Intensity Modulated Radiotherapy in Complex Treatment of Leptomeningeal Disease of Extracranial Solid Neoplasms

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ABSTRACT

Leptomeningeal metastases (LM) are a severe consequence of metastatic distribution of solid malignant tumors. The purpose of this article is to highlight the importance of the intensity modulated radiotherapy (IMRT) to achieve prolonged local tumor control (LTC) in patients with LM.

We present five clinical cases of leptomeningeal disease (LMD) in two patients with breast cancer (BC) and and in another three with malignant melanoma, laryngeal and renal carcinoma. The healing results after intensity modulated whole-brain radiotherapy (IM-WBRT) up to TD 40 Gy with DD 2 Gy, followed by boost radiotherapy (boost-RT) up to TD 50 Gy-54 Gy in the bulky brain metastases was presented. In BC LMD, the concominant RT with targeted therapy (TT) of trastuzumab and denosumab was performed.

Leptomeningeal metastases have a poor prognosis, but precise IMRT with the realization of tolerant doses in normal brain structures and cancericidal doses in pathological brain areas achieves prolonged LTC for one year after RT with good quality of life. LMD in solid tumors requires an individual radiotherapeutic approach on a different target volume and necessary radiation doses, depending on the histological characteristic of tumor cells, as well as on the volume and localization of leptomeningeal metastases.

Keywords

Leptomeningeal metastases, Leptomeningeal disease, Intensity modulated radiotherapy, Whole-brain radiotherapy, Boost radiotherapy, Re-irradiation.

Introduction

Leptomeningeal disease (LMD), also known as neoplastic meningitis, leptomeningeal carcinomatosis or carcinomatous meningitis, is a rare cancer complication occurring in ~5% all cancer patients [1-3], in which malignant cells infiltrate the layers of the central nervous system (CNS) [4,5] and ultimately leads to significant morbidity and mortality [6]. Leptomeningeal metastases (LM) are common in lung, breast, renal cell cancers and melanomas, and is one of the most devastating metastatic disease scenarios

[7]. With improved systemic therapies successfully resulting in more long-term survivors with advanced cancers, the incidence of CNS metastases is increasing [8,9]. Overall, LM likely comprises about 11-20% of CNS metastasis [10,11]. The prognosis is very poor, with median overall survival (OS) of around 3-4 months from diagnosis [12,13]. MRI and CT demonstrate multiple masses within the subarachnoid space, hydrocephalus without a discernible cause, or diffuse leptomeningeal enhancement [14]. In this article, we present the effectiveness of intensity modulated radiotherapy (IMRT) in five clinical cases of LMD after intensity modulated whole-brain radiotherapy (WBRT) with boost RT, after radiosurgery (RS) with WBRT, and after re-irradiation in LM progression, as well as with concominant targeted therapy (TT) in both patients with breast carcinoma (BC).

Clinical Cases

Clinical case № 1

It concerns a 53-year patient, who was operated for kidney carcinoma (with histological result- clear cell renal carcinoma) 13 years ago. Due to complaints of headaches and dizziness after CT, a brain tumor in the area of right lateral ventricle was established. Through 26/May/20 has been carried out craniotomy with a tumor excision of right thalamus. Postoperative MRI brain / June 2020 - State after right parieto occipital craniotomy with tumor excision in the right-sided thalamic periventricular region. Periventricular edema significantly reduced compared to preoperative MRI. Data on periventricular leptomeningeal metastases in the right-sided ventricle (Figure1).

From 26/Jun/20 to 30/Jul/20 intensity modulated whole brain radiotherapy (IM- WBRT) up to total dose (TD) 40 Gy with daily dose (DD) 2 Gy, after which boost in the cerebral ventricle up to TD 50 Gy with DD 2 Gy was conducted (Figure 2). After 10 months of RT, at contrast CT a local tumor control was established (Figure 3).

10 months after completing RT, the patient is without neurological symptoms, without progression of the disease and with good quality of life.

Clinical case № 2

It concerns a woman at 68 years. In 2018, CT is performed due to pain in the lumbar region and generalized bone metastases are proven. Biopsy of right breast establishes invasive ductal carcinoma / moderately differentiated- T3 N1 (G2); positive estrogen and progesterone receptors, HER2/negativ. The patient was referred to conduct 6 courses systemic chemotherapy and TT (denosumab). After 2 years, in October 2020, due to headaches, CT data on brain metastases are established.

Brain MRI with intravenous contrast

Subtentorial leptomeningeal metastases in the two cerebellar hemispheres. Leptomeningeal metastases supraventricular to the right and along the middle line in two cerebral hemispheres and two subcortical metastases up to 12 mm in the left, without the presence of perifocal brain edema. Without visible pathological signals subtitled in the medulla oblongata and in the proximal cervical spinal cord (Figure 4).

Intensity modulated whole brain radiotherapy

(IM WBRT) up to TD 40 Gy with DD 2 Gy, after which boost-RT in the cerebral ventricles and in the right retrobulbar area up to TD 50 Gy with DD 2 Gy was conducted (Figure 5). After the realization of TD 34 Gy in the whole brain, the patient became ill by COVID-19, which was why the RT was discontinued and sent for treatment. Three months later after a negative PCR test for COVID-19, we continued treatment up to TD 40 Gy in the whole brain with Boost RT in the cerebral ventricles and bilateral retrobulbal areas up to TD 50 Gy and double-sided in large cerebellar brain metastases up to TD 54 Gy (Figure 6).

Seven months after RT, the patient is without neurological symptoms, without progression of the disease and with good quality of life.

