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## Clinical Study

## Survival of patients following neurosurgical treatment of colorectal adenocarcinoma metastasis in the Northern Sydney–Central Coast area

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**Abstract**

Cerebral metastases from gastrointestinal primaries constitute about 3–5% of surgically resected brain secondaries. There has been a paucity of regional and worldwide data concerning the survival and clinical course of patients undergoing neurosurgical treatment of cerebral metastases from colorectal origin. The clinical course and survival of 32 patients undergoing neurosurgical intervention for colorectal carcinoma metastases between 1999 and 2007 was examined. The 21 male and 11 female patients examined had a median age of 61.8 years at diagnosis of colorectal cancer; median interval between colorectal cancer diagnosis and cerebral metastatic disease was 27.6 months; and 88% of patients underwent microsurgical resection. Median survival from neurosurgical intervention was 7.5 months. Perioperative mortality was 3%. Age, gender and infratentorial location of lesions had no significant impact on survival. Patients undergoing whole brain radiotherapy (WBRT) had a significantly longer survival than those not undertaking this treatment (median survival 10.6 vs. 5.2 months,  $p = 0.018$ ). A randomised, controlled trial of the utility of WBRT following surgical resection in this tumour subtype seems appropriate.

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**Keywords:** Brain metastases; Colorectal carcinoma; Neoplasms; Surgical resection; Survival

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**1. Introduction**

Metastatic disease to the central nervous system (CNS) is common among cancer sufferers. At the time of death about 10–25% of cancer sufferers have metastases to the CNS. Metastatic disease often comes to the attention of the neurosurgeon due to symptoms of raised intracranial pressure, seizures or focal neurological deficit in a patient with a known diagnosis of cancer. These symptoms may also be the first stage of an eventual diagnosis of advanced, systemic carcinoma. Other patients may present as the result of staging or surveillance investigations in

otherwise asymptomatic individuals. The clinical course of patients who undergo neurosurgical interventions for metastatic disease is best characterised for primary carcinoma of the breast, non-small cell carcinoma of the lung and melanoma primaries. Adenocarcinoma from colonic and other glandular epithelia constitute a relatively small percentage of total CNS metastatic disease coming to neurosurgical treatment; it is the fifth most common source of brain metastasis behind lung, breast, melanoma and renal primaries. Adenocarcinoma of the colon is, however, a common cause of cancer morbidity and mortality in our community but there is a lack of Australian and worldwide data on colonic metastasis managed with neurosurgery. The largest series of surgically treated, colorectal brain metastasis suggested a median survival time of 8.3 months.<sup>1</sup>

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We present our series of neurosurgically managed colorectal metastasis to assist neurosurgeons in their counselling of patients.

## 2. Aims

We aimed to identify patients who had neurosurgical CRC intervention for colorectal adenocarcinoma metastasis in the Northern Sydney / Central Coast Area Health Service (NSCCAHS) by using the Sydney Neuro-Oncology Database (SNOG) and to assess survival outcomes with regard to age at surgical intervention, Karnofsky performance status (KPS), site and extent of CNS metastatic disease and other factors. This study was undertaken to provide some disease-specific information to surgeons to assist them in clinical decision-making and guide patient and family counselling.

## 3. Materials and methods

We obtained approval for this study from the Human Research and Ethics Committees (HREC) of the participating institutions. The databases were analysed using diagnostic reference group codes to identify all patients within NSCCAHS with a diagnosis of craniotomy for metastasis from colorectal adenocarcinoma from 1999 onwards. This included the use of the SNOG Database and the Department of Neurosurgery Database, Royal North Shore Hospital (RNSH). We included all patients who were either admitted by a neurosurgeon or had an inpatient referral and care of a neurosurgeon with a therapeutic intent. All patients had a histopathological diagnosis of adenocarcinoma from colorectal origin. Patients undergoing neurosurgical resection or biopsy had a confirmed pathological diagnosis of colorectal adenocarcinoma. We also included patients who were admitted to the neurosurgical unit with an established diagnosis or a likely diagnosis of CNS colorectal metastasis on clinical grounds and not specifically undergoing resective surgery. Patients undergoing cerebrospinal fluid (CSF) diversion or tumor cyst drainage were also included.

