportional hazards models were employed to analyze the time to occurrence of each recurrence type, treating death as a competing risk. The results of the multivariable analyses are summarized below.

Independent risk factors for LR: Multinomial logistic regression analysis (**Table 6**) identified

Table 4. Comparison of pathological and molecular markers among patients with different recurrence patterns

Variable	LR (n=56)	DBR (n=39)	LMD (n=24)	No-recurrence (n=79)	*P*
Histological subtype (%)					<0.001*
ADC	25 (44.6)	18 (46.2)	5 (20.8)	30 (38.0)	
SCC	12 (21.4)	8 (20.5)	7 (29.2)	10 (12.7)	
Breast cancer	8 (14.3)	4 (10.3)	6 (25)	16 (20.3)	
Melanoma	5 (8.9)	3 (7.7)	2 (8.3)	5 (6.3)	
Others	6 (10.7)	6 (15.4)	4 (16.7)	10 (12.7)	
Ki-67 index (%)					0.058
<10%	8 (14.3)	7 (17.9)	3 (12.5)	15 (19.0)	
10-30%	22 (39.3)	18 (46.2)	9 (37.5)	34 (43.0)	
>30%	26 (46.4)	14 (35.9)	12 (50.0)	30 (38.0)	
Vascular invasion (%)	24 (42.9)	15 (38.5)	13 (54.2)	24 (30.4)	0.036*
Meningeal invasion (%)	11 (19.6)	7 (17.9)	13 (54.2)	9 (11.4)	<0.001*
EGFR positivity (%)	29 (51.8)	19 (48.7)	10 (41.7)	42 (53.2)	0.475
HER2 positivity (%)	6 (10.7)	3 (7.7)	7 (29.2)	10 (12.7)	0.041*
PD-L1 positivity (%)	14 (25.0)	9 (23.1)	5 (20.8)	20 (25.3)	0.884

Note: *P<0.05; ADC, adenocarcinoma; DBR, distant brain recurrence; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; LR, local recurrence; LMD, leptomeningeal disease; PD-L1, programmed death-ligand 1; SCC, squamous cell carcinoma.

Table 5. Comparison of postoperative treatment strategies among patients with different recurrence patterns

Variable	LR (n=56)	DBR (n=39)	LMD (n=24)	No-recurrence (n=79)	*P*
Postoperative radiotherapy modality (%)					0.011*
No radiotherapy	4 (7.1)	5 (12.8)	2 (8.3)	9 (11.4)	
WBRT	6 (10.7)	8 (20.5)	14 (58.3)	9 (11.4)	
SRS	7 (12.5)	10 (25.6)	4 (16.7)	20 (25.3)	
Cavity radiotherapy	46 (82.1)	26 (66.7)	6 (25.0)	57 (72.2)	
Radiotherapy delay ≥4 weeks (%)	11 (19.6)	9 (23.1)	11 (45.8)	66 (83.5)	0.019*
Postoperative targeted therapy (%)	21 (37.5)	17 (43.6)	10 (41.7)	34 (43.0)	0.284
Postoperative immunotherapy (%)	12 (21.4)	9 (23.1)	6 (25.0)	18 (22.8)	0.311
Postoperative hormonal therapy (breast cancer only) (%)	2 (3.6)	1 (2.6)	9 (37.5)	6 (7.6)	0.042*

Note: *P<0.05; DBR, distant brain recurrence; LR, local recurrence; LMD, leptomeningeal disease; SRS, stereotactic radiosurgery; WBRT, whole-brain radiotherapy.

Table 6. Multinomial logistic regression analysis results for LR (reference group: no-recurrence)

Recurrence type	Risk factor	β	SE	Wald X^2	OR (95% CI)	*P*
LR	Maximum lesion diameter >3 cm	0.735	0.265	7.684	2.09 (1.25-3.49)	0.006
	Adjacency to the ventricle or dura mater	0.642	0.258	6.199	1.90 (1.15-3.14)	0.013
	Intraoperative tumor rupture	1.215	0.366	11.017	3.37 (1.64-6.91)	0.001
	Omission of cavity radiotherapy	0.911	0.342	7.106	2.49 (1.27-4.86)	0.008

Note: Model fitting: Hosmer-Lemeshow test P=0.32, Nagelkerke R^2=0.41; CI, confidence interval; LR, local recurrence; OR, odds ratio.

several independent risk factors for LR. A maximum lesion diameter >3 cm (OR=2.09, 95% CI: 1.25-3.49, P=0.006), adjacency to the ventricle or dura mater (OR=1.90, 95% CI:

Table 7. Multinomial logistic regression analysis results for DBR (reference group: no-recurrence)

Recurrence type	Risk factor	β	SE	Wald X^2	OR (95% CI)	*P*
DBR	Number of lesions ≥3	0.988	0.307	10.378	2.69 (1.49-4.85)	0.001
	Squamous cell carcinoma histological type	0.821	0.311	6.967	2.27 (1.23-4.18)	0.008
	Non-gross total resection	0.645	0.267	5.823	1.91 (1.13-3.22)	0.016
	Omission of postoperative WBRT	1.102	0.386	8.133	3.01 (1.42-6.36)	0.004

Note: Model fitting: Hosmer-Lemeshow test *P*=0.41, Nagelkerke R^2=0.38; CI, confidence interval; DBR, distant brain recurrence; OR, odds ratio; WBRT, whole-brain radiotherapy.