Clinical case № 3

It concerns a 48-year-old female patient diagnosed with invasive intraductal carcinoma of the right mammary glands /pT2N0M0, G2, positive estrogen and progesterone receptors, HER2/+ + +/ 10 years ago. Surgery (quadrantectomy with axillary dissection), adjuvant chemotherapy, radiotherapy of right mammary gland with operative scarring to OOD 50 Gy, endocrine therapy,
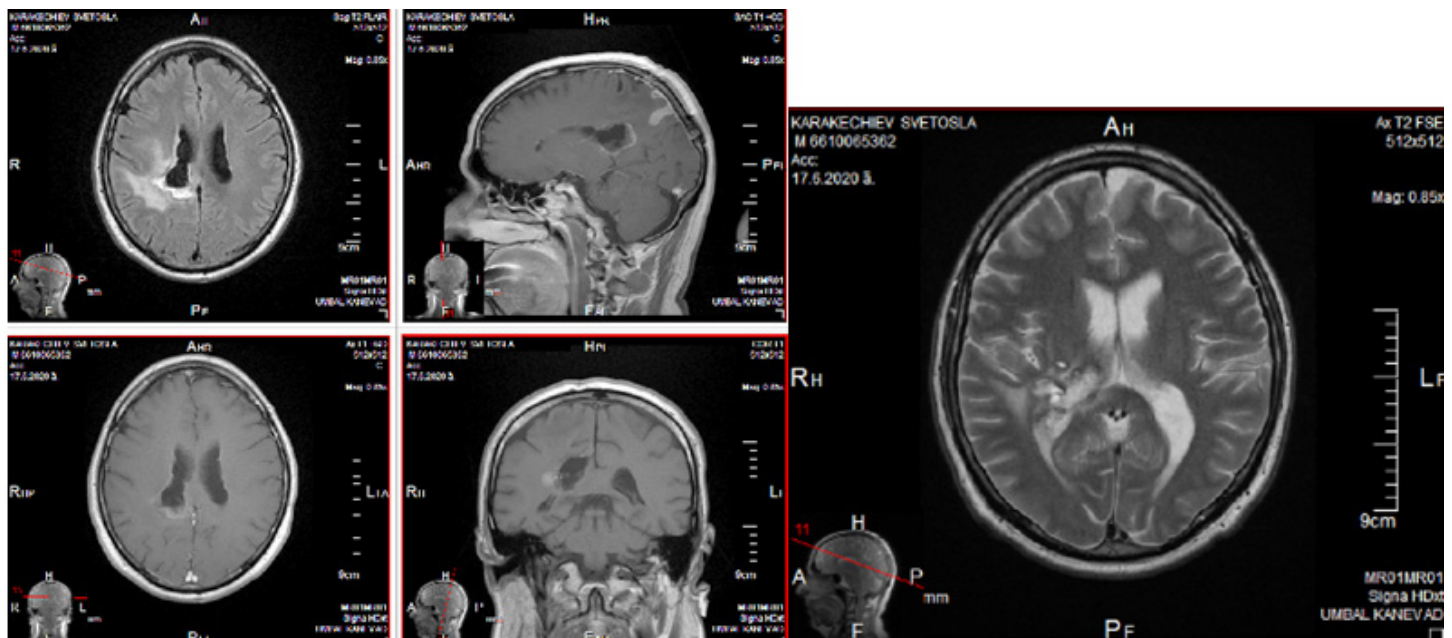