Case-by-case survival was derived from the SNOG and hospital medical record data. Data on patients who were alive at the census date of 1 May 2007 were analysed by survival to that date. The Kaplan–Meier survival analysis was used to generate survival curves and estimate median survival times. We used the log-rank test to compare survival curves for samples split by age, metastasis location, treatment with or without whole brain radiotherapy (+/– WBRT) and KPS > 70 using Stata Data Analysis and Statistical Software Version 8.2 (Stata Corp, College Station, Texas, USA).

## 4. Results

From analysis of the SNOG database, 32 patients were identified from 1999 to 2007 comprising 11 females and 21

males. The median age of the patients at the diagnosis of cerebral metastasis was 65.5 (range 42–84) years and the median age of all patients at the diagnosis of colorectal cancer was 61.75 years. Mean age at diagnosis of CNS metastasis of males was 68.6 years and of females 58.2 years (Table 1).

The primary tumour was located in the colon in 17 patients (53%), the rectum in 10 patients (31%) and was of unknown colorectal location in 5 (16%). The median time

Table 1  
Characteristics of patients with brain metastases from colorectal carcinoma (CRC)

Factor	No.	Mean survival (months)	Median survival (months)	P-value (log-rank)
Female	11	8.46	7.5	0.18
Male	21	8.84	7.88	0.18
Female – mean age at diagnosis of colorectal	55.9			
Male – mean age at diagnosis of CRC	65.8			
Female – mean age at diagnosis of brain metastasis	58.2			
Male – mean age at diagnosis of brain metastasis	68.6			
KPS ≤ 70 at diagnosis of brain metastasis	13	6.83		0.18
KPS > 70 at diagnosis of brain metastasis	19	9.8		0.18
Mean interval from diagnosis to brain metastasis (months)	31.3			
<i>Multiplicity</i>				
Single	23			
Multiple	9			
<i>Location</i>				
Supratentorial	22	9.08	7.7	0.218
Infratentorial	10	6.9	6.37	0.185
<i>Greatest diameter of lesion</i>				
> 3 cm	13	8.4	7	0.85
< 3 cm	14	9.3	8.4	0.85
<i>Neurosurgical intervention</i>				
Stereotactic microsurgical resection	28			
FNAB other organ	2			
Palliation	2			
<i>Whole brain radiotherapy</i>				
No	11	5.44	5.17	0.016
Yes	16	11.06	10.6	0.016
Following surgery	12			
At relapse following surgery	2			
Following relapse surgery	2			
<i>Multiple craniotomy</i>				
Yes	6	12.9		0.099
No	26	8.63		0.099
<i>Survival (months)</i>				
From primary diagnosis		38.24	29.8	
From neurosurgical intervention		8.24	7.57	

KPS = Karnofsky performance score. FNAB = Fine needle aspiration biopsy.

interval between diagnosis of colorectal carcinoma and cerebral metastasis was 27.6 months (mean 31.3 months). The median survival time from the initial diagnosis of colorectal carcinoma was 29.8 months (mean 38.2 months). The overall median survival time from surgical consultation and neurosurgical intervention for cerebral metastasis was 7.57 months (mean 8.24 months). Fig. 1 illustrates the Kaplan–Meier curves for overall survival measured from neurosurgical intervention and from the primary diagnosis of colorectal cancer.

Details pertaining to the initial colorectal surgery were unavailable for many patients due to original treatment at other institutions. The stage of the patients at initial surgery according to the Dukes classification (where available) was Dukes B (2 patients), Dukes C (7 patients, 22%), Dukes D (11 patients, 34%) and unknown in 12 patients (38%). At the time of consultation for surgical resection of cerebral metastasis, hepatic metastases were present in 14 patients (44%) (unknown in 15%) and pulmonary metastases were present in 13 patients (41%) (unknown in 25%).