Table 8. Multinomial logistic regression analysis results for LMD (reference group: no-recurrence)

Recurrence type	Risk factor	β	SE	Wald X^2	OR (95% CI)	*P*
LMD	Primary breast cancer	1.284	0.490	6.857	3.61 (1.38-9.45)	0.009
	Intraoperative tumor rupture	1.554	0.380	16.728	4.73 (2.25-9.94)	<0.001
	Meningeal invasion	1.643	0.385	18.220	5.17 (2.40-11.14)	<0.001
	Radiotherapy delay ≥4 weeks	0.742	0.369	4.046	2.10 (1.02-4.32)	0.044

Note: Sample size explanation: Based on 24 LMD events, the model included only 4 predefined key variables (EPV=6); Model fitting: Hosmer-Lemeshow test *P*=0.28, Nagelkerke R^2=0.53; CI, confidence interval; EPV, events per variable; LMD, leptomeningeal disease; OR, odds ratio.

1.15-3.14, *P*=0.013), intraoperative tumor rupture (OR=3.37, 95% CI: 1.64-6.91, *P*=0.001), and omission of cavity radiotherapy (OR=2.49, 95% CI: 1.27-4.86, *P*=0.008) were all significantly associated with an increased risk of LR. Cause-specific Cox proportional hazards model analysis further confirmed that these variables significantly shortened the time to LR occurrence (all *P*<0.05), with hazard ratios (HRs) consistent in direction and magnitude with the corresponding ORs (Table S1).

Independent risk factors for DBR: Multinomial logistic regression analysis (**Table 7**) revealed several significant independent risk factors for DBR. A number of intracranial metastases ≥3 (OR=2.69, 95% CI: 1.49-4.85, *P*=0.001), the presence of extracranial metastasis (OR=2.27, 95% CI: 1.23-4.18, *P*=0.008), failure to achieve gross total resection (OR=1.91, 95% CI: 1.13-3.22, *P*=0.016), and omission of WBRT (OR=3.01, 95% CI: 1.42-6.36, *P*=0.004) were all significantly associated with an increased risk of DBR. Cause-specific Cox proportional hazards model analysis confirmed that all these factors significantly accelerated the occurrence of DBR (all *P*<0.05), with HRs consistent in direction and magnitude with the corresponding ORs (Table S1).

Independent risk factors for LMD: Multinomial logistic regression analysis (**Table 8**) identified several independent risk factors for LMD. Primary breast cancer (OR=3.61, 95% CI: 1.38-9.45, *P*=0.009), intraoperative tumor rupture (OR=4.73, 95% CI: 2.25-9.94, *P*<0.001), pathologically confirmed meningeal invasion (OR=5.17, 95% CI: 2.40-11.14, *P*<0.001), and radiotherapy delay ≥4 weeks (OR=2.10, 95% CI: 1.02-4.32, *P*=0.044) were all significantly associated with an increased risk of LMD. The cause-specific Cox proportional hazards model analysis (Table S1) further revealed that among the identified independent risk factors, intraoperative tumor rupture (HR=3.85, *P*<0.001) and meningeal invasion (HR=4.92, P<0.001) were specifically associated with a significant shortening of the time to LMD occurrence. Although primary breast cancer and radiotherapy delay were independent risk factors for the incidence of LMD, they did not significantly accelerate its occurrence time in this cohort.

Recurrence risk prediction models

Based on the independent risk factors identified through multinomial logistic regression, separate risk prediction models for LR, DBR, and LMD were constructed. Only variables that were identified as significant independent risk factors in the multivariate analyses were included in each model. In the training cohort, the AUC for the LR model was 0.78 (95% CI: 0.71-0.85), the DBR model achieved an AUC of 0.74 (95% CI: 0.66-0.82), and the LMD model had the highest AUC of 0.81 (95% CI: 0.73-0.89).

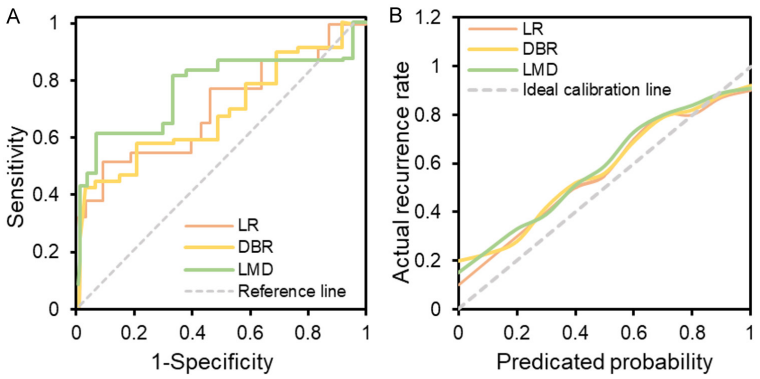

Figure 3. Validation results of the recurrence risk prediction models. A: ROC curve; B: Calibration curve; AUC, area under the curve; DBR, distant brain recurrence; LR, local recurrence; LMD, leptomeningeal disease; ROC, receiver operating characteristic.

