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Prognostic factors following resection of intracranial metastases

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ABSTRACT

Background: The aim of this study was to identify prognostic factors associated with resection of intracranial metastases.

Methods: A retrospective case series including patients who underwent resection of cranial metastases from March 2014 to April 2021 at a single center. This identified 112 patients who underwent 124 resections. The median age was 65 years old (24–84) and the most frequent primary cancers were nonsmall cell lung cancer (56%), breast adenocarcinoma (13%), melanoma (6%), and colorectal adenocarcinoma (6%). Postoperative MRI with contrast was performed within 48 hours in 56% of patients and radiation treatment was administered in 41%. GraphPad Prism 9.2.0 was used for the survival analysis.

Results: At the time of data collection, 23% were still alive with a median follow-up of 1070 days (68–2484). The 30- and 90-day, and 1- and 5-year overall survival rates were 93%, 83%, 35%, and 17%, respectively. The most common causes of death within 90 days were as follows: unknown (32%), systemic or intracranial disease progression (26%), and pneumonia (21%). Age and extent of neurosurgical resection were associated with overall survival ($P < 0.05$). Patients aged >70 had a median survival of 5.4 months compared with 9.7, 11.4, and 11.4 for patients <50, 50–59, and 60–69, respectively. Gross-total resection achieved an overall survival of 11.8 months whereas sub-total, debulking, and unclear extent of resection led to a median survival of 5.7, 7.0, and 9.0 months, respectively.

Conclusion: Age and extent of resection are potential predictors of long-term survival.

Keywords: Brain metastasis, Breast cancer, Nonsmall cell lung cancer, Stereotactic radiosurgery, Whole-brain radiotherapy

INTRODUCTION

The incidence of brain metastases is increasing, likely due to the improved systemic therapies resulting in prolonged overall survival[31,39] and improved radiological techniques, leading to increased diagnosis.[4,5,8,9,31,37,43] On the other hand, improved medical therapies can potentially decrease the incidence of brain metastases.[19] The most common malignancy, leading to brain metastasis, is nonsmall cell lung cancer (NSCLC),[4,5,9,11,28,37,45] followed by breast adenocarcinoma, melanoma, renal cell carcinoma, and colorectal adenocarcinoma.[4,5,8,9,11,14,19,20,28,30-33,37,41,43,45]

Craniotomy and resection of a brain metastasis can prolong overall survival in select patients.[1,4,7,10,11,14,20,26-28,34,41,43,45] Neurosurgeons may also resect metastatic lesions located intraventricularly, those which are durally based, within the pituitary gland and intraosseous within cranial bone. Ideal candidates for surgery include patients with a good performance status diagnosed with a solitary metastasis in a noneloquent area, associated with stable systemic disease.[4,11,27,28,45] Additional advantages of surgical resection include instant relief from symptoms of raised intracranial pressure due to mass effect, treatment of obstructive hydrocephalus without the need for cerebrospinal fluid diversion,[4,26,36,45] to provide histological diagnosis, reduce the need for Dexamethasone, improve functional performance status,[28,35] and facilitate stereotactic radiosurgery (STRS).[35] Surgical resection may not be required in patients with a metastasis <3 cm in maximal diameter, as these lesions can successfully be treated through STRS.[2,21]

MATERIALS AND METHODS

The aim of this study was to identify prognostic factors associated with resection of intracranial metastases. Before data collection, this study was formally registered with the local audit department, the ethics and methodology of the study were reviewed and signed off by the clinical governance lead. A retrospective study was carried out at a single center, Hull Royal Infirmary. Data collection occurred from May 12, 2021, to July 19, 2021. All patients who underwent attempted neurosurgical resection of a cranial metastasis between March 2014 and April 2021 were included in the study. Clinic letters, radiology and histology reports, and operation notes were used for data collection. One hundred and twenty-six patients were identified. However, 14 patients were excluded from the study and the reasons included; no available information, nonmetastatic histological diagnosis such as glioblastoma or lymphoma, biopsy of metastasis, treated through cyst aspiration, and insertion of Ommaya reservoir. Therefore, 112 patients were included who underwent a total of 124 resections. The diagnosis was concluded from the neurosurgical histological result and imaging available to the neuro-oncology multidisciplinary team. Biopsy results for any systemic lesions targeted were not available for analysis as these procedures would have been performed at a different hospital.

Neurosurgery clinic letters describing referral for consideration of whole-brain radiotherapy (WBRT) or STRS were not adequate to be recorded as having received treatment. The treatment reports stating the radiation dose (Gy) and fractions (WBRT) or number of target lesions (STRS) were reviewed to confirm adjuvant radiation administered. The extent of surgical resection was defined as unclear in patients where MRI was contraindicated, if they were too unwell for appropriate investigations, if no MRI was available, or if unable to distinguish residual from recurrent disease. Gross-total resection included cases where a postcontrast MRI did not demonstrate any residual enhancing material whereas cases were classified as sub-total resection if there was a tiny or small volume of enhancing material at the surgical site. Debulking included cases where there was either a large residual or limited resection performed. The extent of surgical resection was formally reported by a neuroradiologist and reviewed by a neurosurgeon.