Perioperative mortality (within 30 days) occurred in one patient who died at 7 days due to progressive systemic disease during palliation. One patient died at 44 days due to venous thromboembolism during palliation. There was a paucity of autopsy data and no autopsy records were available for analysis. Causes of death from treating physicians' opinions were neurological in one patient, progression of systemic disease in 10 patients (31.2%) and unknown in 18 patients (56.2%). As of the analysis date, 2 patients were alive and one patient's status was unknown as they had moved overseas.

The most common surgical intervention was a stereotactic craniotomy and gross macroscopic resection of the metastasis. This was performed in 28 of the 32 patients (88%). Two patients had fine needle aspiration biopsy of lung metastasis and two patients received no neurosurgical intervention due to poor KPS at the time of referral. One of those two patients died 7 days following referral, account-

ing for the perioperative mortality subject. The other patient died at 44 days from thromboembolic disease.

There was no significant difference in survival attributable to gender ( $p = 0.96$ ). The mean survival post surgical intervention was 8.45 months for females and 8.84 months for males. There was also no significant impact of age on patient survival overall ( $p = 0.18$ ); however, upon inspection of the Kaplan–Meier curve (Fig. 2, older patients, age > 70) seemed to have longer survival. Of the 32 patients, 22 (69%) received a single craniotomy for a single cerebral metastasis, five patients (16%) underwent a total of two craniotomies for cerebral relapse in the original field (two patients) and distant areas (three patients) and one patient underwent three craniotomies for a combination of field relapse and distant failure. The mean survival for those patients receiving a single craniotomy (22 patients, 69%) was 8.63 months and mean survival for those receiving multiple craniotomies was 12.9 months (six patients, 19%).

Cerebellar metastasis was diagnosed in 10 of the 32 patients (31%) and among them were one female and nine males. The median survival for patients with infratentorial metastasis was 6.4 months as opposed to 7.7 months for supratentorial metastasis (Fig. 3). Two patients required

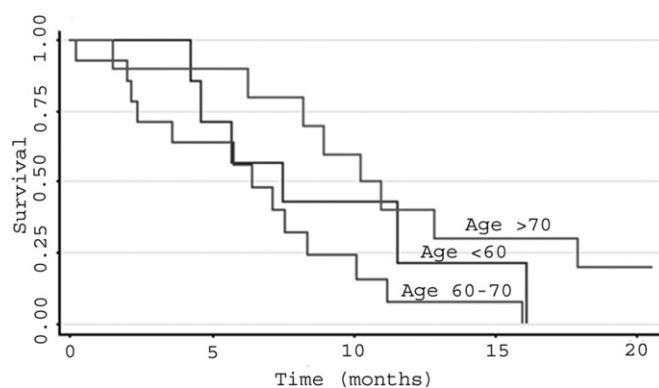


Fig. 2. Disease-specific survival of patients with increasing age: <60 years ( $n = 7$ ), 60–70 years ( $n = 16$ ) and > 70 years ( $n = 9$ ). Log-rank:  $p = 0.181$ .

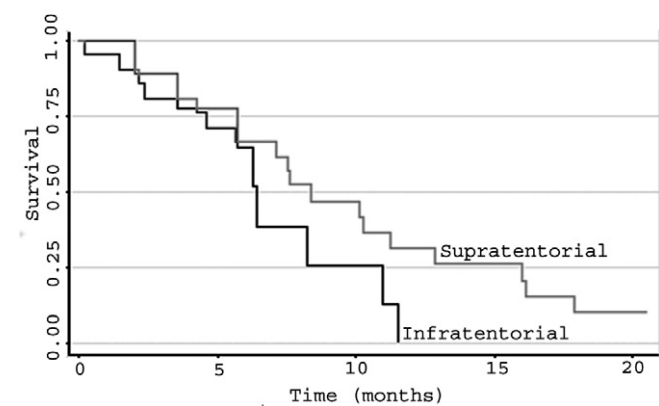


Fig. 3. Disease-specific survival of patients with supratentorial ( $n = 22$ ) or infratentorial ( $n = 10$ ) located metastasis. Log-rank  $p = 0.185$ .

