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## The peculiarities of radiation therapy in patients with brain metastases

**Relevance:** Brain metastases (BM) are the most common intracranial tumor lesions in cancer patients. The introduction of new programs of antitumor treatment utilizing modern antitumor drugs and innovative methods of radiation therapy (RT) will significantly increase the survival of cancer patients. Effective treatment and local follow-up are essential for predicting the overall survival and quality of life (QOL) of the patients with BM.

The purpose of BM treatment is to prevent the death of patients from an intracranial progression of the disease, reduce or prevent neurological symptoms while preserving the patient's QOL as long as possible.

In Kazakhstan, the lack of randomized multicenter studies and sufficient clinical experience of simultaneous total and local radiation exposure remains the reason for uncertain positions of specialists regarding the choice of optimal radiation treatment tactics.

The purpose of this study was the optimization of treatment and improvement of QOL of patients with BM through the optimization of RT protocols.

**Results:** Subjective effect after RT was assessed in 20 patients within 30 days after the end of the course. The assessed parameters included "the reduction of neurological symptoms," "the reduction of headache."

The overall objective effect was achieved within 3 months after the end of the RT course and adjuvant chemotherapy courses. Control MRI of the head with a contrast medium has shown positive dynamics in 12 patients, including 4 patients with non-small cell lung cancer. The stabilization was achieved in 2 patients with kidney cancer against target therapy, in 1 patient with melanoma, in 2 patients with small cell lung cancer, and in 1 patient with breast cancer.

The use of hyper-fractionated RT in multiple brain metastases allowed eliminating the neurological symptoms and led to a 9-month life extension and improved QOL.

**Conclusion:** BM is a serious complication of cancer. The achievements in drug treatment resulted in a higher overall survival of cancer patients what made the brain metastases more common. On the other hand, the possibilities to treat patients with BM are expanding. Microsurgical techniques, stereotactic radiotherapy and radiosurgery are now actively introduced into practice. It necessitates the development of clinical recommendations reflecting current treatment standards for BM based on the results of randomized studies.

**Keywords:** Oncology, radiation therapy (RT), brain metastases (BM), oligometastases.

**Introduction:** Brain metastases (BM) is a serious complication of a tumor process course. BM is observed in approximately 50% of cancer cases and is most often in lung cancer (31–63%), breast cancer (10–30%), kidney cancer, colorectal cancer, and melanoma. BM is most common in the age group of 50–70 years. In children, BM is more often with Ewing's sarcoma, rhabdomyosarcoma, neuroblastoma, and osteogenic sarcoma. The nature and severity of neurological signs depend on the size, number, and location of metastatic foci. Approximately 85% of intracranial metastases are located in the cerebral hemispheres, 17–22% – in the cerebellum, and 4–7% – in the basal nuclei and brain stem [1].

No statistical analysis of BM occurrence is conducted in Kazakhstan. BM can have local and/or generalized symptoms and signs. Its clinical manifestations develop gradually during days or weeks, although in some cases, they can occur acutely, like a stroke or cerebral hemorrhage. The most common symptoms are headaches (35–70%), mental and behavioral disorders (25–80%). The convulsions are possible, especially in the case of melanoma and choriocarcinoma metastases. Paresthesia, sensory deficits, unstable gait, convulsive twitching on one side (hemichorea, hemiballismus), diplopia, ptosis, ataxia, orthostatic hypotension, and hiccups are less common. A complete gener-

al examination is required at a suspicion or detection of BM, especially for patients with brain damage without a detected primary tumor or with a known primary cancer in remission. Karnofsky scale or WHO system shall be used for the initial assessment of the state of patients with CNS damage [2]. Both systems allow quantifying the patient's functional state and predict the quality of life and life expectancy.

The cancer statistics are rather disappointing. More than 10,000,000 new cases of malignant neoplasms are registered worldwide each year. That is, approximately 27,000 patients are diagnosed with cancer every day. Today, more than 14 mln people suffer from cancer worldwide; 8.2 million of them die [3]. WHO predicts that cancer incidence and mortality will double in the next 20 years, that is, the number of new cases will increase from 10 to 20 million, and the mortality from 6 to 12 million. In mature countries, cancer incidence and mortality are decreasing in recent years due to better prevention and diagnostics methods and improved specialized treatment. Along with that, the frequency of brain metastases is growing. The frequency of BM is approximately 7–14 per 100 thousand [4].

According to recent population studies, in almost 20% of adult cancer patients, the primary tumor produces BM

during their lifetime. The frequency of primary detection of BM is very variable and depends on the type of primary tumor. The highest frequency is observed in lung cancer (20%), melanoma (7%), kidney cancer (6.5%), breast (5%), and colorectal cancer (1.8%). BMs are the least common in prostate cancer, kidney cancer [5].

In 2018, 32,228 new cancer cases were registered in Kazakhstan, not including skin cancer (vs. 31,915 in 2017). The crude incidence rate was 175.2 per 100 thousand (vs. 178.1‰ in 2017); the decline rate  $T_{ch} = -1.6\%$ . The incidence rate in North Kazakhstan (289.1‰), Kostanay (268‰), Pavlodar (263.4‰), East Kazakhstan (251.8‰), Akmol- la (224.6‰), West Kazakhstan (207.9‰) and Aktobe (189.7‰) regions and the city of Almaty (190.6‰) was above the national average [6].

The above statistics necessitate the introduction of new cancer treatment programs, including the use of modern antitumor drugs and innovative radiation therapy techniques to significantly increase the survival of cancer patients.

**Materials and methods:** 20 patients aged 30 to 60 years with multiple BM (4 and more) received conformal radiotherapy followed by adjuvant chemotherapy courses in 2016-2018.

Their concomitant diseases mainly included cardiovascular and gastroenterological disorders. The general condition at admission was average, with moderately pronounced cerebral symptoms. Score on the Karnofsky scale - 50-80 points.

The patients underwent CT topography on a 64-slice computer tomograph SOMATOM Definition AS after the manufacture of individual fixation masks. The radiotherapy regimen was selected individually using dosimetric planning on the ECLIPSE 11 System. The conformal radiation therapy course was administered using linear electron accelerator Clinac 2100 with the single boost dose of 3.0 Gy, 5 fractions per week, the total boost dose of 30 Gy, the total brain irradiation to C1. Radiation therapy was

conducted using Kilovoltage onboard imaging (OBI) with KV-image control and accompanied with decongestant, glucocorticoid, anticonvulsant therapy.

**Results:** Subjective effect after radiation therapy was assessed in 20 patients within 30 days after the end of the course. The assessed parameters included "the reduction of neurological symptoms," "the reduction of headache."

The overall objective effect was achieved within 3 months after the end of the RT course and adjuvant chemotherapy courses. Control MRI of the head with a contrast medium has shown positive dynamics in 12 patients, including 4 patients with non-small cell lung cancer. The stabilization was achieved in 2 patients with kidney cancer against target therapy, in 1 patient with melanoma, in 2 patients with small cell lung cancer, and in 1 patient with breast cancer.

**Conclusion:** The use of hyper-fractionated RT in multiple brain metastases allowed eliminating the neurological symptoms and led to a 9-month life extension and improved QOL.

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