Model stability was assessed using five-fold cross-validation, yielding mean AUCs of 0.76, 0.71, and 0.79 for LR, DBR, and LMD, respectively. Calibration curves demonstrated a high concordance between the predicted and observed risks for all three models, and *P* values from the Hosmer-Lemeshow goodness-of-fit test were all >0.05 (**Figure 3**).

Analysis of recurrence patterns stratified by tumor type

Among the 198 patients included in this study, the distribution of primary tumors was as follows: lung cancer, 120 cases (60.6%); breast cancer, 42 cases (21.2%); and other tumors, 36 cases (18.2%). The specific types within the "other tumors" category included: melanoma, 15 cases (7.6%); colorectal cancer, 8 cases (4.0%); renal cell carcinoma, 5 cases (2.5%); gastric cancer, 4 cases (2.0%); and other types, 4 cases (2.0%). Stratification by tumor type revealed significant differences in the incidence of recurrence patterns across subgroups. Among patients with lung cancer (n=120), LR was the most common recurrence pattern (30.0%, 36/120), followed by DBR (21.7%, 26/120), while LMD had the lowest incidence (5.8%, 7/120). Among patients with breast cancer (n=42), 10/42), followed by LMD (21.4%, 9/42) and DBR (14.3%, 6/42). In the group of other tumors (n=36, comprising 15 melanoma cases, 8 colorectal cancer cases, 5 renal cell carcinoma cases, 4 gastric cancer cases, and 4 other types), the incidences of the three recurrence patterns were relatively balanced (LR 27.8%, DBR 19.4%, LMD 22.2%) (Table S2).

Results of univariate analysis stratified by tumor type: Univariate analysis revealed distinct factors associated with recurrence across different tumor types (Table S3).

In the lung cancer subgroup (n=120), LR (n=36) was significantly influenced by tumor diameter >3 cm (*P*=0.012) and lesion proximity to the ventricles or dura mater (P=0.034), with intraoperative tumor rupture showing a trend toward increased LR risk (P=0.083). DBR (n=26) was significantly associated with the presence of ≥3 brain metastases (*P*=0.003), extracranial metastases (*P*=0.029), incomplete resection (P=0.019), and failure to receive WBRT (*P*= 0.025). Due to the limited number of LMD events (n=7), univariate analysis suggested intraoperative tumor rupture (P=0.068) and meningeal invasion (*P*=0.030) as potential risk factors for LMD.

In the breast cancer subgroup (n=42), LMD (n=9) showed significant associations with HER2 positivity (*P*=0.030) and a delay in postoperative radiotherapy ≥4 weeks (*P*=0.032). Intraoperative tumor rupture and meningeal invasion also demonstrated trends toward increased risk (*P*=0.08 and *P*=0.089, respectively). LR (n=10) was associated with tumor diameter >3 cm (*P*=0.047), while DBR (n=6) was associated with the presence of ≥3 brain metastases (*P*=0.039).

In the other tumors subgroup (n=36), characterized by high heterogeneity and limited sample size, the univariate analysis did not identify consistently significant risk factors overall. However, within specific types, LR was associated with proximity to the ventricles or dura mater in melanoma (*P*=0.041), and LMD was associated with intraoperative tumor rupture in colorectal cancer (*P*=0.028). No statistical analysis was performed for tumors with very small sample sizes, such as renal cell carcinoma, as detailed in Table S3.

Results of multivariable analysis stratified by tumor type: Multivariable analysis, incorporating variables with *P*<0.05 from the univariate

analysis as candidates, was performed to identify independent risk factors within each subgroup (Table S4).

In the lung cancer subgroup (n=120), independent risk factors for LR were tumor diameter >3 cm (OR=2.15, 95% CI: 1.18-3.92, *P*=0.012) and proximity to the ventricles or dura mater (OR=1.87, 95% CI: 1.05-3.33, *P*=0.034). The goodness-of-fit of the LR multivariate model was good (Hosmer-Lemeshow test *P*=0.452), with an explained variation (Nagelkerke R^2) of 0.38. For DBR, the presence of ≥3 brain metastases was an independent risk factor (OR=2.74, 95% CI: 1.42-5.29, *P*=0.003). The other factors were not significant, and the goodness-of-fit of the DBR model was good (Hosmer-Lemeshow test *P*=0.521). Due to the limited number of LMD events (n=7), the multivariable model was unstable; only univariate analysis suggested potential risks associated with intraoperative tumor rupture and meningeal invasion.

In the breast cancer subgroup (n=42), independent risk factors for LMD were HER2 positivity (OR=3.28, 95% CI: 1.12-9.61, *P*=0.030) and a delay in postoperative radiotherapy ≥4 weeks (OR=2.45, 95% CI: 1.08-5.56, *P*=0.032). The goodness-of-fit of the LMD multivariate model was good (Hosmer-Lemeshow test *P*=0.387), with an explained variation (Nagelkerke R^2) of 0.45. Due to the limited number of events for LR and DBR, only univariate analyses were informative, indicating an association between LR and tumor diameter >3 cm (*P*=0.047), and between DBR and the presence of ≥3 brain metastases (*P*=0.039).