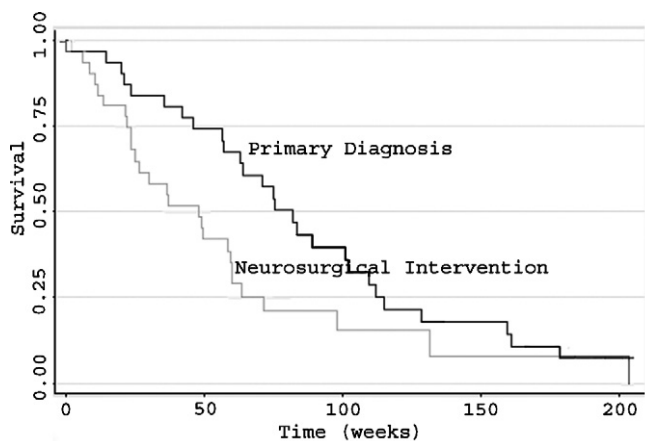


Fig. 1. Disease-specific survival of patients from primary diagnosis and neurosurgical intervention ( $n = 32$ ).

ventriculoperitoneal shunting – one patient for CSF leak following vermian cerebellar metastectomy and one for a midline pineal region metastasis. No patient required repeat surgery for evacuation of haematoma or septic foci. One patient required lumbar CSF diversion for 5 days for CSF wound leakage.

The median survival for patients with lesions with the greatest diameter of <3 cm was 8.4 months as opposed to 7.0 months for lesions > 3 cm. The lesion dimensions were not available for analysis in five patients (16%). No significant survival difference was found ( $p = 0.85$ ).

Over 50% of the patients in this study had radiotherapy after surgical intervention. WBRT was undertaken in 16 of the 32 patients (50%). Of these 16 patients, 13 (41%) had WBRT only, one patient had WBRT combined with stereotactic radiosurgery (SRS) and two patients had WBRT combined with localised field radiotherapy. Stereotactic radiosurgery alone was used in one patient and field irradiation alone was used in one patient. It was unknown if three of the 32 patients (9%) were treated with any form of radiotherapy. Of the patients receiving WBRT, 12 out of the 16 patients (75%) had treatment as soon as practical following surgical treatment (average 14 days post surgery). At diagnosis of cerebral recurrence 25% of patients were treated with WBRT, 50% of whom underwent a repeat surgical resection prior to WBRT. The median survival of patients who had WBRT was significantly better (10.6 months) than for those who had no adjunct radiotherapy (5.2 months) ( $p = 0.016$ ) (Fig. 4).

The median KPS was higher for patients treated with WBRT (80) than for those not treated with WBRT (70).

A survival advantage was demonstrated for patients undergoing multiple lesion resection (median survival 12.9 months) when compared to patients who underwent surgery for resection of a single lesion (median survival 8.6 months), an effect that approached statistical significance ( $p = 0.099$ ). There did not appear to be strict selection criteria for patients to be offered multiple craniotomies. Different neurosurgeons were involved in the care of patients and the decision for surgery was based

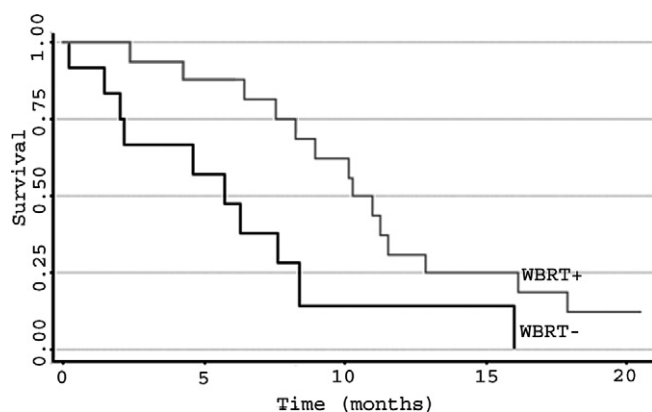


Fig. 4. Disease-specific survival of patients treated with whole brain radiotherapy (WBRT+) ( $n = 16$ ) or not treated with WBRT (WBRT-) ( $n = 11$ ). Log-rank  $p = 0.016$ .

