

Brain metastasis from colorectal carcinoma. Clinical picture, treatment and prognosis

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SUMMARY

The occurrence of brain metastasis from colorectal carcinoma (BM-CRC) ranges from 0.06–4%. Their rare occurrence makes various issues associated with these lesions controversial. Based on the literature data, this article presents population characteristics and clinical features of BM-CRC, their treatment methods and prognostic factors in these patients. It has been demonstrated that BM-CRC is mainly detected in patients with advanced CRC (III° and IV°) and is usually preceded by lung and liver metastases. The authors report population-based characteristics of BM-CRC, i.e. greater frequency in males and mean patient age of 51–73 years, and clinical features, such as supratentorial location in over a half of cases, the occurrence of a single BM-CRC in a half of patients and median size of 24–33 mm. Moreover, the authors discuss treatment methods in BM-CRC, including surgery (stereotactic radiosurgery, SRS), whole brain radiotherapy (WBRT) and systemic treatment, applied either alone or in combination. The observation made in literature reports that aggressive surgery or SRS prolong survival and improve quality of life, particularly when combined with WBRT, has been confirmed. WBRT alone remains the mainstay of palliative BM-CRC treatment. It is also used in patients ineligible for surgery or SRS, with multiple BM-CRC, with poor performance status and with uncontrolled extracranial disease. Patients with BM-CRC present poor prognosis. Median overall survival (OS), as presented in the references from 2014–2016, ranges from 2 to 7 months. Higher OS rates are reported in selected groups of patients, mainly those primarily treated with surgery or SRS (5–14 months). The main positive prognostic factors in patients with BM-CRC are: the Karnofsky Performance Score (KPS) ≥70, BM-CRC number not greater than 2 and no active extracranial CRC.

Key words: colorectal carcinoma, brain metastases

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INTRODUCTION

According to the literature data, the occurrence of brain metastasis from colorectal carcinoma (BM-CRC) ranges from 0.06–4% [1–8]. Some authors have suggested that the occurrence of BM-CRC is systematically increasing as CRC treatment is becoming more and more effective and survival of patients is prolonged, and as imaging is developing [3, 5, 7, 9]. However, the study of Christensen et al. from 2016, based on an analysis of over 100,000 CRC patients, failed to confirm these observations; BM-CRC was found in 1.55% of patients [2].

BM-CRC is typically detected in late, advanced stages of CRC (III°, IV°), usually following lung, liver or bone metastases [1, 2, 4, 7, 9–11]. The average time from CRC diagnosis to BM-CRC occurrence is 21–35 months [2, 4, 6, 10–14]. In the literature analysis conducted by Christensen et al., this time ranged from 20 to 40 months in 28 reports and from 21 to 34 months in 11 reports [2], while in the study of Mege et al. from 2017, it was 28 (15–40) months [1]. It must be emphasized that the literature has known cases of BM-CRC occurring after 5 or even 10 and 15 years after CRC diagnosis [1, 10, 13–18].

In 2015, Yeager et al. suggested that the presence of a RAS mutation in CRC patients is associated with a greater risk of lung, bone and brain metastases [19]. The investigations of Nieder et al. from 2016 did not support these observations [20], but data presented by Christensen et al., also in 2016, suggest that a KRAS mutation increases the risk of BM-CRC [2].

The primary location of CRC has probably no statistically significant influence on BM-CRC occurrence [1, 4, 6, 8]. In the material presented by Mege et al., who included 1864 patients

with BM-CRC, 885 (47%) patients were diagnosed with carcinoma in the colon and 816 (44%) had a rectal disease [1]. In the study of Gu et al., the respective values were 44% and 49% [8], Michl et al. report the rates of 47% and 42%, while Fountzilias et al.: 47.5% and 50% [4]. In their analysis from 2016, Christensen et al. suggest, however, that BM-CRC is more common in patients with rectal carcinoma [2].

POPULATION AND CLINICAL CHARACTERISTICS OF BM-CRC

Most literature data show that BM-CRC is more common in males, who account for 56–61% of cases [1, 2, 6–8]. The mean age of patients with BM-CRC ranges from 51 to 73 years [1–4, 6, 7, 11, 21].