Figure 1: MRI before the RT- MRT data on leptomeningeal metastases in the right-sided brain ventricle and ependimal metastasis with perifocal edema was visualized.
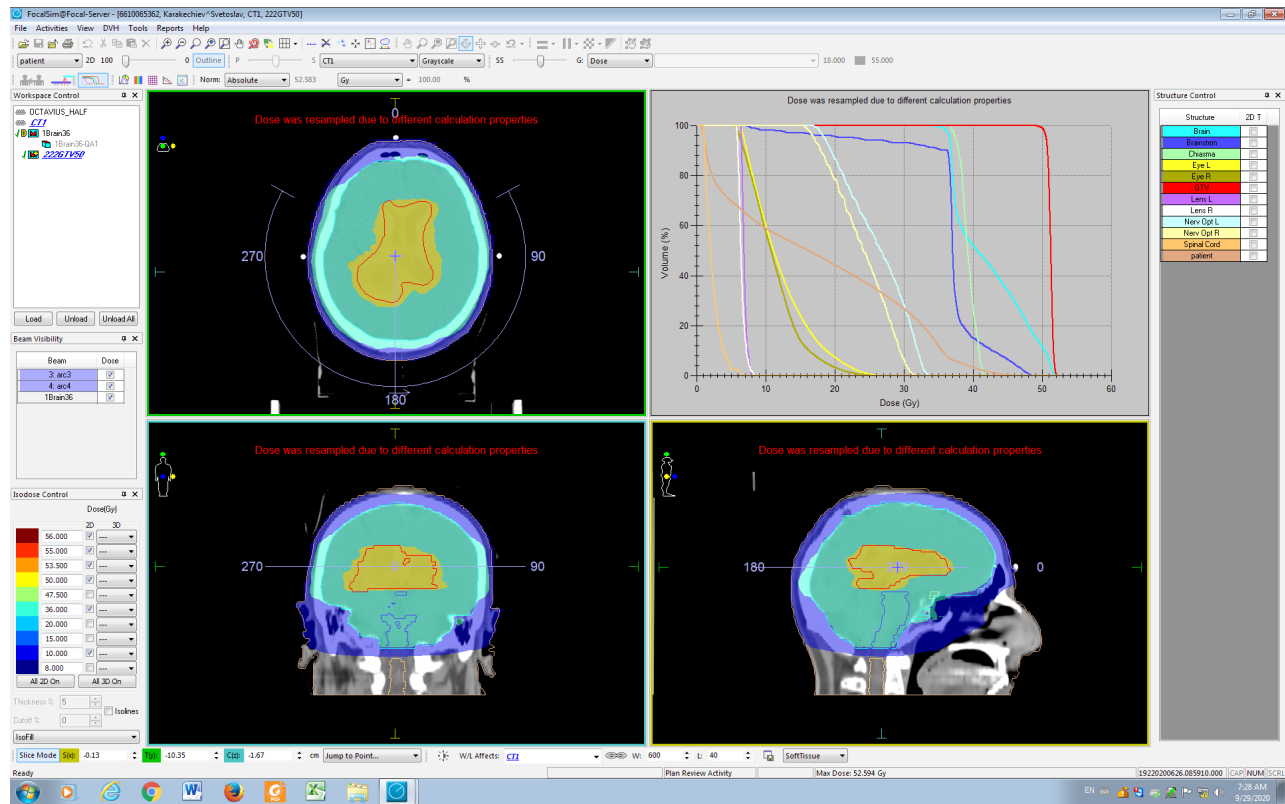
Figure 2: Intensity modulated whole brain radiotherapy up to TD 40 Gy with DD 2 Gy, after which boost RT in the cerebral ventricle up to TD 50 Gy with DD 2 Gy.
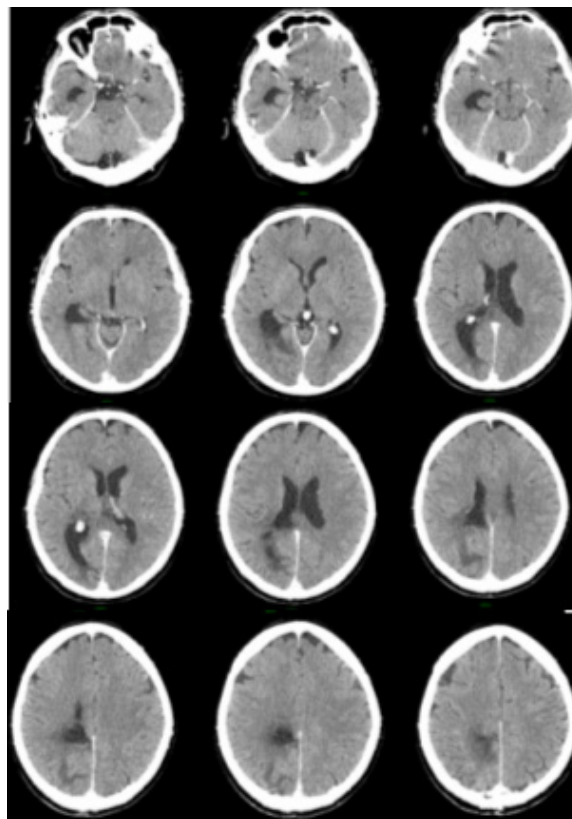

Figure 3: CT of the brain after 10 months of RT- No contrast-reinforcing zones, rather encephalomalacic areas on the right frontal parietal, was visualized.
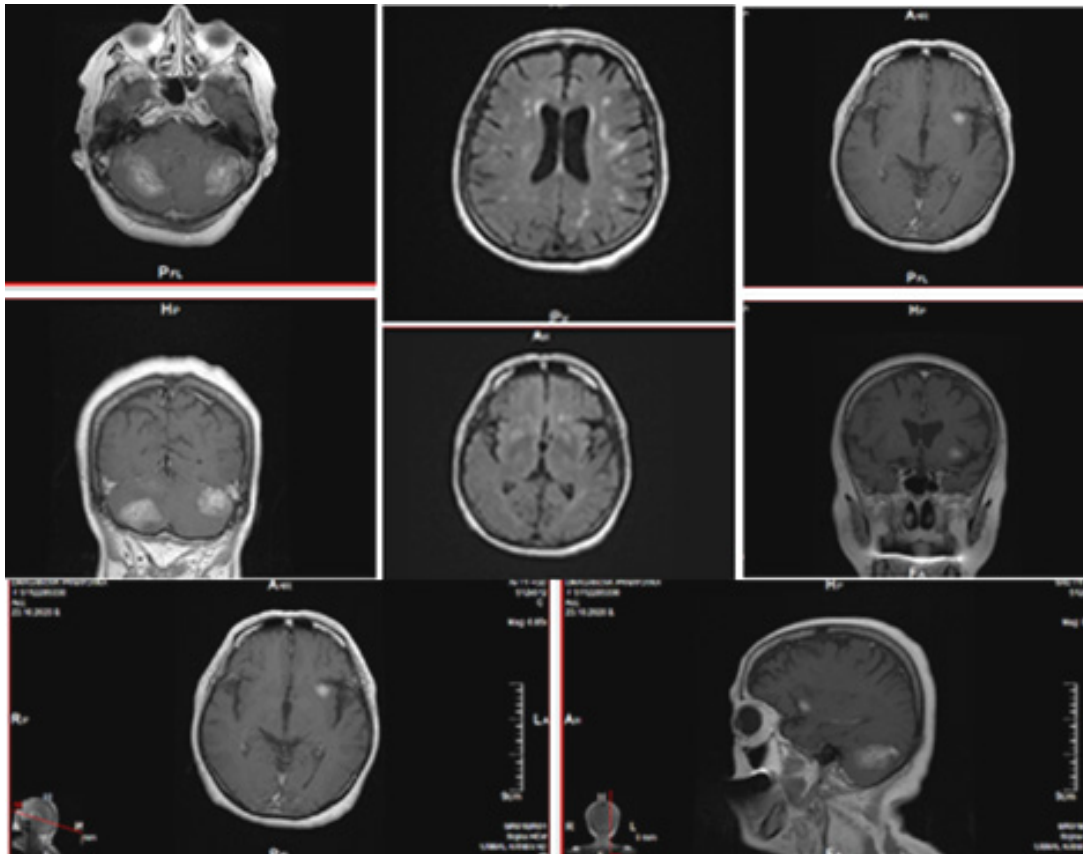
Figure 4: AX T1 FLAIR MRI, COR T1 FLAIR MRI and SAG T1 FLAIR MRI - postcontrast images showing hyperintense leptomeningeal brain lesions, mainly infratentorial in the cerebellum and supratentorial, without visible pathological signals subtitled in the medulla oblongata and in proximal cervical spinal cord.
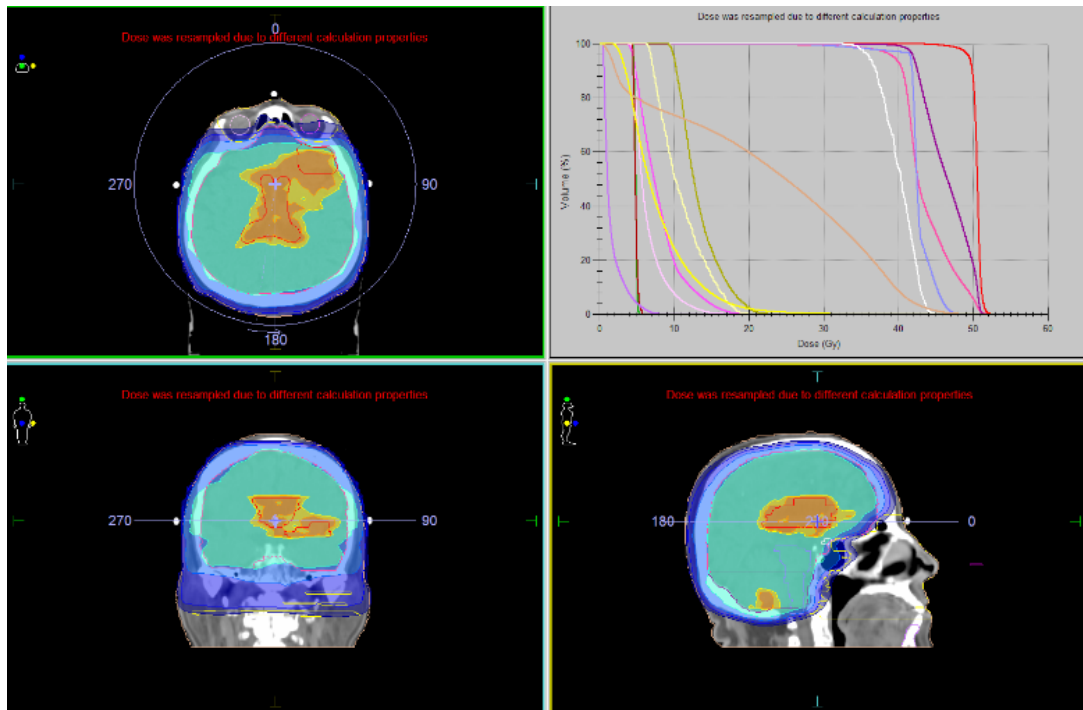