Statistical analysis was carried out using GraphPad Prism 9.2.0 and $P < 0.05$ was deemed statistically significant. For the survival analysis, 1 month was defined as 28 days. Kaplan–Meier graphs were used and the statistical significance was calculated through the Log rank (Mantel–Cox) test.

RESULTS

The median age was 65 years old (24 to 84). The male-to-female ratio was 1:1.54 with 44 (39%) males and 68 (61%) females. There were 81 patients (72%) with a solitary cranial metastasis, 29 (26%) with multiple intracranial metastases, and in 2 (2%), MRI was contraindicated with only a preoperative CT available. The metastasis location most frequently involved the frontal lobe (frontal, frontoparietal, and frontotemporal [53 patients, 47%]), [Table 1]. Ninety-five (85%) were supratentorial intraparenchymal metastases,

Table 1: Location of the primary neurosurgical target.

	Patients (*n*=112)	
	Left	**Right**
Intrinsic		
Frontal	23 (21%)	24 (21%)
Frontoparietal	2 (2%)	2 (2%)
Frontotemporal	1 (1%)	1 (1%)
Parietal	7 (6%)	9 (8%)
Parieto-occipital	3 (3%)	1 (1%)
Temporal	3 (3%)	5 (4%)
Temporoparietal	2 (2%)	0
Occipital	7 (6%)	5 (4%)
Cerebellar	3 (3%)	2 (2%)
Extrinsic		
Cerebellopontine angle	1 (1%)	
Supratentorial dural based	6 (5%)	
Extradural/intraosseous	1 (1%)	
4th ventricle	1 (1%)	
Left lateral ventricle	1 (1%)	
Pituitary	1 (1%)	
Multiple		
Right parietal bone and left temporal brain	1 (1%)	

5 (6%) were dural based, 2 (2%) were intraventricular, and 1 (1%) was within the pituitary gland. The most common presenting symptoms before dexamethasone treatment included: headaches (32%), motor deficit (31%), speech disturbance (31%), visual deterioration (15%), and seizures (13%), [Table 2].

The primary histological diagnosis was NSCLC in 63 patients (56%) which included one patient with an adenocarcinoma metastasis within a gliosarcoma, breast adenocarcinoma in 14 (12%), melanoma in 7 (6%), colorectal adenocarcinoma in 7 (6%), renal cell carcinoma in 6 (5%), esophageal adenocarcinoma in 4 (4%), endometrial sarcoma in 2 (2%), endometrial adenocarcinoma in 1 (1%), ovarian adenocarcinoma in 2 (2%), bladder transitional cell carcinoma in 1 (1%), anal squamous cell carcinoma in 1 (1%), prostate adenocarcinoma in 1 (1%), ethmoid air sinus adenocarcinoma in 1 (1%), and small cell lung cancer in 2 (2%).

Postoperative MRI with contrast was carried out within 48 hours of surgery in 63 patients (56%), between 3 and 7 days in 6 (5%) and was delayed or not performed at all in 41 patients (37%). MRI scanning was contraindicated in 2 patients (2%). Gross-total resection was achieved in 46 patients (41%), sub-total in 26 (23%), debulking in 9 (8%), and the extent of surgical resection was unclear in 31 patients (28%). Adjuvant STRS to the resection cavity was not carried out. However, 46 (41%) underwent radiation treatment for residual, recurrent, or additional intracranial metastatic disease. This included 27 (24%) who received WBRT, 18 (16%) received STRS, and 1 (1%) who received both WBRT and STRS [Supplementary Figure 1].

Table 2: Preoperative clinical presentation.

	Patients (*n*=108)*	Symptom	Patients (*n*=108)*
Motor deficit**	34 (31%)	Facial asymmetry	8 (7%)
		Limb weakness	31 (29%)
Visual deterioration	16 (15%)	Visual field deficit	14 (13%)
		Reduced visual acuity	4 (4%)
Seizures	14 (13%)	Tonic–clonic seizures	8 (7%)
		Focal seizures	4 (4%)
		Absence seizures	1 (1%)
		Nocturnal seizure	1 (1%)
Speech disturbance	33 (31%)	Dysphasia	14 (13%)
		Confusion	18 (17%)
		Dysarthria	4 (4%)
Reduced mobility	19 (18%)	Ataxia	2 (2%)
		Gait disturbance	3 (3%)
		Impaired limb coordination	5 (5%)
		Impaired balance	3 (3%)
		Falls	7 (6%)
Headaches			35 (32%)
Vomiting			4 (4%)
Nystagmus			1 (1%)
Dysgraphia			1 (1%)
Hearing loss			1 (1%)
Sensory deficit			3 (3%)
Low conscious level			2 (2%)
Personality change			10 (9%)
Memory loss			7 (6%)
Unintentional weight loss			1 (1%)
Reduced appetite			1 (1%)