In publications from 2011–2016, which present from 60 to 227 patients, a single BM-CRC was noted in 11–54% of cases [7, 8, 10, 11, 18, 22, 23], 2–3 BM-CRC were found in 8.6–31% of cases [7, 8, 10, 11, 23], and more than 3 BM-CRC were detected in 17.3–58% of cases [7, 8, 10, 11, 22, 23]. In a systematic review based on Pub Med, EMBASE and Cochrane data from 1983–2015, which was published by Mege et al. in 2017, a single BM was found in 54% of cases of 2077 patients with BM-CRC (11–100%) [11, 24].

BM-CRC is characterized by supratentorial location in 42.5–66.7% of patients [4, 7, 8, 11, 15, 23, 25–26]. In the study of Mege et al. this location was found in 58% of patients (36–73%) [1]. The median size of BM-CRC ranges from 24 to 33 mm according to Mege et al. [1, 23, 26–29]. In works from 2017, Paix et al. and Page et al. reported 28 mm (17–90 mm) and 27 mm (6–61 mm), respectively [5, 21].

The most common signs and symptoms of BM-CRC are: headache [1, 5, 18, 22, 24, 25, 27–32], motor disorders [1, 18, 22, 24, 25, 27–32], memory disturbances [18, 22, 25], cerebellar ataxia [1, 22, 25, 27–29, 31], epilepsy [1, 5, 18, 22, 24, 25, 29, 31], vision disorders [18, 25], nausea and vomiting [18, 22], and focal neurological signs [25].

BM-CRC TREATMENT

The treatment of BM-CRC involves neurosurgery, whole brain radiotherapy (WBRT), stereotactic radiosurgery (SRS) and systemic treatment, either alone or in combination [1–5, 7–15, 18, 20–18, 30–46]. The treatment method

mainly depends on the patient's performance status, the number and location of BM-CRC and the presence of extracranial disease.

In the group of 1980 patients with BM-CRC, presented in 2017 by Mege et al. in their literature review from the years 1983–2015, surgery alone was employed in 231 (12%) patients, WBRT alone in 737 (37%) patients, SRS alone in 359 (18%) patients, surgery combined with WBRT in 301 (19%) patients, surgery combined with SRS in 75 (4%) patients, WBRT combined with SRS in 59 (3%) patients and surgery combined with WBRT and SRS in 18 (1%) patients; chemotherapy attempts were made in 10% of these patients. The best supportive care (BSC) alone, mainly based on steroids, was used in 10% of patients [1].

Surgical treatment

The most suitable candidates for primary surgical treatment are:

- patients with a single supratentorial BM-CRC that is possible to be resected radically;
- patients with the Karnofsky Performance Score (KPS) of 70 and more;
- patients with no evident neurological deficits;
- patients with controlled extracranial disease.

Surgical treatment is also justified in selected patients irrespective of extracranial disease control. They include individuals with large BM-CRC that cause significant neurological deficits and/or intracranial hypertension (mass effect), patients with lesions located in the posterior part of the intracranial space, patients at risk of secondary hydrocephalus or brain stem compression, and patients with hemorrhagic or necrotic tumors.

Moreover, patients with multiple BM-CRC can also benefit from surgery. Even if resection of all metastatic lesions is not possible, removal of the most dangerous ones may reduce neurological symptoms and improve the efficacy of subsequent WBRT [9, 11, 13, 16, 23, 26, 28, 30, 33, 39, 41].

In selected cases, aggressive surgical treatment undoubtedly prolongs survival even in the presence of extracranial metastases from CRC [1, 3, 7, 8, 9, 13, 16, 22, 26–28, 30, 33]; this refers mostly to patients with a limited number of BM-CRC [1–3, 13, 26–28, 33, 39, 41].

It must also be underlined that surgical treatment of BM-CRC has recently become more effective and safer thanks to, among others, intraoperative mapping and neuronavigation.

The role of adjuvant WBRT after BM-CRC surgery is controversial [1, 31]. Most researchers believe that a combination of these methods is more effective than surgery alone [1, 15, 23, 26–28, 33, 38, 39, 46], even in patients with a single BM-CRC [1, 24]. Go et al. emphasize that even though WBRT conducted after surgery or SRS does not evidently benefit survival, it surely reduces the occurrence of new BM-CRC and decreases the risk of death due to neurological complications [9].