Figure 5: Intensity modulated whole brain radiotherapy to TD 40 Gy with DD 2 Gy, after which boost RT in the cerebral ventricles and in the right retrobulbar area up to TD 50 Gy with DD 2 Gy.
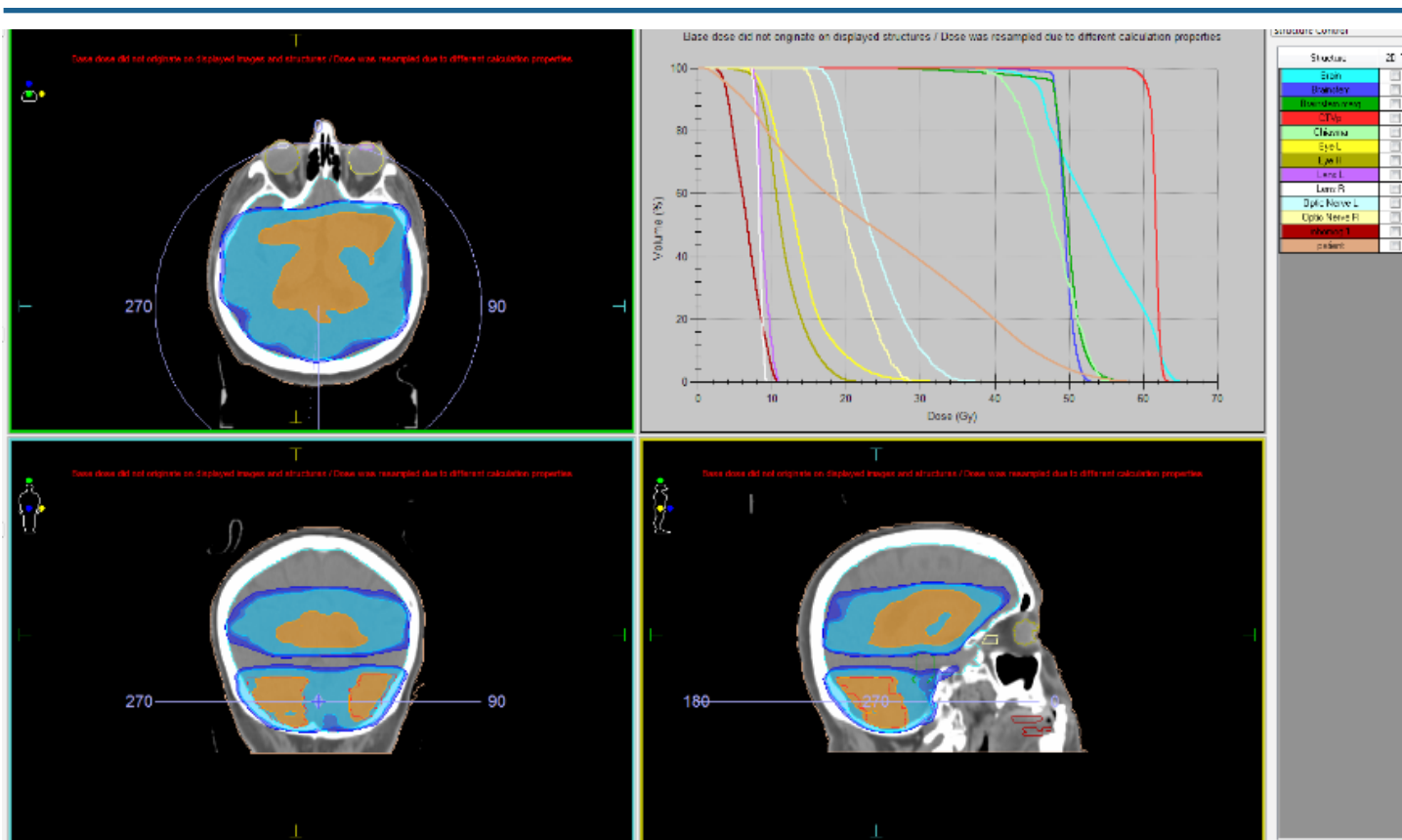
Figure 6: Intensity modulated whole brain radiotherapy after three months after a negative PSR test for Kovid-19 up to TD 40 Gy in the whole brain with Boost RT in the cerebral ventricles and bilateral retrobulbar areas up to TD 50 Gy and double-sided in large cerebellar brain metastases up to TD 54 Gy.