**Missing information on the clinical presentation of 4/112 (4%) patients from the total sample size. *Neurological deficits were before administration of dexamethasone

Of the total 112 patients, 10 (9%) underwent further resections of brain metastases, including 10 redo resections for recurrence at the surgical site and two resections of discrete lesions at a different intracranial site [Table 3]. Of the 124 tumor resections, 9 (7%) returned to theater for emergency neurosurgical intervention which included evacuation of intracranial hematoma (3, 2%), washout of brain abscess or subdural empyema (5, 4%), and decompressive craniectomy (1, 1%). There were 3 (2%) arterial territory cerebral infarcts and 4 (3%) new symptomatic venous thromboembolic events [Table 4]. The surgical mortality (death within 30 days due to an operative complication) was 1/124 (<1%).

At the time of data collection, 26/112 (23%) were still alive and the median follow-up for those patients was 1070 days (68–2484). Including the total patient cohort, the rates of overall survival were as follows: 1 month = 93%, 6 months = 58%, 1 year = 35%, and 5 years = 17%, with a median survival of 233 days [Figure 1]. Of the 19 patients who died within 90 days of surgery, 5 (26%) had respiratory failure (causes included pneumonia, pulmonary embolism, and mediastinal lymphadenopathy), 5 (26%) had cancer progression (three had new systemic metastases and two had new intracranial metastases), and 6 (32%) had an unknown cause of death [Table 5].

Of the 10 patients who underwent redo resection and/or resection of an additional cranial metastatic lesion [Table 3], 5 (50%) were alive at the time of data collection with a median follow-up of 1377 days (1099–2848). The median overall survival including all 10 patients was 1101 days (101–2848).

Age was significantly associated with survival (Log rank [Mantel–Cox] $P = 0.009$), with an age >70 being a negative prognostic predictor of survival [Table 6]. Extent of neurosurgical resection was significantly associated with survival (Log rank [Mantel–Cox] $P = 0.022$), with gross-total resection being a positive predictor of survival. Squamous subtyping of NSCLC was a negative predictor of survival (Log rank [Mantel–Cox] $P = 0.048$) [Figures 1 and 2]. On recursive partitioning analysis [Figure 3] using extent of resection and age, age <70 and confirmed gross-total resection yield a median survival of 27.5 months which was statistically significant (Log rank [Mantel–Cox] $P = 0.0001$).

Table 3: Redo resection for recurrent intracranial metastatic disease.

Age	Primary cancer	Secondary location	Extent of primary resection	Radiation treatment	Days from primary resection to further neuro-oncological surgery		Overall survival (days)
					Redo resection (s)	Different metastasis	
54	Colorectal adenocarcinoma	Left frontal	Unknown*	None	157	-	2484 (Alive)
69	Breast adenocarcinoma	Left occipital	Unknown**	None (Was referred for WBRT)	884, 1236	-	1402 (Deceased)
66	NSCLC	Right frontal	Gross total	Yes (WBRT after 2nd surgery)	-	126	1700 (Alive)
57	NSCLC	Right frontal	Sub-total	None (was referred for STRS)	50	-	101 (Deceased)
69	NSCLC	Right temporal	Gross total	None	238	-	1377 (Alive)
42	Breast	Right occipital	Gross total	None	1068	-	1103 (Alive)
37	Esophageal adenocarcinoma	Right cerebellum	Debulking	Yes (STRS after primary surgery, received 6x STRS in total)	483	14	1099 (Alive)
60	Renal cell carcinoma	Right frontoparietal	Debulking	None (Not suitable for STRS as tumor invaded into wound)	76	-	195 (Deceased)
84	Endometrial adenocarcinoma	Left frontal	Sub-total	None	628	-	972 (Deceased)
70	NSCLC	Right temporal	Gross total	Yes (WBRT after 2nd surgery)	206	-	345 (Deceased)

NSCLC: nonsmall cell lung cancer, WBRT: whole-brain radiotherapy, STRS: stereotactic radiosurgery. *MRI demonstrating metastatic disease was performed at day 45 postoperatively, therefore unable to determine if this was residual disease following sub-total resection or recurrent disease following gross-total resection. **No postoperative MRI

DISCUSSION

Our study demonstrated that achieving gross-total resection can lead to prolonged survival. However, there was a large number of patients (37%) where MRI scanning was either delayed or not performed at all, resulting in patients with an unclear extent of surgical resection. Neurosurgical services in England are commissioned by the National Health Service (NHS) based on guidelines written by the National Institute for Health and Care Excellence (NICE).[23] At present, NICE recommends MRI scanning within 72 hours of resection of malignant gliomas; however, this is not the case for brain metastases. It is common practice at Hull Royal Infirmary to perform an intraoperative ultrasound to evaluate the extent of resection; however, these results were not available for analysis. The long-term radiological follow-up was not assessed in our study. Our current protocol is MRI scanning every 3 months if residual disease is identified; however, once adjuvant STRS is completed the radiological follow-up is managed by the primary oncologist.

