



## ORIGINAL ARTICLE

# Brain metastasis in advanced colorectal cancer: results from the South Australian metastatic colorectal cancer (SAmCRC) registry

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### ABSTRACT

**Objective:** Brain metastasis is considered rare in metastatic colorectal cancer (mCRC); thus, surveillance imaging does not routinely include the brain. The reported incidence of brain metastases ranges from 0.6% to 3.2%.

**Methods:** The South Australian mCRC Registry (SAmCRC) was analyzed to assess the number of patients presenting with brain metastasis during their lifetime. Due to small numbers, a descriptive analysis is presented.

**Results:** Only 59 patients of 4,100 on the registry at the time of analysis had developed brain metastasis (1.4%). The clinical characteristics of those with brain metastasis were as follows: the median age was 65.3 years and 51% were female. Where the V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (*KRAS*) mutation status of the tumor was known, the majority harbored a *KRAS* mutation (55%); 31 (53%) underwent craniotomy and 55 (93%) underwent whole-brain radiotherapy. The median survival time from diagnosis of brain metastasis was 4.2 months (95% confidence interval 2.9–5.5). Patients who underwent craniotomy and radiotherapy had superior survival compared to those who underwent whole-brain radiotherapy (8.5 months vs. 2.2 months, respectively). Data from the SAmCRC (a population-based registry) confirm that brain metastases are rare and the median time to development is approximately 2 years.

**Conclusions:** Brain metastasis is a rare outcome in advanced CRC. Patients within the registry tended to be female, young in age, and harbored with higher rates of *KRAS* mutations. Whether routine surveillance brain scanning should be considered remains controversial given the relative rarity of developing brain metastases in mCRC and ultimately, most patients with central nervous system involvement die from their extracranial disease.

### KEYWORDS

Brain metastasis; colorectal cancer; survival; surveillance

## Introduction

Patterns of care for patients with metastatic colorectal cancer (mCRC) have evolved leading to longer survival with the median now reaching 30 months<sup>1,2</sup>. Brain metastasis is considered rare in mCRC and surveillance imaging does not routinely include the brain in neurologically asymptomatic

patients<sup>3,4</sup>. The reported incidence of brain metastasis ranges in the literature from 0.6% to 3.2%<sup>5</sup>. In this setting, brain metastases usually occur in advanced stages of the disease and are usually observed concomitant with liver involvement (50%) or lung metastases (80%)<sup>6,7</sup>.

Central nervous system (CNS) metastases are a late manifestation of mCRC and confer significant morbidity and poorer median survival on such patients, with a life expectancy without treatment of approximately 4 to 6 weeks. The vast majority of mCRC patients that develop brain metastases are treated with palliative intent, since most are expected to die from their extracranial disease<sup>8,9</sup>. To date,

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there is no consensus on their management, which is usually determined by the presence of disseminated disease, patient performance status, and previous response to treatments. Many affected patients will suffer considerable loss of autonomy due to neurocognitive and functional deficits, as well as morbidity associated with steroids and anticonvulsants. Only a small number of patients who can have surgical resection with or without postoperative whole-brain radiotherapy (WBRT) are considered, with more encouraging outcomes [median overall survival (mOS) of approximately 8 months]<sup>10-12</sup>. Over the last few years, stereotactic radiosurgery has become another treatment modality with outcomes appearing to be comparable to those of surgical resection for patients with oligometastases that are small and present minimal mass effects. The advantages of this treatment are its minimal invasiveness, low rate of post-treatment complications, and a high rate of local tumor control<sup>13</sup>.

The incidence of brain metastases in oncology is gradually increasing, which can be explained in part by earlier detection with new imaging techniques and in part by longer survival due to advances in systemic treatments for metastatic disease. In this study, we have analyzed the South Australian mCRC population-based registry to assess the frequency of brain metastasis, the timing of presentation, as well as potential risk factors in the South Australian population, which may together guide those mCRC patients who are at a higher risk of developing brain metastases.

## Patients and methods

The SAmCRC registry is a state-wide, population-based database of all patients diagnosed with synchronous or metachronous mCRC since February 2006. The registry is managed by a committee of surgeons, oncologists, epidemiologists, and clinical trial and data collection experts. The clinical membership is drawn from the state's major public hospitals (Flinders Medical Center, Royal Adelaide Hospital, and The Queen Elizabeth Hospital) and associated private hospitals. The SAmCRC registry data were analyzed to assess the number of patients detected to have developed brain metastasis during their lifetime. For this study, we included data which were collected between February 2, 2006 and March 31, 2016. Patient characteristics were reported and overall survival was analyzed using the Kaplan-Meier method. Statistical analysis was performed using SPSS version 18.0 (IBM software) and GraphPad Prism version 5 (GraphPad Software, San Diego). The local Human Research Ethics Committee (TQEH/FMC/LMH) approved the study

protocol (Ethics reference number is 2006133).