targeted therapy with trastuzumab was conducted. Two years after the diagnosis, local relapse was manifested, surgically removed by a simple mastectomy followed by subsequent healing chemo, targeted and endocrine therapy. In the next 8 years, a consistent solitar liver and pulmonary metastases are diagnosed sequentially, which have been surgically removed and followed by another course of chemo and targeted therapy. On the occasion of an epileptic seizure, a CT of the brain with venous contrast, the infra- and subtentorial metastasis were found. The MRI of neuroaxial reports leptomeningeal brain metastases, mainly infratentorial in the cerebellum and medulla oblongata, with mild compression of the brainstem. The spinal axis has no visible pathological changes (Figure 7 and 8).

It was assessed for whole brain radiotherapy (WBRT) to TD 40 Gy with DD 2 Gy, which is currently being conducted (Figure 9), after which boost-RT in the cerebellum, medulla oblongata, cerebral ventricles and retrobulbar areas bilaterally to TD 50 Gy with DD 2 Gy (Figure 10). Along with the radiotherapy, targeted therapy was performed with Herceptin.

After the completion of the radiotherapy, the targeted therapy was continued. After 2 months of RT in June 2020, a control MRI was performed, which revealed a significant reduction in leptomeningeal metastases. Residual lesions are predominantly in the cerebellum, but metastatic involvement of the spinal axis /

cervical region is already reported. (Figure 11 and 12).

4 months after completion of RT and 3 months of targeted therapy, a control MRI was performed, which showed a reduction in leptomeningeal metastases in the cerebellum with persistence of lesions in the cervical spinal cord (Figures 13-15).

One year after RT, MRI reported progression of LM in cerebellum and in cervical part of spinal axis (Figure 16).

We estimated to perform re-irradiation in the massive metastases of the cerebellum up to TD 20 Gy with DD 2Gy and RT in the LM-infiltrated cervical part of spinal axis up to TD 45Gy with DD 1,8Gy (Figure 17/ A, B). At present, the patient conducts this RT.