Stereotactic radiosurgery (SRS)

The most suitable candidates for SRS are:

- patients with 1–3 BM-CRC not greater than 3–3.5 cm in diameter;
- patients with BM-CRC located in all brain regions, also in areas that are unavailable for surgery;
- patients without or with minor neurological signs;
- patients with controlled extracranial disease [1, 9, 13, 28, 42, 43].

SRS can be used:

- alone as an independent treatment method in selected patients with BM-CRC;
- as the primary treatment method in combination with WBRT;
- as postoperative treatment;
- as a radiation boost method after WBRT;
- as treatment of recurrences after surgery and/or WBRT;

and its efficacy has been supported in observations of most authors [1, 4, 5, 7, 13, 21, 23, 27, 28, 31–33, 41, 43].

The maximum permitted single radiation dose for a tumor smaller than 2 cm in diameter is 24 Gy, while doses of 18 Gy and 15 Gy are used for tumors of 2.1–3 cm and 3.1–4 cm in diameter, respectively. Patients with BM-CRC located in or adjacent to the brain stem and optic chiasm receive lower radiation doses. The most common is a single SRS dose of 20 Gy with 14 Gy in a 70% isodose. In the case of hypofractionated SRS, a dose of 33 Gy is delivered in 3 fractions of 11 Gy each, every 2 days with 23.1 Gy in a 70% isodose [5].

Studies that compare the efficacy of SRS and surgical treatment evoke certain doubts; indications for each of these methods are partly similar and partly significantly different. The advantages of surgery include the removal of greater tumors (over 3 cm) and rapid regression of neurological signs and symptoms upon

metastasis resection. SRS in turn is less troublesome for the patient and is able to treat metastases located in regions that are unavailable to surgery. Patients treated with surgery or SRS alone require careful and frequent follow-up visits as they are at risk of both local relapse and occurrence of BM-CRC in the non-irradiated part of the brain.

Whole brain radiotherapy (WBRT)

WBRT remains the mainstay of palliative BM-CRC treatment. It is mainly used in patients with multiple BM-CRC, those who are ineligible for surgery or SRS, with poor performance status and with uncontrolled extracranial disease [1, 4, 20, 28, 44]. The most frequently applied doses are: 35–37.5 Gy in 14–15 fractions of 2 Gy each, 30 Gy in 10 fractions of 3 Gy each and 20 Gy in 5 fractions of 4 Gy each [1, 10, 13, 20].

There is undoubtedly a group of patients who do not benefit from WBRT and should be treated symptomatically only (best supportive care, BSC) in the form of antiedematous (corticosteroids, osmotic diuretics), antiepileptic or antithrombotic drugs, etc. [1].

Systemic therapy Chemotherapy

Usually, most patients receive palliative chemotherapy due to other extracranial metastases from CRC before the occurrence of BM-CRC. However, these drugs only slightly cross the blood–brain barrier, hence literature evidence concerning chemotherapy efficacy in BM-CRC is lacking [1, 13]. Few authors suggest that the continuation of standard chemotherapy (oxaliplatin, irinotecan, fluoropyrimidine) may prolong survival, but more so due to its effect on extracranial metastases than on BM-CRC [1, 13, 23, 35].

Single attempts have been made at using anti-VEGF (vascular endothelial growth factor) antibodies, such as bevacizumab, or anti-EGFR (epidermal growth factor receptor) antibodies, such as gefitinib, erlotinib or afatinib, either alone or in combination with chemotherapy [4, 35, 36].

As of today, however, there are no sufficient data to formulate any conclusions about optimal systemic treatment of patients with BM-CRC [1].