## Results

### Population

At the time of analysis, more than 4,000 mCRC patients were enrolled into the registry between February 2, 2006 and March 31, 2016. Only 59 patients developed brain metastasis (1.4% of our total population). The median follow-up time was 23 months at the time of analysis. Demographic and CRC data are summarized in **Table 1**. The clinical characteristics of those with brain metastases compared to those across the whole registry were as follows: median age at diagnosis, 65.3 years vs. 70.8 years; 51% vs. 43% women; metastatic sites at initial diagnosis, 54% lung (32 patients had

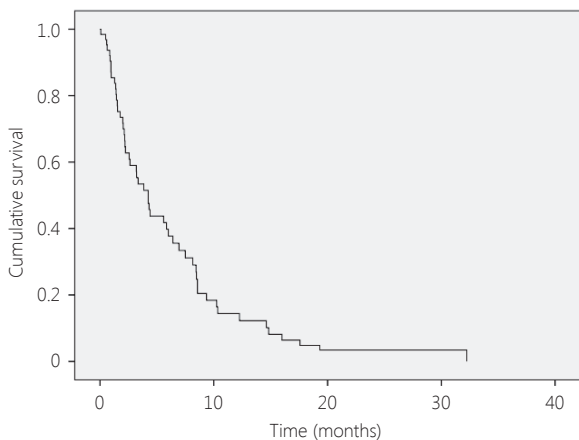
**Table 1** Patient's characteristics

Characteristics	Brain metastasis (n=59)	Registry population (n=4100)
Median age (years) at diagnosis	65.3 (37.5–86.7)	70.8 (17.2–104.8)
Female	51%	43%
Health service area		
City	69.5%	68%
Rural	28.8%	29%
Interstate	1.7%	3%
Primary tumor location		
Left colon	36%	36%
Right colon	29%	36%
Rectum	34%	28%
Stage		
Dukes A/B/C	1.7%/15.3%/15.3%	1.4%/12.7%/19.6%
Metastatic	67.8%	65.3%
Tumoral grade		
Well differentiated	5.1%	4.6%
Poorly differentiated	18.6%	26%
Moderately differentiated	71.2%	53%
Unknown	5.1%	16%
KRAS mutant	55%	42%
Clinical trials participation	12%	–

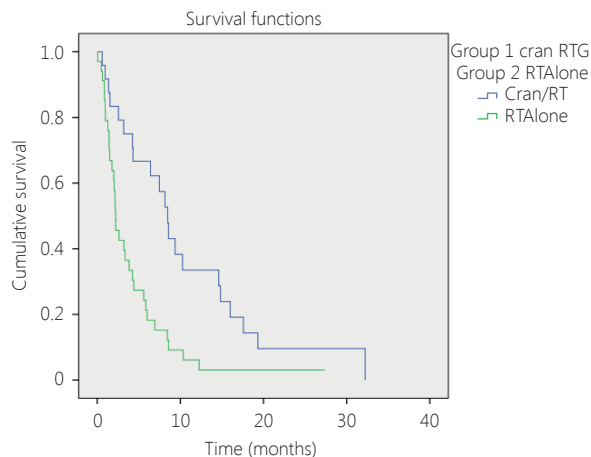
lung involvement) vs. 15%, 47% liver (28 patients had hepatic secondaries documented) vs. 35%, and 7% bone vs. 2.6%. The primary site of CRC was 29% right-sided colon and 70% left-sided CRC (34% rectum, 36% left colon/sigmoid) for the brain metastasis group. This was in contrast to those across the whole registry, where there was 36% right primary and 28% rectum. The left colon prevalence was identical for both groups (36%). Where the *KRAS* status was known (27 patients in our cohort), 55% of them had *KRAS* exon 2 mutations compared to 42% across the whole registry. Regarding prior surgery for lung/liver metastases, 25% (15/59) underwent liver resection and lung metastases were resected from only 5 patients (8%). The median number of prior lines of chemotherapy before diagnosis of brain metastasis was 2 (range: 0–4 lines).