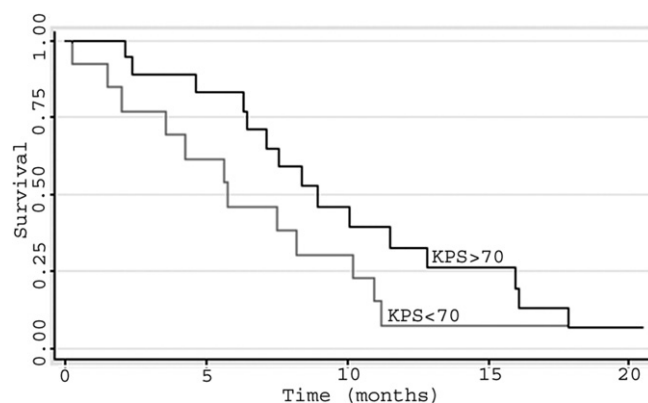


Fig. 5. Disease-specific survival of patients with Karnofsky performance score (KPS) of > 70 ( $n = 19$ ) or <70 ( $n = 13$ ). Log-rank  $p = 0.184$ .

upon discussion with the patient and relatives in the light of clinical evidence to date. Patients who survive longer post initial metastectomy were more likely to be offered repeat resection at local or distant failure.

KPS was available for all patients prior to craniotomy. Predictably, better performance status prior to craniotomy equated to a longer survival (Fig. 5). Patients with a pre-operative KPS > 70 ( $n = 19$ , 59%) had longer median survival (9.8 months) than patients with a pre-operative KPS  $\leq 70$  ( $n = 13$ , 41%) of 6.8 months, but this was not significant. Follow-up KPS, after surgery, was not available for analysis.

## 5. Discussion

The treatment of metastatic brain disease is multi-modal, comprising surgery, radiotherapy and, in some instances, chemotherapy. Initial trials of surgery failed to show a clinical benefit to patients; however, since the trials of Vecht<sup>2</sup> and Patchell,<sup>3</sup> neurosurgery has become increasingly important. These trials not only demonstrated the benefits of surgical intervention for single and oligometastasis (<3 lesions), they also demonstrated the diagnostic importance of surgery with around 5% of lesions not being metastatic disease.<sup>2</sup> Trials of surgery, radiation therapy including WBRT and SRS, however, have been comprised largely of multiple different primary cancers.<sup>2,3</sup> The overall prognosis for patients, as a whole, with metastatic brain disease is poor. The median survival for those patients left untreated is around 1 month.<sup>2,3</sup> Once again, taking the group as a whole, the addition of corticosteroids doubles this median survival and the addition of WBRT extends this to 4–6 months.<sup>4</sup> Another study suggests that median survival for patients with colorectal brain metastasis treated with corticosteroids and WBRT is about 3 months.<sup>5,6</sup> For surgically treated lesions, comprising all histologic subtypes, in highly functioning patients, combined with post-operative radiotherapy, the median survival is 7.1 months.<sup>4</sup> About half of all patients with metastatic brain disease die from neurological causes and half from the progression of systemic disease.<sup>2</sup>

Salvati et al. presented neurosurgical results of resection of single brain metastases from gastrointestinal cancer in 34 patients between 1960 and 1989.<sup>7</sup> Of these patients, 10 had metastases from small intestinal carcinoma. Overall survival was 10 months but no distinction was made specifically for colorectal carcinoma. Lung metastases were diagnosed in 27% of patients and liver metastases in 12%. All patients except for three died of progression of systemic disease. Farnell et al. analysed the results of 150 patients with colorectal carcinoma CNS metastases between 1976 and 1992.<sup>8</sup> Of the cohort, 50 patients underwent craniotomy and resection of single brain metastases and 35 of these subsequently underwent WBRT. Patients receiving supportive care only (corticosteroids) survived around 6 weeks. The 79 patients who received corticosteroids and WBRT only had a median survival of 3.6 months. The median survival for those patients treated surgically and with radiotherapy was 9.8 months for 44% of patients and 10.7 months for 30% of patients.<sup>9</sup> Alden et al. followed 19 patients treated for colorectal metastases.<sup>10</sup> Five patients underwent craniotomy and had a median survival of 4.1 months. Sato et al. in 1993 reported a median survival of 7 months after neurosurgical resection of colorectal metastases.<sup>11</sup>