Schackert *et al*. found in their series of 127 patients; gross-total resection was associated with a longer duration of survival when compared to those with a residuum and median survivals of 10.6 and 5.8 months, respectively.[34] Olesrud *et al*. found in their study of 68 patients; no residual tumor, nonmeasurable residual tumor, and measurable residual tumor were associated with median survivals on 12.0, 9.5, and 5.6 months, respectively.[25] Sivasanker *et al.* found in their series of 124 patients; those who achieved gross-total resection had a median survival of 12.5 months and those who did not survived for a median of 4.2 months; however, this did not reach statistical significance.[38] Tendulkar *et al.* showed in their study of 271 patients; a median survival of 10.6 months following gross-total resection compared to 8.7 following subtotal resection; however, this did not reach statistical significance.[42] On the other hand, Jünger *et al*. found no difference in overall survival when comparing gross-total versus subtotal resection in 197 patients.[15]

Fluorescence-guided surgery using 5-aminolevulinic acid (5-ALA) has been shown to increase the likelihood of achieving gross-total resection in glioblastoma multiforme.[40] 5-ALA-guided resection of cerebral metastases has been attempted; however, the rate of tumor fluorescence is variable and its utility remains unclear.[12,16,17,44] Supramarginal resection can also be performed to reduce the probability of residual tumor; however, this is not common

Table 4: Postoperative complications and return to theater.

	Tumor resections (*n*=124)	Details		Postoperative day	Duration of survival (days)
Arterial territory infarct*	3 (2%)	Left posterior cerebral		2	160 (Deceased)
		Left anterior cerebral		2	1147 (Alive)
		Right anterior cerebral[1]		1	56 (Deceased)
Intracranial hemorrhage	3 (2%)	Extradural hematoma		2	252 (Deceased)
		Intracerebral hematoma		1	88 (Deceased)
		Intracerebral and intraventricular hematoma		0	11 (Deceased)
Surgical site infection**	5 (4%)	Brain abscess[1]		44	56 (Deceased)
		Brain abscess		69	124 (Deceased)
		Brain abscess		47	129 (Deceased)
		Subdural empyema[2]		28	1377 (Alive)
		Subdural empyema		12	145 (Deceased)
Cerebral edema	2 (2%)	Intraoperative brain swelling, prophylactic craniectomy. Returned for autologous bone cranioplasty		8	125 (Alive)
		Decompressive craniectomy[3]		3	97 (Alive)
Ventriculoperitoneal shunt inserted for hydrocephalus	4 (3%)	Location of metastasis excised	4th ventricle	12	129 (Deceased)
			Left temporal[2]	303	1377 (Alive)
			Right cerebellar	265	303 (Deceased)
			Lateral ventricle[3]	49	97 (Alive)
Venous thromboembolism**	4 (3%)	Pulmonary embolism[1]		6	56 (Deceased)
		Pulmonary embolism		8	37 (Deceased)
		Deep vein thrombosis		3	208 (Deceased)
		Deep vein thrombosis		34	100 (Deceased)

*As stated by the postoperative MRI. Extent of neurological deterioration not documented. Does not include patients with small areas of restricted diffusion adjacent to the surgical resection site. **All patients returned to theater for drainage of intracranial pus and removal of infected bone flap. ***Does not include two patients who were diagnosed and anti-coagulated preoperatively and one patient who was found to have an incidental, asymptomatic pulmonary embolism on a staging CT chest/abdomen/pelvis scan 59 days following surgery. [1]The same patient, [2]the same patient, [3]the same patient

practice in the UK.[29] Intraoperative imaging modalities such as ultrasound can be used to facilitate gross-total resection.[6]

Our study demonstrates that redo resection can be safely performed in patients with recurrent intracranial metastases with good overall survival. However, earlier detection of recurrent disease and treatment with STRS could obviate the need for redo resection. 2/10 patients who underwent redo resection had an unknown extent of resection following their primary surgery. On the other hand, 4/10 of those who underwent redo resection had an MRI scan demonstrating gross-total resection following the primary surgery [Table 3]. Recurrence at the surgical site following gross-total resection could be due to new metastasis through disruption to the blood–brain barrier in the area, or it could be due to local residual tumor cells within the surrounding brain parenchyma which do not enhance during the contrast MRI. Yoo *et al*. demonstrated that extended microsurgical resection into the adjacent brain parenchyma of metastases located in noneloquent areas can significantly reduce the recurrence rate when compared to gross-total resection.[45] STRS to the resection cavity is routinely performed in some countries with the aim of reducing recurrent disease following gross-total resection;[3,15] however, this is not commissioned in the UK and STRS is mostly used for residual disease and concurrent metastatic lesions.[22]

Our study is limited by lacking postoperative Karnofsky performance status; this is likely a prognostic predictor of survival and can also affect a patient's suitability for adjuvant radiation treatment. There was no patient reported quality of life assessment. Furthermore, we do not state the value in symptomatic relief provided by surgical resection, such as relieving headaches or improving neurological deficits secondary to mass effect and cerebral edema. We also do not present the details of systemic treatments such as chemotherapy, as this service is managed in a different hospital.