### Overall and brain metastases-free survival

Complete details and follow-up data were available for 58 patients. The median interval between diagnosis of the primary cancer and identification of brain metastasis was 1.9 years (range: 0–6 years). The mOS from diagnosis of brain metastasis was 4.2 months (95%CI 2.9–5.5 months) (**Figure 1**). Excluding 8 patients that presented with synchronous cerebral metastasis, the median time to CNS metastases was 2.05 years (range: 0.3–6.0 years) and median survival was 3.8 months (95%CI 2.0–5.7 months). Thirty-one patients (53%) underwent craniotomy and 93% underwent WBRT. The mOS for patients that underwent craniotomy and radiotherapy was 8.5 months (95% CI 6.9–10 months) compared to 2.2 months (95% CI 1.5–2.9 months) with WBRT alone (**Figure 2**).



**Figure 1** OS from diagnosis of brain metastases



**Figure 2** Survival craniotomy/radiotherapy vs. radiotherapy alone

### Discussion

A diagnosis of brain metastases from CRC is an uncommon clinical situation and the risk factors for developing CNS secondaries are poorly understood. Although the number of studies reviewing brain metastases from CRC has been limited to date, the incidence is estimated to be between 0.6% and 3.2%. However, the small sample size and statistical variations of these studies, the differences in diagnostic methods, and the lack of neurological symptoms in some patients make it very difficult to establish the true incidence of brain metastases. The incidence of CNS metastases observed in our study (1.4%) is similar to what has been previously observed<sup>5</sup>. It is thought that the incidence of brain metastases recorded from all solid tumors has steadily increased over the last two decades due to the increase in survival of patients, better radiological diagnostic methods, and in particular, the widespread use of magnetic resonance imaging (MRI) to detect small metastases. However, in the specific case of CRC, the incidence seems to have remained somewhat unchanged, as supported by the outcome of our analysis<sup>5,14</sup>.

Brain metastases in mCRC are generally associated with advanced stage and most diagnoses of CNS secondaries are metachronous. In the literature, brain metastases from mCRC are reported mainly in patients with lung and liver metastases: between 55% to 85% of brain metastasis diagnoses are associated with lung involvement and between 22% and 60% with hepatic secondaries—these numbers are also consistent with our results where we observed a high rate of lung involvement in the brain metastasis group (54%) compared to the whole registry (15%)<sup>8,9,15</sup>. The high percentage of concurrent or antecedent pulmonary

metastases supports the hematogenous dissemination theory proposed in 1928 by Ewing<sup>16</sup>, according to which tumor cells, after reaching the lungs, eventually travel through the blood, flow into the left side of heart, and then embolize to other organs, including the brain. Some authors have postulated that a diagnosis of pulmonary metastases in mCRC patients may confer an increase in the risk of developing CNS metastases, supporting Ewing's theory<sup>17</sup>. Chyun<sup>18</sup> also noted that the lag time from primary CRC diagnosis to pulmonary metastases occurred three times earlier among patients who subsequently developed brain metastases. In our registry, we found also that approximately half of the diagnoses of brain metastases were associated with co-existing hepatic involvement (47%), although this was not dramatically higher than those of the whole registry population (35%). Cascino<sup>19</sup> and Temple<sup>7</sup> reported similar findings with 50% and 76% of patients, respectively, presenting with evidence of liver metastases at the time of their CNS diagnosis. Other authors have proposed an opposite theory whereby different molecular features of the cancer explain the pattern of brain metastases. Across the literature, *KRAS* mutations in mCRC correlate with poor OS and increased incidence of both lung and brain metastases<sup>20-22</sup>. In our study, noting the small number in whom the *KRAS* mutation status was known, 55% of patients with brain metastases presented with *KRAS*-mutated cancers compared to 43% of the overall population, in keeping with this hypothesis. The impact of other somatic mutations on the development of brain metastases in the mCRC context is currently unclear. Some authors have proposed mutations in phosphatidylinositol-4, 5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*) and v-raf murine sarcoma viral oncogene homologe B1 (*BRAF*) as predictors of CNS involvement in mCRC patients; however, the evidence is scarce and even contradictory<sup>20,22,23</sup>. *BRAF* and *PIK3CA* statuses were not available in our registry for the brain metastasis group, again based on small numbers.