The subgroup of other tumors (n=36), comprising melanoma, colorectal cancer, renal cell carcinoma, gastric cancer, and others exhibited high heterogeneity and small sample size, leading to unstable multivariable models and precluding the identification of reliable independent risk factors. Univariate analysis indicated an association between LR and proximity to the ventricles or dura mater in melanoma (*P*=0.041), and between LMD and intraoperative tumor rupture in colorectal cancer (*P*= 0.028). The sample size for renal cell carcinoma was too small for statistical analysis.

Performance evaluation of prediction models across tumor types: Based on the aforementioned analyses, risk prediction models for LR, DBR, and LMD were constructed for the lung cancer, breast cancer, and other tumor subgroups. In the lung cancer subgroup, the LR model incorporated tumor diameter >3 cm and proximity to the ventricles or dura mater, achieving an AUC of 0.76 (95% CI: 0.68-0.84), with a sensitivity of 72.2% and specificity of 74.5%. The DBR model, which included only the presence of ≥3 brain metastases, yielded an AUC of 0.73 (95% CI: 0.64-0.82), with a sensitivity of 69.2% and specificity of 70.6%. The LMD model, limited by a low number of events (n=7), showed an AUC of 0.69 (95% CI: 0.55-0.83), indicating limited predictive utility. In the breast cancer subgroup, the LMD model included HER2 positivity and a delay in postoperative radiotherapy ≥4 weeks, demonstrating the best predictive performance with an AUC of 0.83 (95% CI: 0.72-0.94), sensitivity of 77.8%, and specificity of 82.4%. For LR and DBR, which had limited events (LR n=10, DBR n=6), univariate analysis suggested potential associations with tumor diameter >3 cm and ≥3 brain metastases, respectively. The corresponding AUCs were 0.78 (95% CI: 0.65-0.91) for LR and 0.75 (95% CI: 0.61-0.89) for DBR, and these results should be interpreted with caution. For the other tumors subgroup, which included melanoma, colorectal cancer, renal cell carcinoma, gastric cancer, and others, high heterogeneity and limited event numbers resulted in generally modest predictive performance. The AUCs for the LR, DBR, and LMD models were 0.65, 0.72, and 0.70, respectively, and should be considered exploratory. Details are provided in Table S5.

Discussion

A retrospective analysis was conducted on 198 patients who underwent surgery for brain metastases from malignant tumors. The incidences, temporal characteristics, and clinicopathologic risk factors of the three primary postoperative intracranial recurrence patterns - LR, DBR, and LMD - were systematically delineated. Significant biological and prognostic differences among these recurrence patterns were confirmed, and independent risk factors specific to each recurrence type were identified. These findings provide an evidence-based foundation for individualized postoperative risk stratification and informed adjuvant treatment decisions.

LR was the most common postoperative pattern (47.1%), followed by DBR and LMD. Although the incidence of LMD was low (12.1%), its first recurrence occurred significantly later (median 14.6 months), suggesting either spread during surgery or delayed progression of micrometastases after systemic therapy, particularly in breast cancer patients. A 2024 study from the Moffitt Cancer Center reported that WBRT or systemic therapy extended the median onset of breast cancer-related LMD from 5.3 to 14.1 months [24]. Several factors were identified as significant independent risk factors for LR, including large tumor volume (>3 cm), adjacency to the ventricle or dura mater, intraoperative tumor rupture (OR≈3.4), and omission of cavity radiotherapy (OR≈2.5), which were consistent with previous reports [25, 26]. These findings highlight the importance of achieving local control of the surgical cavity. DBR was associated with multiple lesions (≥3), extracranial metastasis, non-gross total resection, and failure to receive WBRT, which markedly reduced intracranial spread (OR≈3), in line with the 2022 ASCO-Society for Neuro-Oncology-American Society for Radiation Oncology recommendations [27]. Risk factors for LMD were more complex; primary breast cancer (OR≈3.6), intraoperative tumor rupture (OR≈2.9), pathological meningeal invasion (OR≈3.3), and a delay in radiotherapy ≥4 weeks (OR≈2.1) were all significantly associated with increased risk. In this study, primary reasons for delayed radiotherapy included postoperative complications (e.g., delayed wound healing), the need to prioritize systemic therapy, and limited accessibility to radiotherapy resources, all of which potentially delayed the initiation of adjuvant treatment. Recent studies have indicated that in breast cancer, especially HER2-positive disease, prolonged survival results in a longer latency period for LMD, whereas intraoperative rupture and meningeal invasion promote subarachnoid spread [28]. A delay in radiotherapy may provide a time window for tumor cell colonization and dissemination. This finding aligns with the 2023 ASCO report, which stated that timely radiotherapy significantly reduces the risk of LMD [29].