The dose and duration of dexamethasone administration are missing. Dexamethasone can provide symptomatic relief and reduce the risk of neurological deterioration while awaiting surgery. Hutchinson *et al*. showed in a randomized controlled clinical trial that dexamethasone was associated with a higher incidence of unfavorable outcome (moderately severe disability to dead) in patients with chronic subdural hematoma; in particular, dexamethasone was associated with a higher incidence of infection.[13] While these results may

Table 5: Patients who died within 3 months of neurosurgical intervention.

Age (Years)	Extent of intracranial disease	Secondary location	Extent of resection	Primary cancer	Survival (days)	Cause of death
70	Multiple	Left occipital	No postoperative MRI	Small cell lung cancer	37	Respiratory failure. Pulmonary embolism with community acquired pneumonia. Intracranial metastatic disease progression
71	Solitary	Right frontal	Gross total	Small cell lung cancer	89	Unknown
67	Multiple	Left cerebellum	Gross total	NSCLC	47	Unknown
63	Solitary	Right frontoparietal	No postoperative MRI	NSCLC	88	Unknown
58	Multiple	Left temporoparietal	Increased tumor volume	NSCLC	52	Intracranial metastatic disease progression
70	Solitary	Left frontal	Gross total	NSCLC	19	Acute pancreatitis
72	Solitary	Left temporal	No postoperative MRI	NSCLC	13	Bowel perforation, peritonitis, and sepsis
74	Solitary	Right parietal	Gross total	NSCLC	39	Respiratory failure. Community acquired pneumonia on a background of pulmonary fibrosis
74	Solitary	Right frontotemporal	Sub-total	NSCLC	81	Unknown
59	Solitary	Left frontal	No postoperative MRI	NSCLC	20	Respiratory failure. Hospital acquired pneumonia with ongoing heavy cigarette smoking
68	Solitary	Right frontal (hemorrhagic)	No postoperative MRI	NSCLC	10	Respiratory failure. Hospital acquired pneumonia on a background of severe COPD. Developed atrial fibrillation due to sepsis.
60	Solitary	Right frontal	No postoperative MRI	NSCLC	87	Unknown
62	Solitary	Left occipital	Gross total	NSCLC	76	Systemic disease progression with metastases to liver and myocardium and intracranial disease progression
46	Multiple	Right frontal	Gross total	Melanoma	56	Postoperative complication. Anterior cerebral artery territory infarct, surgical site infection with intracerebral abscess, venous thromboembolism
78	Multiple	Right frontal	Gross total	Esophageal adenocarcinoma	27	Unknown
74	Multiple	Left temporal	Gross total	Breast adenocarcinoma	23	Systemic disease progression with liver, spleen, kidney, and lung metastases
63	Solitary	Pituitary	Debulking	Colorectal adenocarcinoma	57	Systemic disease progression with liver metastasis and diabetes insipidus due to pituitary dysfunction
71	Solitary	Left parietal (hemorrhagic)	No postoperative MRI	Renal cell carcinoma	54	Respiratory failure. Mediastinal lymphadenopathy and pleural effusion
62	Solitary	Left frontal	No postoperative MRI	Endometrial sarcoma	11	Postoperative complication. Intracerebral hematoma with intraventricular extension

NSCLC: Nonsmall cell lung cancer

not be applicable to neuro-oncology patients; in our study, 4% died within 90 days of surgery due to pneumonia and 4% returned to theater due to surgical site infection.

Data on cigarette smoking were missing from our study. Concurrent cigarette smoking increases the risk of surgical site infection, pneumonia, and perioperative

Table 6: Survival analysis.