Clinical case № 4
Concerned for a patient at the age of 70. In 1995, was diagnosed with locally advanced laryngeal carcinoma. Radical laryngectomy with post-operative telegamatherapy up to 60 Gy was performed. By 2018 he conducted regular inspections. Due to headache a CT with venous brain contrast were performed and two brain metastases were identified (Figure 18), In March 2021 radiosurgery (RS) were conducted with a 15 Gy dose fraction (Figure 19). 2 months later, due to the seizure symptoms, a MRI demonstrated multiple sub- and supratentorial leptomeningeal metastases (Figures 20 and 21). We have judged re-irradiation in the whole brain in two
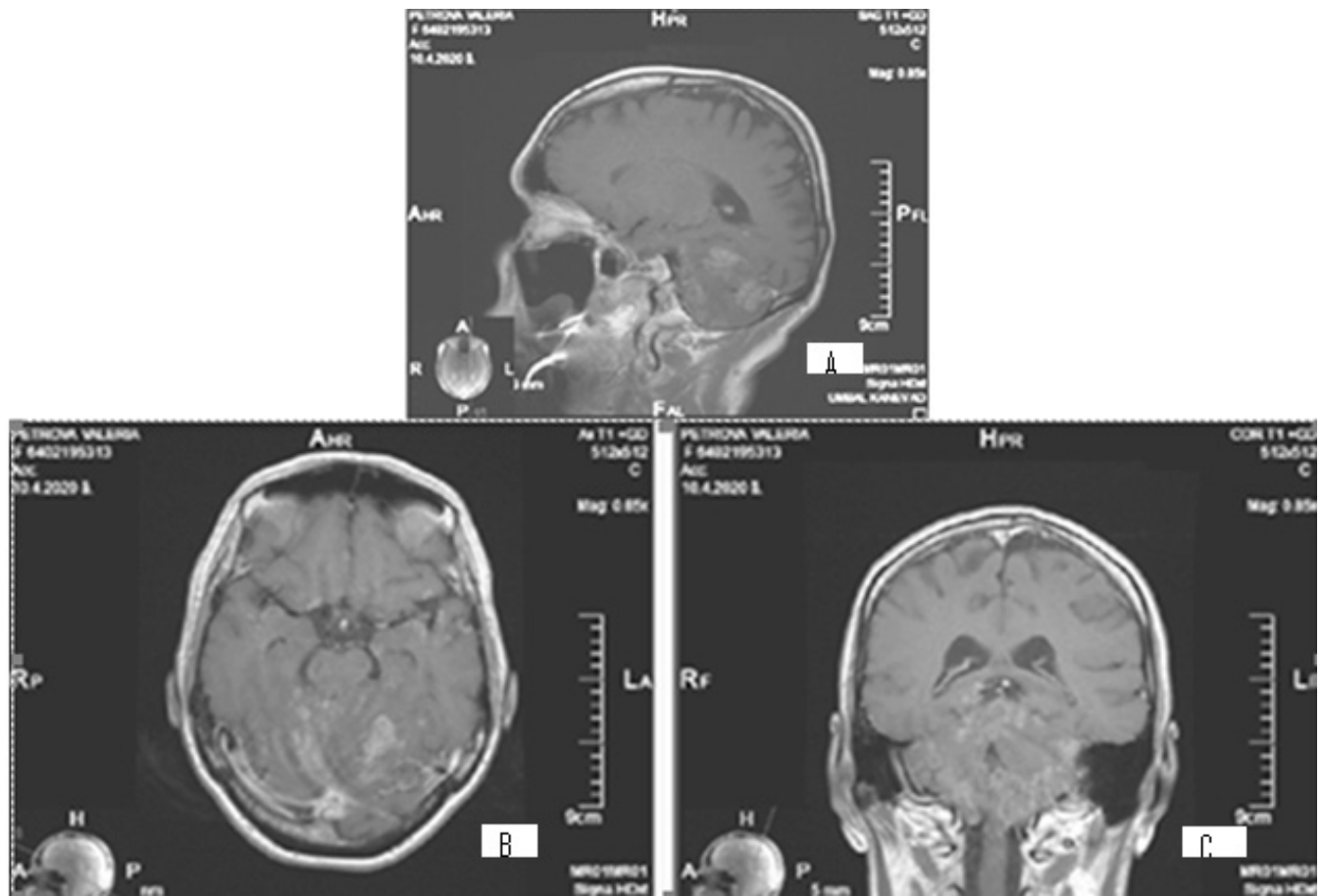
Figure 7: A/SAG T1 FLAIR MRI; B/ AX T1 FLAIR MRI and C/COR T1 FLAIR MRI- postcontrast images showing hyperintense leptomeningeal brain lesions, mainly infratentorial in the cerebellum and medulla oblongata, with mild compression of the brainstem.
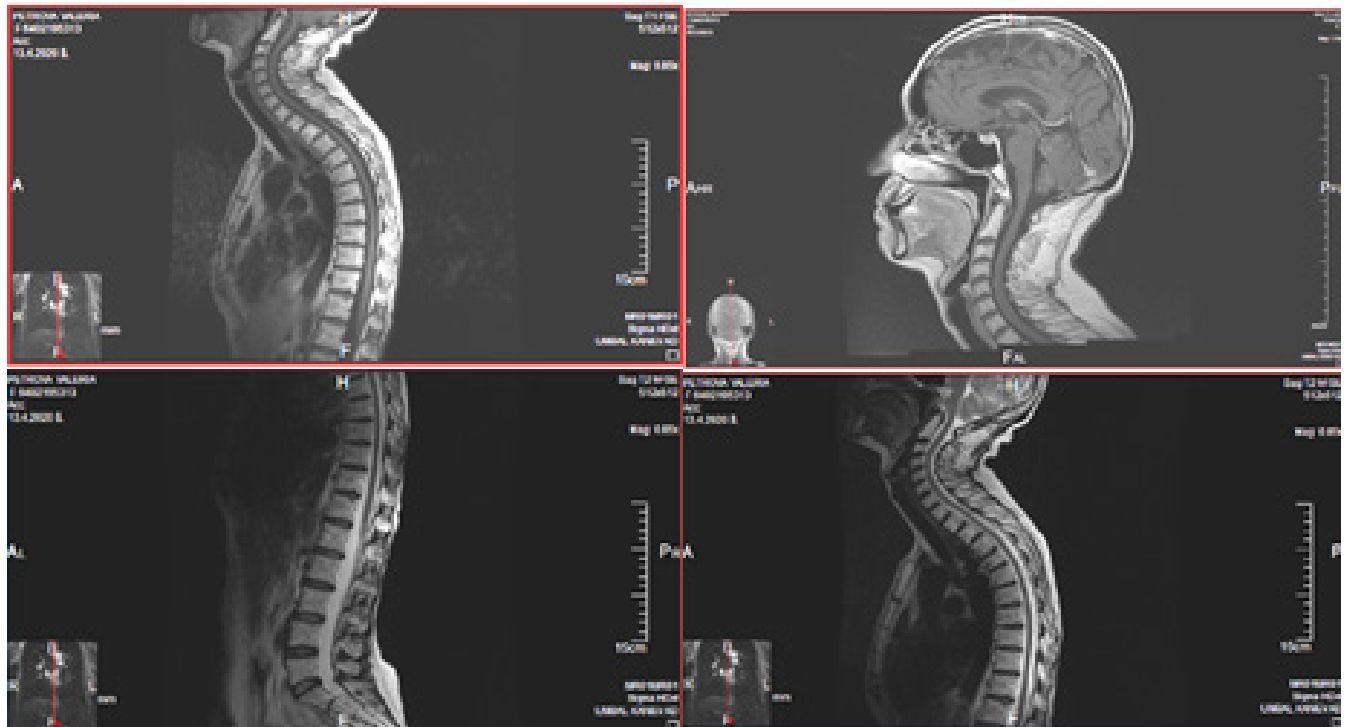