The results indicated that lung cancer was predominantly characterized by LR, while breast cancer was prominently associated with LMD, suggesting that the recurrence pathways of these two tumors are fundamentally different. This difference is not incidental but reflects the biological behavior of the primary tumor in brain metastasis. Lung cancer often harbors driver mutations such as EGFR and anaplastic lymphoma kinase, which enhance the tumor cells' ability to degrade the extracellular matrix and migrate by activating the phosphoinositide 3-kinase/protein kinase B/mechanistic target of rapamycin pathway. This makes lung cancer cells more likely to grow locally in the brain through infiltrative growth rather than distant dissemination [30]. Additionally, brain metastases from lung cancer are often located in the supratentorial cortex, near the ventricles or dura mater-areas that are difficult to resect surgically and prone to tumor residue [31]. Residual tumor cells proliferate rapidly in the local microenvironment, ultimately leading to LR. In contrast, HER2-positive breast cancer activates downstream mitogen-activated protein kinase and phosphoinositide 3-kinase pathways through overexpression of HER2/neu, promoting the expression of vascular endothelial growth factor and intercellular adhesion molecule 1 in tumor cells. This enhances their ability to penetrate the blood-brain barrier and adhere to the leptomeningeal matrix [32]. Clinical studies have confirmed that the risk of LMD in patients with brain metastasis from HER2-positive breast cancer is higher than in HER2-negative patients [33], which is consistent with the HR of 3.2 for HER2 positive patients in this study.

The highest rate of en bloc resection was observed in the LR group, likely due to the presence of large lesions adjacent to critical structures, which favored this surgical approach. In contrast, piecemeal resection was performed in 62.5% of LMD cases, and the intraoperative rupture rate reached 41.7%, indicating that piecemeal resection increased the risk of rupture, which was closely linked to LMD development. Even when en bloc resection was performed, avoiding rupture was essential to reduce the risk of LMD. Risk prediction models for LR, DBR, and LMD were constructed by integrating preoperative, intraoperative, and postoperative factors, achieving AUC of 0.78, 0.74, and 0.81, respectively. These models facilitate the identification of high-risk patients and guide treatment decisions. However, the models were

evaluated solely through internal five-fold cross-validation and lacked external validation, so their generalizability remains uncertain. Further verification in multicenter, large-sample cohorts is required. Emphasis should be placed on preventing intraoperative rupture, administering cavity radiotherapy without delay to high-risk LR patients, prioritizing WBRT for high-risk DBR patients, and initiating WBRT promptly alongside targeted therapy for high-risk LMD patients, while tailoring individualized follow-up schedules.

Recurrence patterns and associated risk factors showed significant variation across different primary tumor types. The results indicated that the independent risk factors for LR in lung cancer were tumor size >3 cm and proximity to the ventricles or dura mater. This suggests that incomplete surgical resection is the core driver of LR in lung cancer. Brain metastases from lung cancer with a diameter >3 cm often lack a complete pseudocapsule, making them prone to fragmentation during surgery [34]. Lesions adjacent to the ventricles or dura mater often require a reduced resection margin to preserve neurological function, further increasing the risk of residual tumor. In this study, the incidence of LR in lung cancer patients who received postoperative cavity radiotherapy was significantly reduced, with a notable interaction with tumor size. This supports the mechanism that radiotherapy reduces LR by targeting residual tumor cells locally, consistent with the biological characteristics of local residue driving recurrence in lung cancer [35]. Lung cancer patients most frequently experienced LR, with risk factors including tumor diameter >3 cm and proximity to ventricles or dura mater. DBR was primarily associated with the presence of ≥3 brain metastases, which aligns with the findings of Rashid et al. (2025), who reported significantly increased local recurrence rates after radiotherapy for larger tumor sizes (e.g., ≥2 cm) in brain metastasis patients from Brigham and Women's/Dana-Farber [36]. Breast cancer patients exhibited a significantly higher incidence of LMD compared to other tumor types. LMD was independently associated with HER2 positivity and a delay in radiotherapy ≥4 weeks. The doubling time of HER2-positive breast cancer cells is short, and minimal residual LMD lesions post-surgery can progress from "subclinical" to "clinically visible metastasis" within 4 weeks. Radiotherapy is crucial for suppressing postoperative minimal residual lesions, but breast cancer cells have "time-dependent" sensitivity to radiotherapy. Residual cells may enter the logarithmic growth phase and acquire radiotherapy resistance through epithelial-mesenchymal transition. In this study, the median time to LMD occurrence in the radiotherapy delay group was 5.2 months, significantly shorter than the 11.8 months in the timely radiotherapy group, confirming the importance of "early intervention". This finding corresponds with the natural history studies of LMD in HER2-positive breast cancer by Ratosa et al., which indicated that prolonged survival in the HER2-positive subtype may extend the latency period for LMD development [37, 38]. For other tumor types, due to limited sample size and high heterogeneity, stable predictive factors could not be established. However, some univariate signals suggested potential cancer-specific mechanisms. The prediction models showed good discriminatory ability for LR and DBR in lung cancer (AUC≈0.73-0.76), with the best performance observed for the LMD model in breast cancer (AUC=0.83). Models for other tumor types demonstrated weaker predictive power. These results underscore the tumor type-specific nature of recurrence patterns and suggest that future risk stratification and management strategies should be tailored based on distinct tumor characteristics.

This study was based on the mutually exclusive classification of the first recurrence event. However, it has several limitations that warrant cautious interpretation of the results. First, its single-center, retrospective design may introduce selection and information biases. The limited sample size resulted in insufficient statistical power for some subgroups, particularly the LMD subgroup, which had only 24 events. Although the number of variables in the modeling was strictly controlled, model stability requires validation in larger samples. Second, the follow-up period was relatively short for some patients (minimum of 6 months), while the median time to first recurrence for LMD was later (14.6 months). In accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines [39], later LMD events may not have been fully captured,

potentially leading to an underestimation of the cumulative incidence and an inaccurate median recurrence time. Furthermore, the study was based on mutually exclusive classification of the first recurrence event, and no cases with multiple simultaneous initial recurrence patterns were observed in the cohort. However, patients could experience different recurrence types sequentially over time, suggesting a need for future exploration of potential associations between recurrence types through longitudinal pattern mapping. Another limitation is the considerable variation in the types and efficacy of systemic therapies, which were not fully incorporated into the analysis. Additionally, heterogeneity in molecular marker testing may have influenced the findings' generalizability.