	Patients	Median survival		*P* value
		Days	Months (28 day)	Log rank (Mantel-Cox)
Total sample	112	233	8.3	-
Gender				
Male	44 (39%)	160	5.7	0.051
Female	68 (61%)	259	9.3	
Age				
<50	14 (13%)	272	9.7	0.009
50–59	22 (20%)	320	11.4	
60–69	43 (38%)	319	11.4	
>70	33 (29%)	151	5.4	
Intrinsic cerebral lesions				
Preoperative seizures				
Yes	13 (12%)	215	7.7	0.980
No	83 (74%)	235	8.4	
Location				
Frontal	48 (43%)	215	7.7	0.065
Frontoparietal	4 (4%)	145	5.2	
Frontotemporal	2 (2%)	170	6.1	
Parietal	15 (13%)	1033	36.9	
Parieto-occipital	4 (4%)	171	6.1	
Occipital	12 (11%)	181	6.5	
Temporal	9 (8%)	330	11.8	
Temporoparietal	2 (2%)	315	11.2	
Hemisphere				
Left	49 (44%)	215	7.7	0.575
Right	47 (42%)	241	8.6	
Primary cancer histology				
NSCLC*	64 (65%)	208	7.4	0.849
Breast adenocarcinoma	14 (14%)	303	10.8	
Colorectal adenocarcinoma	7 (7%)	349	12.5	
Melanoma	7 (7%)	160	5.7	
Renal cell carcinoma	6 (6%)	326	11.6	
NSCLC				
Nonsquamous	56 (87%)	214	7.6	0.048
Squamous	8 (13%)	152	5.4	
Number of intracranial metastases				
Solitary	81 (74%)	259	9.3	0.165
Multiple	29 (26%)	160	5.7	
Radiation treatment				
STRS or WBRT	41 (37%)	319	11.4	0.129
None	71 (63%)	185	6.6	
Extent of resection				
Gross total	46 (41%)	330	11.8	0.022
Sub-total	26 (23%)	160	5.7	
Debulking	9 (8%)	195	7.0	
Unclear	31 (28%)	252	9.0	

*Included one patient with a lung adenocarcinoma which had metastasized into a CNS gliosarcoma. NSCLC: Nonsmall cell lung cancer, STRS: stereotactic radiosurgery, WBRT: whole-brain radiotherapy

mortality.[18,24] Cigarette smoking can also cause other medical comorbidities such as chronic obstructive pulmonary disease which could contribute to poor clinical outcome. In our study, squamous NSCLC carried a shorter duration of survival than nonsquamous NSCLC ($P = 0.048$), this could potentially be explained by the greater association between cigarette smoking in squamous NSCLC than adenocarcinoma.

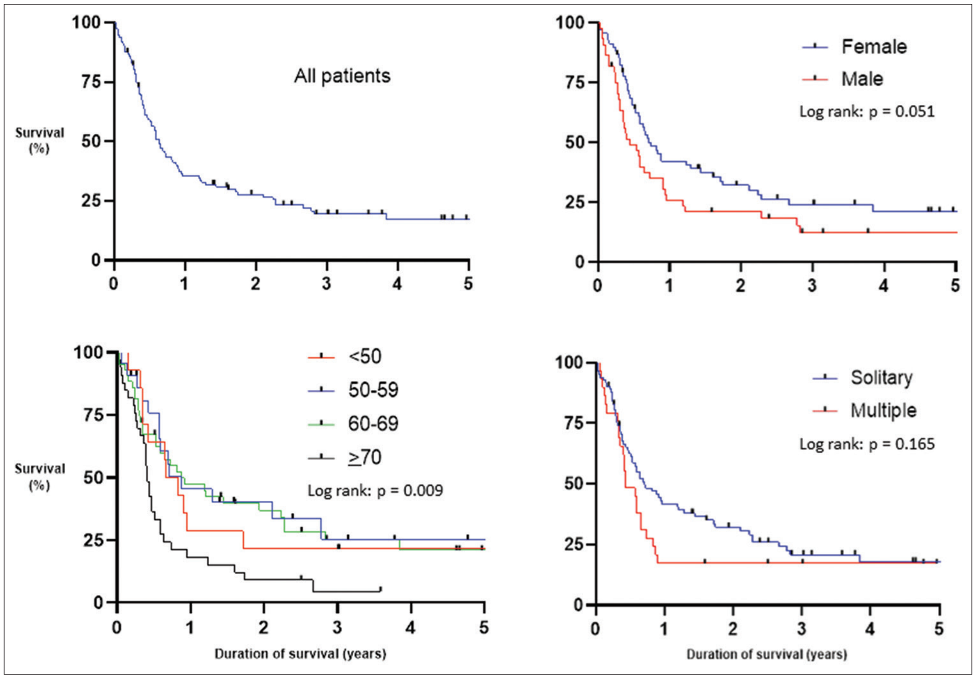

Figure 1: Kaplan–Meier graphs for survival analysis including all patients and then stratified by gender, age, and multiplicity of intracranial disease (median survivals and *P* values are displayed in Table 6).