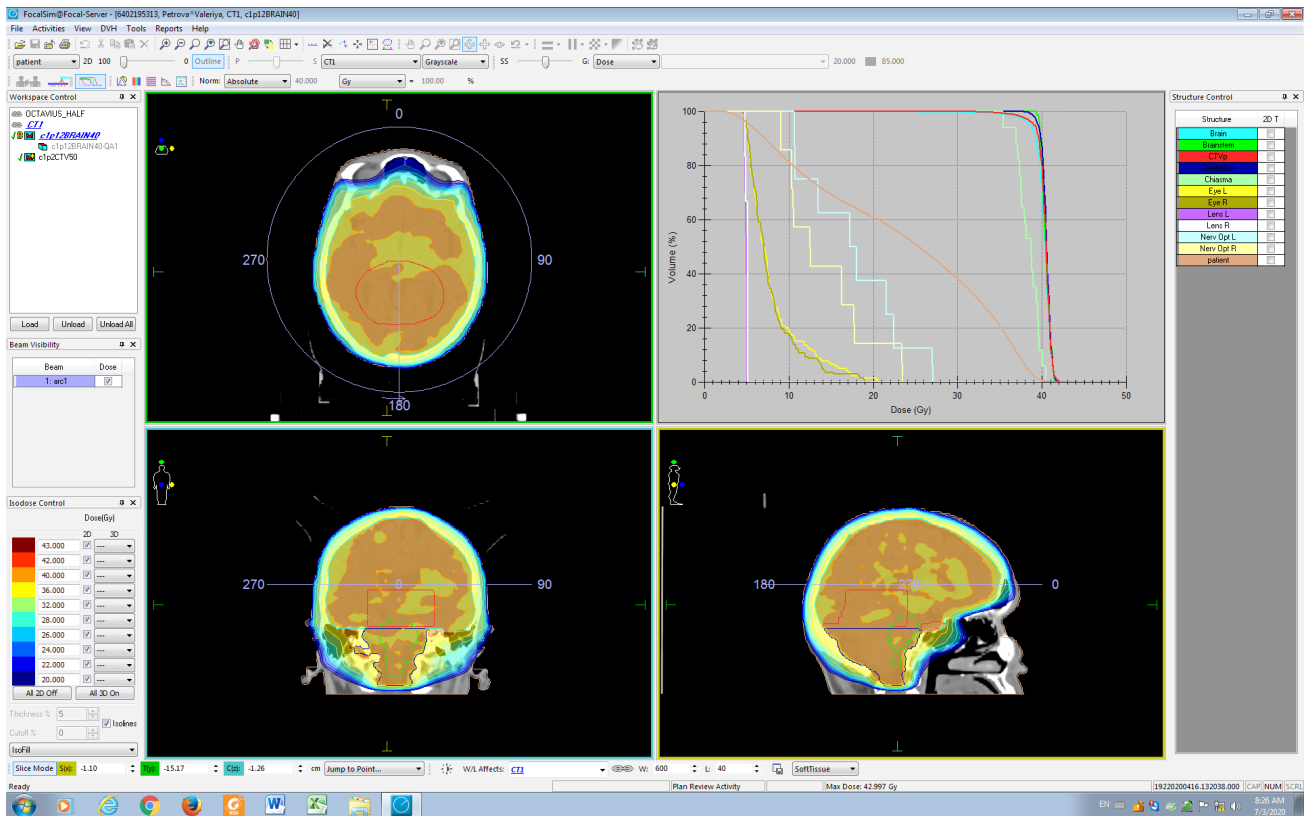**Figure 8:** SAG T2 MR Images without pathological lesions in the spinal cord.

Figure 9: Whole brain radiotherapy (WBRT) with VMAT technique to TD 40 Gy with DD 2 Gy.