In conclusion, the findings of this study should be interpreted in light of the limitations mentioned above. Future multicenter, large-scale, prospective studies are needed to further validate the risk factors for LMD and other recurrence patterns, explore recurrence patterns across various tumor types and molecular subtypes, assess the impact of novel systemic therapies on recurrence, and incorporate radiomic and liquid biopsy data to develop more precise dynamic prediction models. These models could optimize postoperative individualized risk stratification and inform adjuvant treatment strategies.

Conclusion

This study identified distinct incidence characteristics and independent risk factors for postoperative intracranial recurrence patterns (LR, DBR, and LMD) following surgery for brain metastases from malignant tumors. LR was primarily associated with large tumor volume, proximity to ventricle or dura mater, intraoperative tumor rupture, and omission of cavity radiotherapy. DBR was closely linked to multiple lesions, extracranial metastasis, incomplete gross resection, and the absence of WBRT. Risk factors for LMD included primary breast cancer, intraoperative tumor rupture, meningeal invasion, and delayed radiotherapy. The risk prediction model developed using these factors demonstrated robust performance, offering a foundation for individualized adjuvant therapy and follow-up strategies.

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Disclosure of conflict of interest

None.

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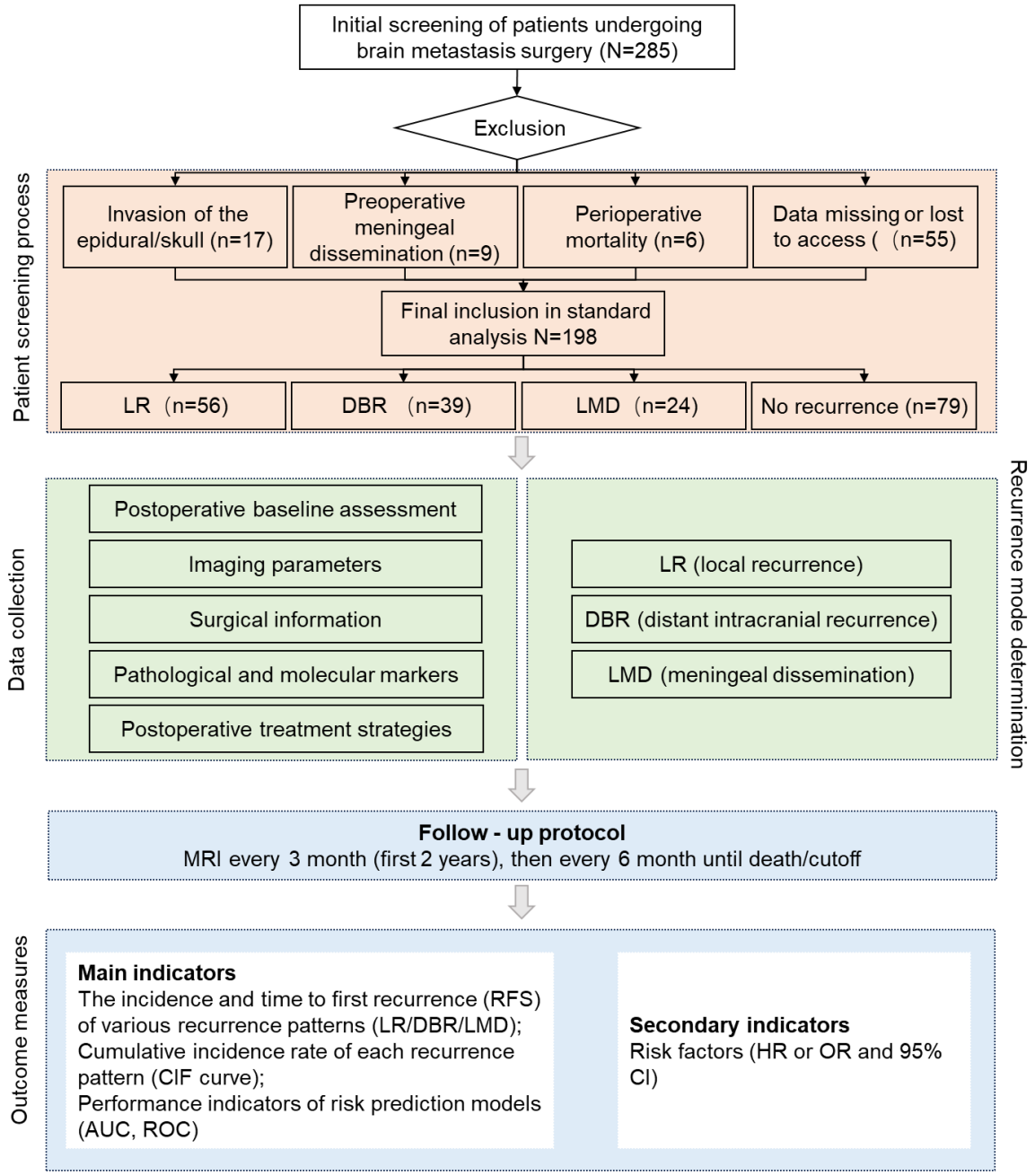

Figure S1. Flowchart for screening research subjects. AUC, area under the curve; DBR, distant brain recurrence; LR, local recurrence; LMD, leptomeningeal disease; ROC, receiver operating characteristic; CIF, cumulative incidence function; RFS, recurrence-free survival; OR, odds ratio; HR, hazard ratio; CI, confidence interval.