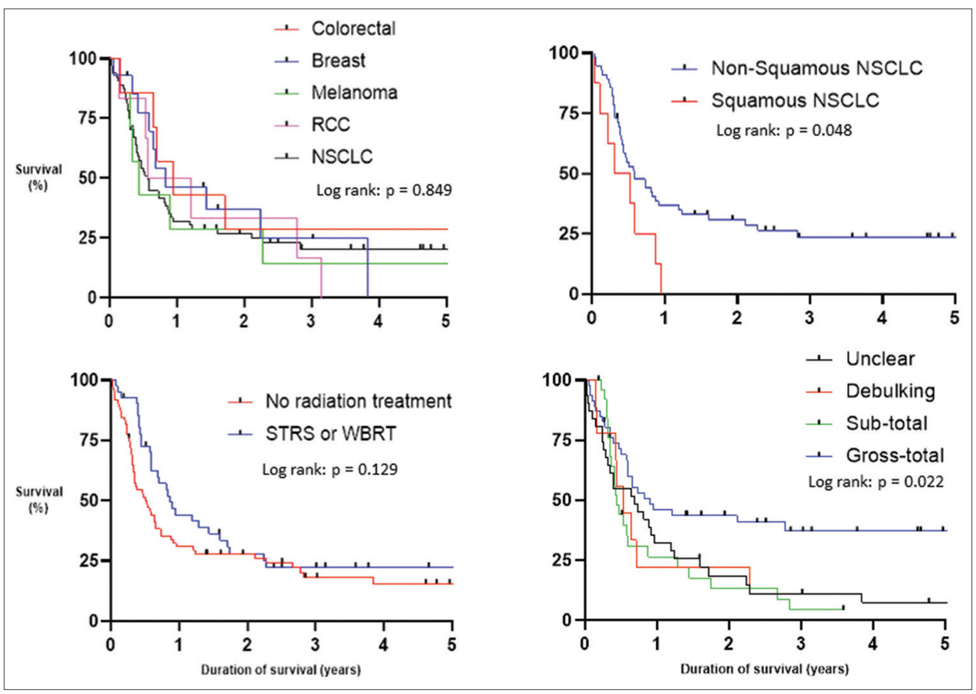

Figure 2: Kaplan–Meier graph for survival analysis stratified by histological diagnosis, adjuvant radiation treatment, and extent of neurosurgical resection (median survivals and *P* values are displayed in Table 6).

Death due to an unknown cause within 90 days of surgery occurred in 5% of the patients. These patients could have potentially died of a preventable cause such as surgical site infection, seizures, or venous thromboembolism. However, these patients may have chosen to not undergo further hospital admission, to focus on palliative symptomatic relief in their home. Furthermore, postmortem investigations are seldom performed in patients with metastatic cancer

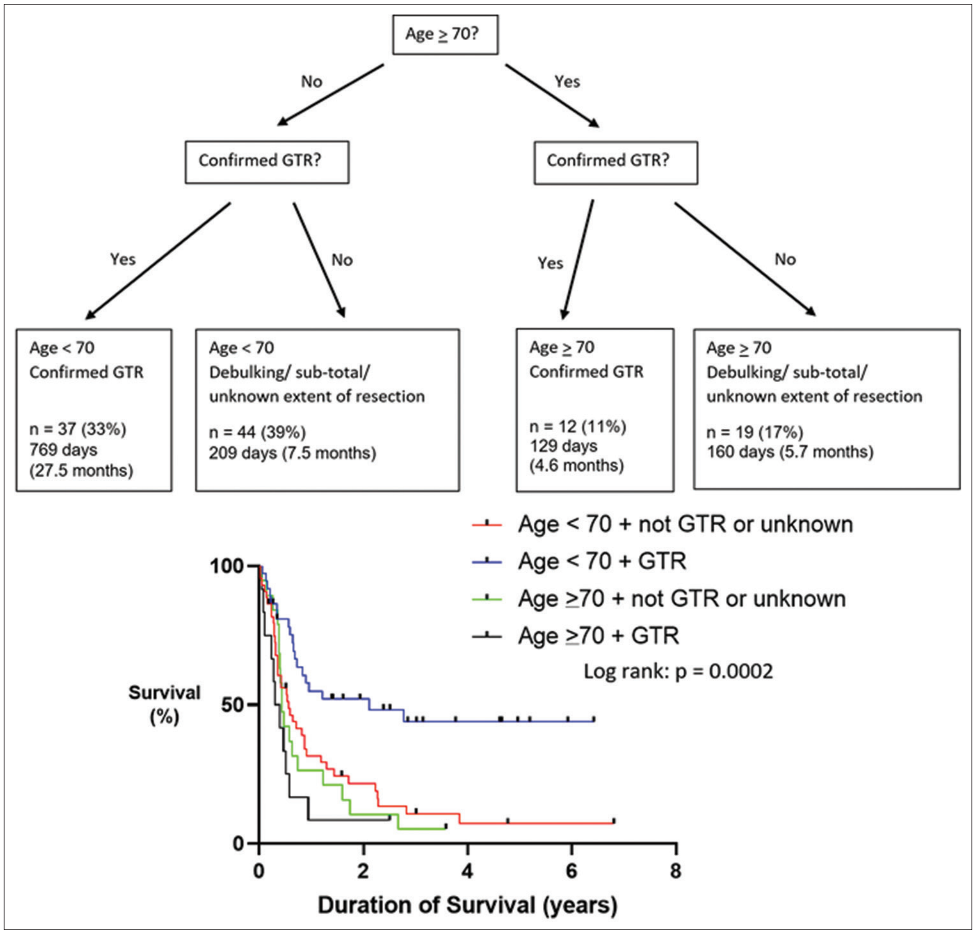

Figure 3: Recursive partitioning analysis using age and extent of resection. GTR: Gross-total resection.

because it often does not add helpful information to the family members and can cause distress. While this is understandable, it is difficult to improve our service when there is missing information on the causes of postoperative death.

