

## Is there an Ethnic Predisposition to Developing Brain Metastases (BM) in Asian Patients with Colorectal Cancer?

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### ABSTRACT

#### **BACKGROUND**

Most common sites of metastases in patients with colorectal cancer (CRC) include liver and lung. Brain metastases are very rare but their presence is associated with a poor prognosis and shorter survival. We report our investigation into the impact of race/ethnicity on the incidence of BM in CRC patients.

#### **METHOD**

We retrospectively reviewed patients diagnosed with CRC from 2010 - 2018 at a single institution and analyzed any association of development of brain metastases with race and ethnicity. Race and ethnicity were defined in accordance with federal standards set by the US Census.

#### **RESULT**

We identified 264 CRC patients and 76(29%) were identified as Asian. Of those 76 patients, 5(7%) developed brain metastases. All 5 patients were male and stage IV at initial diagnosis. Brain metastases was a late stage phenomenon. Median time to development of brain metastases was 29 months (Range: 26 - 33). Median overall survival after BM diagnosis was 5.5 months (Range: 4 - 11). Overall survival was longest for the patient who had both radiation and surgery.

#### **CONCLUSION**

Our study showed an incidence of brain metastases of 7% in the Asian sub-population compared to the historical control of 0.6% - 3.2% in the overall population. These results at the least warrant further investigation in a larger patient population of brain metastases in CRC patients with emphasis on molecular markers.

#### **KEYWORDS**

Colorectal cancer; Brain metastases; Radiation therapy; Surgery

### **1. INTRODUCTION**

Colorectal cancer (CRC) is the third most common cancer in United States, and carries racial/ethnic disparities in both incidence and mortality. More than 50% of patients

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with CRC die from their cancer [1]. Approximately 20% of patients with CRC already have developed metastases at the time of diagnosis [1]. The most common sites of metastasis are the liver and the peritoneum [1,2]. With

availability of effective systemic therapies, the life of CRC patients can be prolonged which thereby increases the risk of metastases at uncommon sites, such as the brain [3].

Most common primary sites that lead to development of brain metastases include lung cancer (40% - 50%), breast cancer (5% - 15%), testicular cancer (10% - 15%), and melanoma (10%). Brain metastases from CRC are very rare, with a reported incidence ranging from 1% to 4% [4,5]. Brain metastases usually develop late in the disease when majority of the patients have already metastases to other organs before brain metastases are diagnosed [4-6]. However, anecdotal reports of sole site of metastatic disease in brain in a patient with CRC have been reported [7].

Although brain metastases from CRC are less common than those from lung, breast and malignant melanoma, their effect on prognosis is equally serious. The reported incidence of BM from CRC may be increasing because of improved diagnostics and increased survival of patients, but this is not well documented [8,9]. We report our investigation into the impact of race/ethnicity on the incidence of BM in CRC patients using retrospective data (2010 - 2018) at a single institution.

## **2. METHOD**

We retrospectively reviewed patients diagnosed with CRC and collected data on age, race/ethnicity, stage, treatment modalities, metastatic sites, and survival. Race and ethnicity were defined in accordance with federal standards set by the US Census. Following this, race/ethnicity was self-declared and/or based on the primary language declared and categorized as non-Hispanic White, Hispanic White, non-Hispanic Black, Asian, or Unknown/Other. CRC location was classified as right-sided, left-sided or rectal.

## **3. RESULT**

We identified 264 CRC patients (Median age: 61; Range: 38 - 99). Among them 123 identified as non-Hispanic white, 28 non-Hispanic black, 26 Hispanic white, and 9 declared other. There were 76(29%) who identified as Asian. Of those 76 patients, 5(7%) developed BM. All 5 patients were male and stage IV at initial diagnosis. BM was a late stage phenomenon with rectal primary and lung metastases seemly associated with an increased risk in the specific cohort. Molecular markers such as KRAS were available in 3 patients without clear association. Median time to development of BM was 29 months (Range: 26 - 33). Median overall survival after BM diagnosis was 5.5 months (Range: 4 - 11). Overall survival was longest for the patient who had both radiation and surgery.

## **4. DISCUSSION**

Our study showed an incidence of BM of 7% in the Asian sub-population compared to the historical control ranging from 0.6% to 3.2% with a weighted mean of 1.55 % (95 % CI 1.48% - 1.63%) in the overall population [6-11]. In addition, autopsy studies reported an incidence of 0.9% and 2.7%, fairly consistent with the numbers seen in clinical studies [9-12]. With the development of more cytotoxic and targeted agents, the survival has improved in patients with mCRC. It is possible that the true incidence of brain metastases might be higher than what has been reported previously as some patients don't show any neurological symptoms, and that brain imaging is not included in regular staging.

Most brain metastases from solid malignancies result from haematogenous spread. Majority of the brain metastases develop in the cerebrum (80%), followed by cerebellum (15%) and brainstem (5%) [13]. Though it seems that most important risk factor for developing BM was lung metastases, but it is not known at present whether patients with lung and liver metastases secondary CRC should undergo any imaging for earlier detection of

brain metastases [14,15]. In addition, due to being a rare incidence currently, it may not cost-effective.

Historically, the aim of treating brain metastases was focused mainly on palliating neurologic symptoms. But with the improvement in overall survival for patients with mCRC following the introduction of new agents, the management policy for brain metastases has also been revised. Treatment options usually involve multimodality approaches that include surgery, radiotherapy, radiosurgery and rarely systemic therapy, depending on the number of CNS lesions, location, and patient's performance status [14,15]. All such factors have to be considered as quality of life (QoL) and neurocognitive function are often impaired in these patients either due to treatment of brain metastases or progression of extracranial metastases.

As expected from experience in other solid tumors, the survival of CRC patients with brain metastases is dismal, at a reported median of less than 3 months [6-13]. Therefore, early recognition and management is crucial both for improved survival and quality of life [16].

Some investigators also tried to associate pattern of metastases with different molecular pathways such as mutations in RAS, BRAF, and PIK3CA, expression of NCAM, EGFR, and CXCR4, MGMT methylation and increase in the tumor marker such as CEA and CA19.9 [17-23]. However, current data was unable to prove the predictive significance of any of these markers. Our study also included 3 patients with KRAS mutation and no association was found.

## **5. CONCLUSION**

Previous studies have not associated risk or incidence of brain metastases to race or ethnicity in patients with CRC. Our study indicated an incidence of brain metastases of 7% in the Asian sub-population compared to the historical control of 0.6% - 3.2% in the overall population. The previous investigators have suggested a possibility of regional differences in occurrence of brain metastases in patients with mCRC. Our results at the least warrant further investigation in a larger patient population of BM in CRC patients with emphasis on molecular markers. Recognition of brain metastases in CRC patients is clinically relevant secondary to multiple lines of therapy as mentioned earlier and its grave impact on outcome.

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