A review of 100 patients with colorectal metastases between 1980 and 1994 by Hammoud et al. showed a median age of 61 years and the interval between the diagnosis of the primary tumour and brain metastases was a median of 26 months.<sup>12</sup> Multiple brain lesions were identified in 36% of patients and supratentorial lesions in 52% of patients. The median survival of these patients from the time of diagnosis of cerebral metastases was 5 months. The thirty-six patients who underwent craniotomy and resection of the lesion had a median survival of 9 months. The subgroup of 57 patients treated with WBRT demonstrated a median survival of only 3 months. In this study, 45% of patients died of neurological causes and 10% as a result of progression of systemic disease. These 100 patients were selected from a base of 150 patients and the reason for the exclusion of those 50 was obscure at the time of the report. This study identified resection of the lesion as the only significant variable determining survival.

The largest series of surgically treated colorectal metastasis, by Wroński et al., found a median survival time from craniotomy of 8.3 months for 73 patients.<sup>1</sup> Our study also demonstrated a similar median survival time of 7.57 months after neurosurgical intervention. Our study confirmed a strong association between CNS metastases from colorectal carcinoma and pulmonary metastases (probably greater than 40%) and supports the role of CNS MRI at time of pulmonary metastatic diagnosis to exclude CNS metastases.<sup>13</sup>

Infratentorial lesions occurred in 28% of our patients and was characterised by a shorter, but not significant, overall median survival when compared to patients with supratentorial lesions. Other studies have reported the incidence of infratentorial lesions to be as high as 55% for

colorectal metastasis.<sup>10</sup> Our incidence rate is consistent with the findings of the largest series of surgically treated colorectal CNS metastases and represents a site incidence consistently higher in the posterior fossa than other types of primary tumour.<sup>14–18</sup> Interestingly, 90% of infratentorial lesions occurred in males. Wroński et al. demonstrated a statistically significant survival disadvantage for infratentorially located lesions. Although our study suggests a definite trend in agreement with this finding, lack of subject numbers may account for the lack of statistical significance.

We analysed the effects of different variables that included age, gender, size of the lesion and KPS. These variables did not significantly alter the median survival for patients. This result is consistent with the largest series.<sup>1</sup> However, we demonstrated that patients treated with WBRT had significantly improved overall survival. The largest study series to date of the use of WBRT in colorectal adenocarcinoma suggested no significant survival advantage for those having WBRT. In that study, 33 patients received WBRT after craniotomy. Of the 45 patients who were not treated this way, 10 received WBRT at diagnosis of cerebral metastasis and then surgery at “treatment failure”, although there is no mention of the time period between WBRT and surgery. Survival significance was calculated between the 33 patients and the 45 (10 of whom received WBRT). This may have accounted for the some of the lack of statistical significance attained in that study.

Our study showed a statistically significant improvement in survival for patients undergoing WBRT. The selection of patients for WBRT following resection of their metastatic disease did not seem to be governed by strict clinical criteria. Multiple oncologists were involved with adjuvant treatment and clinical decisions to offer WBRT were based upon discussions with patients and families regarding the available evidence and the patients' wishes. There did not seem to be a great disparity in KPS between the two groups.