TREATMENT OUTCOMES IN PATIENTS WITH BM-CRC

Patients with BM-CRC definitely present poor prognosis, worse than patients with BM from non-small cell lung carcinoma or breast cancer [1, 3, 11, 13, 22]. Median overall survival (OS), as presented in the references from 2014–2016, ranges from 2 to 7 months [2–4, 6, 7, 10]. In the analysis of 1980 patients with BM-CRC, presented in 2017 by Mege et al. and based on data from 1983–2015, median OS was 6 (3–14) months [1]. Higher OS rates have been reported in highly selected groups of patients [7, 9, 22, 27, 38]. This phenomenon is clearly represented in the analysis of Mege et al. by the relationship of treatment outcomes with the employed treatment method: median survival ranged from 0.5 to 2.5 months in the case of non-causal treatment, 2–9 months for WBRT, 3–16.2 months for surgery alone, 7.6–14 months for surgery with adjuvant WBRT and 5.1–9 months for SRS [1, 18, 22, 26, 30, 32, 38, 41].

Pietrantonio et al. reported median OS of 6 months in 227 patients with BM-CRC; 47.0% of patients survived 6 months, and 22.3% of patients survived 12 months. Median OS in patients with KPS of 90–100, 70–80 and <70 was 12, 6 and 4 months, respectively. OS reached 7 months in patients with 1 BM-CRC, 5 months with 2–3 BM-CRC and 4 months with >3 BM-CRC. In patients with supratentorial BM-CRC, OS reached 7 months, while in those with both supra- and subtentorial BM-CRC, OS was 4 months. With no extracranial metastases, median OS was 11 months, whereas the presence of other lesions (in the lungs, liver and/or bones) decreased it to 5 months. OS was 2 months longer in patients after neurosurgery compared with those who had not received surgical treatment (7 vs 5 months), and 3 months longer in patients after SRS compared with those who had received WBRT (7 vs 4 months) [7].

In 128 patients, Michl et al. (2015) reported 6-month OS of 26.8%, 12-month OS of 11%, 24-month OS of 2.6% and 5-year OS of 0.4% (1 patient); median OS was 2 months [6]. In the group of 93 patients presented by Gu et al., (2015), median OS was 9.6 months; 27.7% of patients survived 12 months, and 9.9% of patients survived 24 months [8].

In 2016, Nieder et al. presented an analysis of 57 patients with BM-CRC. Patients treated with BSC only were characterized by median OS of 0.6 months, those treated with primary WBRT – 3.0 months, and those treated with primary neurosurgery – 12.7 months. Patients with KPS <70, 70, 80, 90 and 100 survived 1.1 months, 4.0 months, 3.6 months, 5.7 months and 37.0 months, respectively. In patients with BM-CRC being the only distant metastasis, median survival was 9.6 months, while in patients with extracranial metastasis – only 3.6 months [20].

In a small group of patients (15), Paix et al. (2017) noted median survival of 8 months (4.7–11.3 months); 58.7% of patients survived 6 months, 42.8% of patients survived 12 months, 34.2% of patients survived 18 months, and 22.8% of patients survived 24 months; all patients were treated with SRS [5]. In the group of 40 patients, Fountzilias et al. (2017) reported median OS of 3.2 months [4].

PROGNOSTIC FACTORS

The most common prognostic factors in patients with BM-CRC, as mentioned in the literature, include:

- a. the Karnofsky performance status; KPS <70 is considered to indicate extremely poor prognosis [1, 7, 10, 20, 33, 34, 40, 43, 44]. Among 227 patients with BM-CRC from 8 Italian cancer centers, KPS = 90–100 was a good prognostic factor [7];
- b. the RPA (recursive partitioning analysis) index according to Gaspar et al. [45]; RPA I° or II° are considered good prognostic factors [1, 18, 22, 23, 25, 32, 40–42];
- c. number of BM-CRC [5, 10, 13, 30, 32, 33, 40, 41]; 1–2 brain metastases are considered a good prognostic factor [7, 13, 16, 22, 27, 28, 30, 40, 41, 44]; the best prognosis is observed in patients with a single BM-CRC [9, 27, 30].
- d. extracranial disease status: the lack of active CRC, which means controlled underlying disease, is a positive prognostic factor [9, 16, 18, 27, 28, 30, 32, 33, 40, 41, 43, 44, 46].

Other potential prognostic factors, such as the size and location of BM-CRC [7, 18, 32, 33, 40, 41], patient's age [7, 9, 27, 32, 33, 40, 41], or time from CRC diagnosis to BM-CRC occurrence [32], are mentioned less frequently.

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