Table S1. Results of Cox proportional hazards model analysis based on competing risks

Recurrence type	Risk factor	β	Standard error	Wald X^2	HR (95% CI)	*P*	Proportional hazards assumption test*
LR							
	Maximum lesion diameter >3 cm	0.682	0.263	6.732	1.98 (1.18-3.32)	0.010	0.412
	Adjacency to the ventricle or dura mater	0.751	0.255	8.692	2.12 (1.29-3.49)	0.003	0.387
	Intraoperative tumor rupture	1.178	0.352	11.202	3.25 (1.59-6.63)	0.001	0.305
	Omission of cavity radiotherapy	0.892	0.338	6.972	2.44 (1.26-4.73)	0.008	0.451
DBR							
	Number of lesions ≥3	0.958	0.310	9.552	2.61 (1.43-4.76)	0.002	0.218
	Extracranial metastasis	0.813	0.308	6.967	2.25 (1.23-4.12)	0.008	0.365
	Failure to achieve gross total resection	0.658	0.265	6.171	1.93 (1.15-3.24)	0.013	0.294
	Omission of postoperative whole-brain radiotherapy (WBRT)	1.082	0.382	8.033	2.95 (1.39-6.25)	0.005	0.179
LMD							
	Primary breast cancer	1.281	0.490	6.832	3.60 (1.38-9.40)	0.093	0.102
	Intraoperative tumor rupture	1.348	0.348	15.001	3.85 (1.92-7.72)	<0.001	0.063
	Pathologically confirmed meningeal invasion	1.593	0.405	15.482	4.92 (2.30-10.51)	<0.001	0.088
	Radiotherapy delay ≥4 weeks	0.745	0.366	4.142	2.11 (1.03-4.32)	0.067	0.227

Note: CI, confidence interval; DBR, distant brain recurrence; HR, hazard ratio; LR, local recurrence; LMD, leptomeningeal disease; WBRT, whole-brain radiotherapy.

Table S2. Incidence of recurrence patterns stratified by tumor type

Tumor type	Total cases, n	LR cases, n (%)	DBR cases, n (%)	LMD cases, n (%)	No-recurrence cases, n (%)
Lung cancer	120	36 (30.0)	26 (21.7)	7 (5.8)	51 (42.5)
Breast cancer	42	10 (23.8)	6 (14.3)	9 (21.4)	17 (40.5)
Other tumors*	36	10 (27.8)	7 (19.4)	8 (22.2)	11 (30.6)
Melanoma	15	5 (33.3)	3 (20.0)	2 (13.3)	5 (33.3)
Colorectal cancer	8	2 (25.0)	2 (25.0)	2 (25.0)	2 (25.0)
Renal cell carcinoma	5	2 (40.0)	1 (20.0)	2 (40.0)	0 (0)
Gastric cancer	4	1 (25.0)	1 (25.0)	1 (25.0)	1 (25.0)
Others	4	0 (0)	0 (0)	1 (25.0)	3 (75.0)
Total	198	56 (28.3)	39 (19.7)	24 (12.1)	79 (39.9)

Note: DBR, distant brain recurrence; LR, local recurrence; LMD, leptomeningeal disease.