An important finding of our analysis was that the median time between the diagnosis of mCRC and the development of brain metastases was 1.9 years (range: 0–6 years), which is consistent with the timeframe reported in other publications. There is increasing evidence suggesting that brain metastases are observed more commonly in left-sided CRC (about 60% of cases) than in proximal colon cancers<sup>24,25</sup>. Our results were consistent with the association between primary tumor location and the development of brain metastases, although it would appear that the higher rate observed with left-sided primaries may be driven by the rectal subgroup. Although less common, Hammoud<sup>26</sup> reported that patients with brain

metastases from metastatic proximal colon cancers were associated with shorter survival times compared with distal mCRC patients with CNS involvement (3 vs. 6 months,  $P < 0.005$ ). Small numbers in our series did not allow us to conduct a comparison of survival alongside primary cancers.

The mOS from the diagnosis of brain metastasis in our series was 4.2 months (95% CI 2.9–5.5 months). This poor survival is similar to what has been reported in the existing literature. In our study, one possible explanation for this ominous prognosis is the fact that 54% of our patients presented with lung metastases, and in 47% of cases, there was liver involvement. It must also be noted that these patients were pre-treated with a median number of 2 lines of chemotherapy prior to the diagnosis of brain metastases (range: 0–4 lines). It is reported that mCRC patients with uncontrolled extracranial metastases have worse outcomes compared to mCRC brain patients who have no extracranial lesions<sup>27</sup>. Unfortunately, we do not collect data in our registry on patient progression and hence, we cannot report on the control of extracranial disease at the time of brain metastasis.

Another possible explanation for such a limited survival could be the low proportion of patients who underwent aggressive therapies for their brain metastases. None of our patients received stereotactic radiotherapy and just half underwent surgical resection. Surgery combined with WBRT is proven to be the most effective treatment for isolated CRC brain metastasis in patients who are ideal surgical candidates<sup>10-12,26</sup>. Farnell<sup>28</sup>, for instance, published interesting work looking at the survival rates of 150 mCRC patients treated with different treatment modalities and determining the main characteristics in long-term survivors. He reported a mOS of 10.5, 11.25, 4, and 2 months for patients receiving a combination of surgery and radiotherapy, surgery alone, radiotherapy alone, and best supportive care only, respectively. Twenty-four patients survived > 1 year after brain metastasis diagnosis. Among these long-term survivors, 79% were treated surgically and 38% presented with no additional systemic disease. These aggressive interventions are only reasonable for patients with minimal CNS disease burden in terms of number of metastases, and where surgically accessible. Thus, patients with better initial prognosis with their CNS disease are more likely to receive aggressive intervention.

Given the low incidence of brain metastases in mCRC, there are no studies looking at the cost-effectiveness of brain imaging in this setting, as opposed to other solid tumors that frequently metastasize to the brain (lung cancer or melanoma)<sup>29</sup>. With regard to screening for intracranial

metastases in mCRC, no consensus has been reached concerning when to use contrast-enhanced computed tomography (CT) or MRI<sup>30</sup>. The latter is currently the investigation of choice given its significant sensitivity/specificity compared to CT in the detection of metastatic disease within the brain and in determining the location and number of metastases, especially small lesions < 5 mm in diameter<sup>31,32</sup>.

In our cohort, the patients who developed brain metastases tended to be younger, be female, present with more lung involvement, and present with primary tumors that were more often rectal and *KRAS*-mutant. Clinicians should be mindful of including imaging of the brain in their surveillance protocol for mCRC patients with the aforementioned features in the later stages of disease. The potential benefits of an early diagnosis of brain metastases in patients with good performance status may allow treatment options such as surgical resection and stereotactic radiotherapy techniques to be considered, and ultimately, increase life expectancy in very selected patients.

There are limitations of our registry cohort as reported. Differences in performance status and disease extent within the brain, and systemically between those patients proceeding to craniotomy and radiotherapy and those having radiotherapy alone may have played a part in the survival difference reported. Unfortunately, these data are not recorded in our registry. Furthermore, complete details on molecular results are also not available based on the differences in practice over the lifetime of the registry.

## Conclusions

Brain metastases remain a rare diagnosis in mCRC patients, with an incidence of 1.4% from our registry results. Female, *KRAS* mutations, rectal primary cancer, and young age seem to confer an increased risk for the development of CNS metastases, although the numbers of patients with brain metastases are too small to truly draw any significant conclusion. Although routine surveillance scanning remains controversial in this context, we suggest considering brain imaging in patients with these characteristics as early detection and proper staging may lead to better selection of patients for more aggressive modalities of treatment and potentially improved outcomes.

## Conflict of interest statement

No potential conflicts of interest are disclosed.

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