In an attempt to identify prognostic groups, the Radiation Therapy Oncology Group (RTOG) conducted recursive partitioning analysis on multiple prognostic factors of 1176 patients.<sup>4</sup> All primary tumour subtypes were included. Three critical prognostic indicators were identified and these were age, performance status and presence of extraneural metastasis. Patients in RTOG Class 1 had good performance status, were aged less than 65 years and had no metastatic disease outside the nervous system and controlled primary malignancy. These patients had an overall median survival of 7.1 months. Patients with poor performance were in Class 3, irrespective of other factors, and had a median survival of only 2.3 months. Class 2 represents an intermediate mix of patient groups and carries a median survival of 4.2 months. Table 2 illustrates the results of several RTOG trials and an overview of recursive partitioning analysis data for multiple tumour subtypes.

In addition to these factors, the mode of therapy of these patients is also extremely important.<sup>4</sup> Although patients in

Table 2  
Recursive partitioning analysis data and the Radiation Therapy Oncology Group studies<sup>4</sup>

Group	KPS	Systemic disease	Median survival (months)
1 (age 65 y or younger)	≥70	Controlled primary disease, no extracranial metastases	7.1; 13.5 for single metastasis, 6.0 for multiple metastases
2	Not group 1 or 3	Not group 1 or 3	4.2; 8.1 for single metastasis, 4.1 for multiple metastases
3	<70		2.3

KPS = Karnofsky performance status.

RTOG Class 1 have the best survival with multimodality treatment, fewer than 20% of patients with cerebral metastasis fall into this treatment category.<sup>4</sup> In our current study, only one patient could be classified as RTOG Class 1. This patient had a survival of 27.6 weeks following neurosurgical intervention. As many patients have active systemic disease this automatically places them into Class 2 provided they have high performance scores. RTOG Class 2 patients in our study (76.6%) fared better than expected (median survival of 35.5 weeks (8.8 months)). Although patient samples are relatively small, this figure compares favorably with RTOG Class 1 patients from much larger studies<sup>3–5</sup> having median survival of 8.9 months when treated with resection and WBRT. Class 3 patients represented a relatively small proportion of study subjects, probably as a result of selection factors. RTOG Class 3 patients in our study, predictably, fared poorly (median survival 2.7 months). This figure was equivalent to documented survival figures without surgical intervention.<sup>4</sup>

## 6. Conclusions

Our study confirms a median survival of 7.57 months and a mean of 8.24 months for all patients undergoing neurosurgical treatment for colorectal CNS metastases comparable to the largest presented series. This survival is significantly shorter than for other primary tumours<sup>14–19</sup> and probably can be related to the relatively advanced stage of systemic disease in these patients. Although there

Table 3  
Survival of patients with colorectal carcinoma from diagnosis of brain metastasis

Authors	Initial treatment	No. patients	Median survival (months) from intervention
Wroński et al. <sup>1</sup>	Craniotomy	73	8.7
Farnell et al. <sup>8</sup>	Craniotomy	50	10
Hammoud et al. <sup>12</sup>	Craniotomy	36	9
Fowler et al. <sup>This study</sup>	Craniotomy	32	7.57
Farnell et al. <sup>8</sup>	WBRT	79	3.6
Hammoud et al. <sup>12</sup>	WBRT	57	3

WBRT = Whole Brain Radiotherapy.

is, in our study, a suggestion of decreased survival for infratentorial lesions, the exact reason(s) for this is obscure.

We agree that aggressive neurosurgical management of single metastases in accessible lesions remain a worthwhile therapeutic intent, providing the best palliation with a longer survival. Surgical intervention can be achieved with minimal perioperative mortality and morbidity. Although most patients with colorectal metastases fall into RTOG Class 2, their survival with multimodal therapy seems on average as good as RTOG Class 1 for other primary tumour subtypes (Table 3). This suggests that systemic, extra-neural metastases may be irrelevant for colorectal cancer in determining neurosurgical candidacy save for metabolic and systemic derangements caused by the same.

Importantly, our study shows an improved survival for those undergoing WBRT following neurosurgical treatment for colorectal metastases. Although numbers in this study are smaller than for previous series, it is reasonable, given the conflicting findings with previous studies, to suggest a prospective randomised study of the use of WBRT in this specific tumour type.

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