Table S3. Univariate analysis results by tumor type

Tumor subgroup	Recurrence pattern	Variable	Recurrence group (n=119)	No-recurrence group (n=79)	*OR (95% CI)*	*P*
Lung cancer (n=120)	LR (n=36)	Tumor diameter >3 cm	28/36 (77.8%)	25/51 (49.0%)	2.15 (1.18-3.92)	0.012
		Proximity to the ventricle or dura mater	30/36 (83.3%)	32/51 (62.7%)	1.87 (1.05-3.33)	0.034
		Intraoperative tumor rupture	10/36 (27.8%)	8/51 (15.7%)	1.89 (0.92-3.88)	0.083
		No cavity radiotherapy received	8/36 (22.2%)	6/51 (11.8%)	1.67 (0.78-3.58)	0.187
	DBR (n=26)	≥3 brain metastases	18/26 (69.2%)	15/51 (29.4%)	2.74 (1.42-5.29)	0.003
		Extracranial metastases	22/26 (84.6%)	30/51 (58.8%)	2.12 (1.08-4.16)	0.029
		Incomplete resection	12/26 (46.2%)	10/51 (19.6%)	2.33 (1.15-4.72)	0.019
		No WBRT received	10/26 (38.5%)	8/51 (15.7%)	2.45 (1.12-5.36)	0.025
	LMD (n=7)	Intraoperative tumor rupture	4/7 (57.1%)	8/51 (15.7%)	3.12 (0.92-10.56)	0.068
		Meningeal invasion	3/7 (42.9%)	6/51 (11.8%)	4.25 (1.15-15.70)	0.030
		Radiotherapy delay ≥4 weeks	3/7 (42.9%)	10/51 (19.6%)	2.18 (0.68-6.98)	0.189
Breast cancer (n=42)	LMD (n=9)	HER2 positive	6/9 (66.7%)	5/17 (29.4%)	3.28 (1.12-9.61)	0.030
		Radiotherapy delay ≥4 weeks	5/9 (55.6%)	4/17 (23.5%)	2.45 (1.08-5.56)	0.032
		Intraoperative tumor rupture	4/9 (44.4%)	3/17 (17.6%)	2.67 (0.89-8.01)	0.080
		Meningeal invasion	3/9 (33.3%)	2/17 (11.8%)	2.83 (0.85-9.41)	0.089
	LR (n=10)	Tumor diameter >3 cm	7/10 (70.0%)	5/17 (29.4%)	3.00 (1.02-8.80)	0.047
		Proximity to ventricles/dura mater	6/10 (60.0%)	9/17 (52.9%)	1.33 (0.38-4.61)	0.652
		Intraoperative tumor rupture	2/10 (20.0%)	3/17 (17.6%)	1.17 (0.19-7.21)	0.860
		No cavity radiotherapy received	1/10 (10.0%)	2/17 (11.8%)	0.83 (0.06-11.21)	0.893
	DBR (n=6)	≥3 brain metastases	4/6 (66.7%)	4/17 (23.5%)	6.00 (1.07-33.59)	0.039
		Extracranial metastases	5/6 (83.3%)	8/17 (47.1%)	5.33 (0.58-48.84)	0.144
		Incomplete resection	2/6 (33.3%)	3/17 (17.6%)	2.33 (0.30-18.23)	0.412
		No WBRT received	1/6 (16.7%)	1/17 (5.9%)	3.17 (0.20-50.40)	0.390
Other tumors (n=36)						
Melanoma (n=15)	LR	Adjacency to the ventricle or dura mater	4/5 (80.0%)*	3/10 (30.0%)*	N/C	0.041
Colorectal cancer (n=8)	LMD	Intraoperative tumor rupture	2/2 (100%)*	0/6 (0%)*	N/C	0.028
Renal cell carcinoma (n=5)	-	-	-	-	-	N/A
Gastric cancer (n=4)	-	-	-	-	-	N/A
Other tumors (n=4)	-	-	-	-	-	N/A

Note: CI, confidence interval; DBR, distant brain recurrence; HER2, human epidermal growth factor receptor 2; LR, local recurrence; LMD, leptomeningeal disease; N/A, not applicable; N/C, not calculated; OR, odds ratio; WBRT, whole-brain radiotherapy.

Table S4. Multivariable analysis results by tumor type

Tumor subgroup	Recurrence pattern	Independent risk factor	*β*	*SE*	*Wald* χ^2	*OR (95% CI)*	*P*	*Hosmer-Lemeshow P*	*Nagelkerke* R^2
Lung cancer (n=120)	LR	Tumor diameter >3 cm	0.765	0.302	6.421	2.15 (1.18-3.92)	0.012	0.452	0.38
	LR	Proximity to the ventricles or dura mater	0.626	0.295	4.510	1.87 (1.05-3.33)	0.034	-	-
	DBR	≥3 brain metastases	1.008	0.342	8.692	2.74 (1.42-5.29)	0.003	0.521	0.32
Breast cancer (n=42)	LMD	HER2 positivity	1.188	0.545	4.752	3.28 (1.12-9.61)	0.030	0.387	0.45
	LMD	Radiotherapy delay ≥4 weeks	0.896	0.418	4.592	2.45 (1.08-5.56)	0.032	-	-
Other cancers (n=36)	LR/DBR/LMD	No stable independent risk factors identified	-	-	-	-	-	-	-

Note: CI, confidence interval; DBR, distant brain recurrence; HER2, human epidermal growth factor receptor 2; LR, local recurrence; LMD, leptomeningeal disease; OR, odds ratio.

Table S5. Stratified prediction model performance

Tumor subgroup	Recurrence pattern	Number of predictors	AUC (95% CI)	Sensitivity	Specificity
Lung cancer	LR	2	0.76 (0.68-0.84)	72.2%	74.5%
Lung cancer	DBR	1	0.73 (0.64-0.82)	69.2%	70.6%
Lung cancer	LMD	-	0.69 (0.55-0.83)*	57.1%	68.6%
Breast cancer	LR	-	0.78 (0.65-0.91)*	70.0%	76.5%
Breast cancer	DBR	-	0.75 (0.61-0.89)*	66.7%	70.6%
Breast cancer	LMD	2	0.83 (0.72-0.94)	77.8%	82.4%
Other cancers	LR	-	0.65 (0.50-0.80)*	60.0%	63.6%
Other cancers	DBR	-	0.72 (0.57-0.87)*	57.1%	72.7%
Other cancers	LMD	-	0.70 (0.55-0.85)*	62.5%	64.3%

Note: AUC, area under the curve; DBR, distant brain recurrence; LR, local recurrence; LMD, leptomeningeal disease.