During the time period of data collection, there has been a change in the preferred adjuvant radiation treatment in our service. In 2017, Brown *et al*. demonstrated that when compared against WBRT, STRS is associated with a longer duration of cognitive-deterioration-free survival and no difference in overall survival for patients undergoing adjuvant radiation treatment to the surgical cavity following resection of a solitary brain metastasis.[3] Our study includes patients who underwent surgery between March 2014 and April 2021, and in the early years, WBRT was common practice; however, currently, STRS is most frequently used. As our study was retrospective, it did not include cognitive-deterioration-free survival as an outcome. A significant number of patients did not receive cranial radiation treatment and potential explanations for this include; the patient died before treatment was administered, patient choice, radiation treatment not offered in cases where a solitary metastasis had been completely resected as this is not recommended by NHS England, and logistical errors as the service transitioned from WBRT to STRS as these treatments are carried out by different clinical teams working in separate hospitals.

Given the impact of the COVID-19 pandemic on neuro-oncology services in the UK (37), this could have led to a reduction in overall survival for some patients in this study.

CONCLUSION

Cranial metastatic disease represents a heterogeneous patient population with multiple factors influencing the clinical outcome, therefore, when considering neurosurgical intervention, each case should be considered on an individual basis. There are ongoing advancements, with new medical therapies becoming available for different types of cancer in which neurosurgeons may not be aware of. Therefore, input from oncologists who treat the primary disease is crucial when selecting patients who would be suitable candidates for neurosurgical intervention. Early postoperative MRI scanning is recommended to identify residual tumor or new discrete lesions which could benefit from adjuvant STRS. If required, redo resection can successfully be performed with benefits to overall survival. In our study, age and extent of surgical resection were prognostic predictors of survival.

Declaration of patient consent

Patient's consent not required as patient's identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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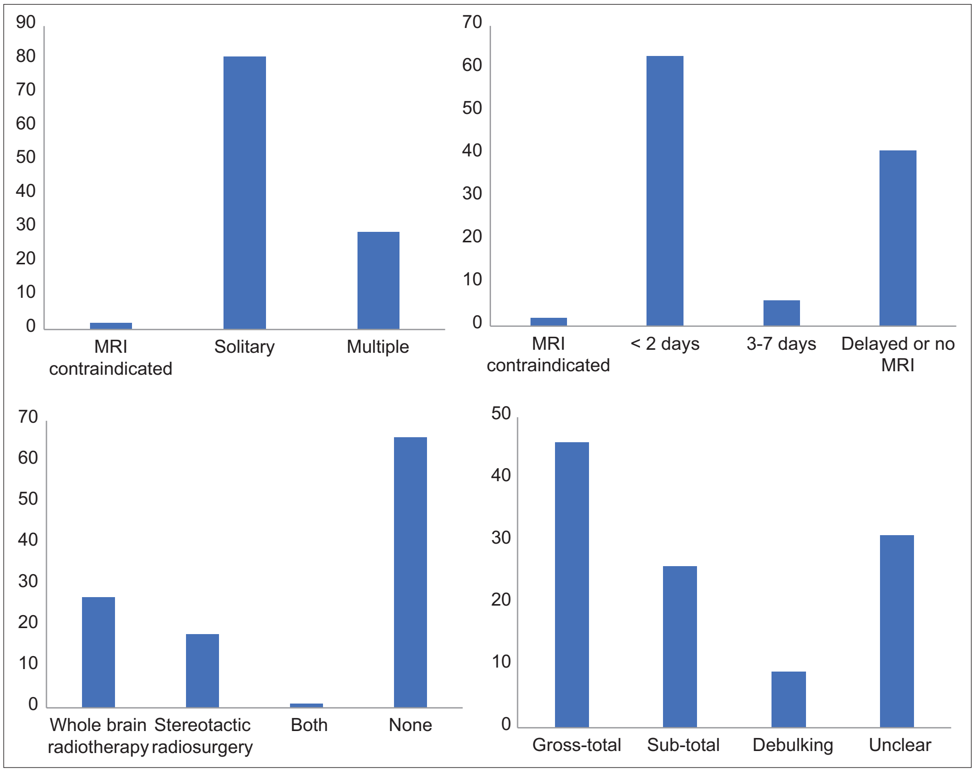
SUPPLEMENTARY FIGURE



Supplementary Figure 1: Bar charts showing multiplicity of intracranial disease, day postoperative MRI performed and extent of resection and adjuvant radiation treatment.