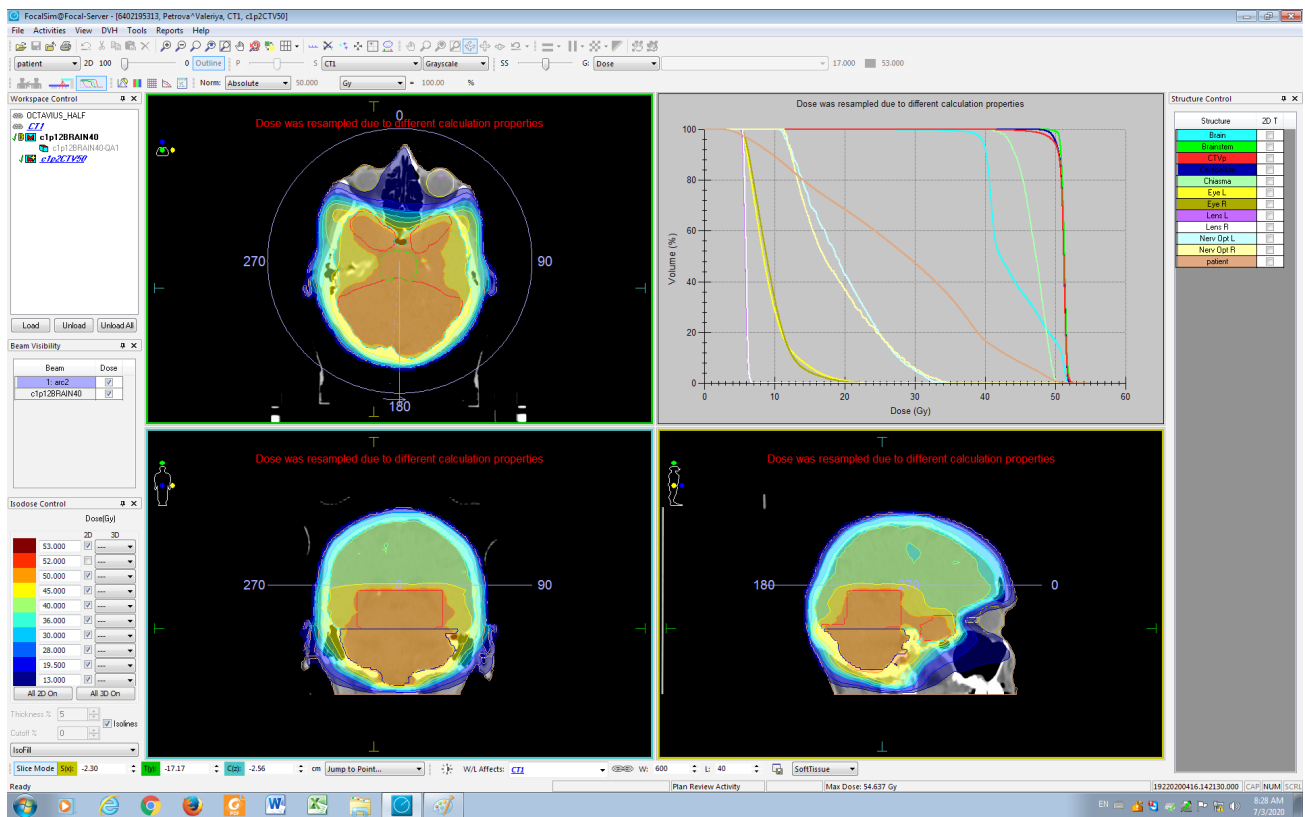**Figure 10:** Boost- RT with VMAT technique in the cerebellum, medulla oblongata, cerebral ventricles and retrobulbar areas bilaterally up to TD 50 Gy with DD 2 Gy.
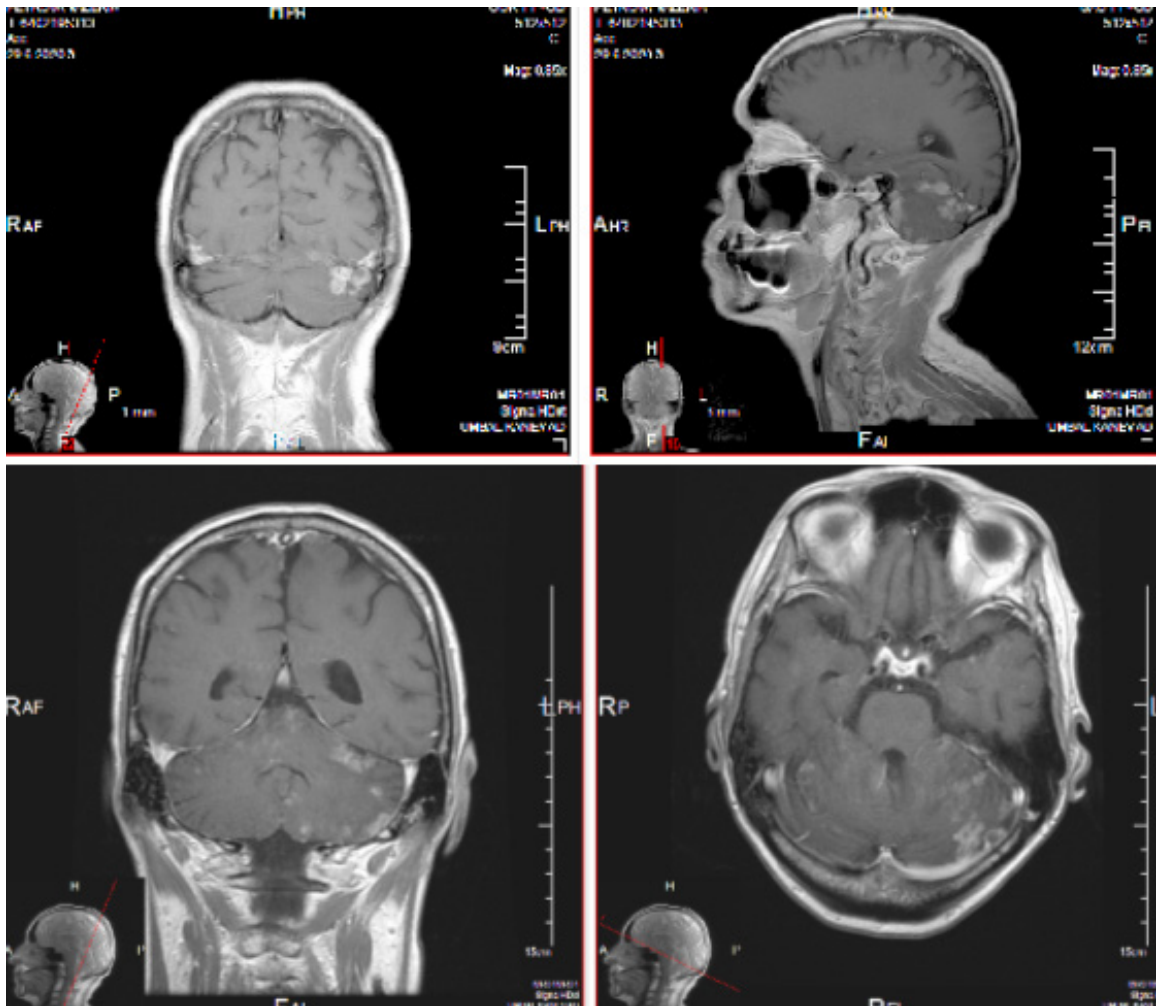
Figure 11: COR T1 FLAIR MRI; SAG T1 FLAIR MRI; AX T1 FLAIR MRI after 2 months of RT.

Figure 12: A/SAG T1 FLAIR MRI of cervical spinal axis after 2 months of RT - metastatic involvement of the spinal axis / cervical region.
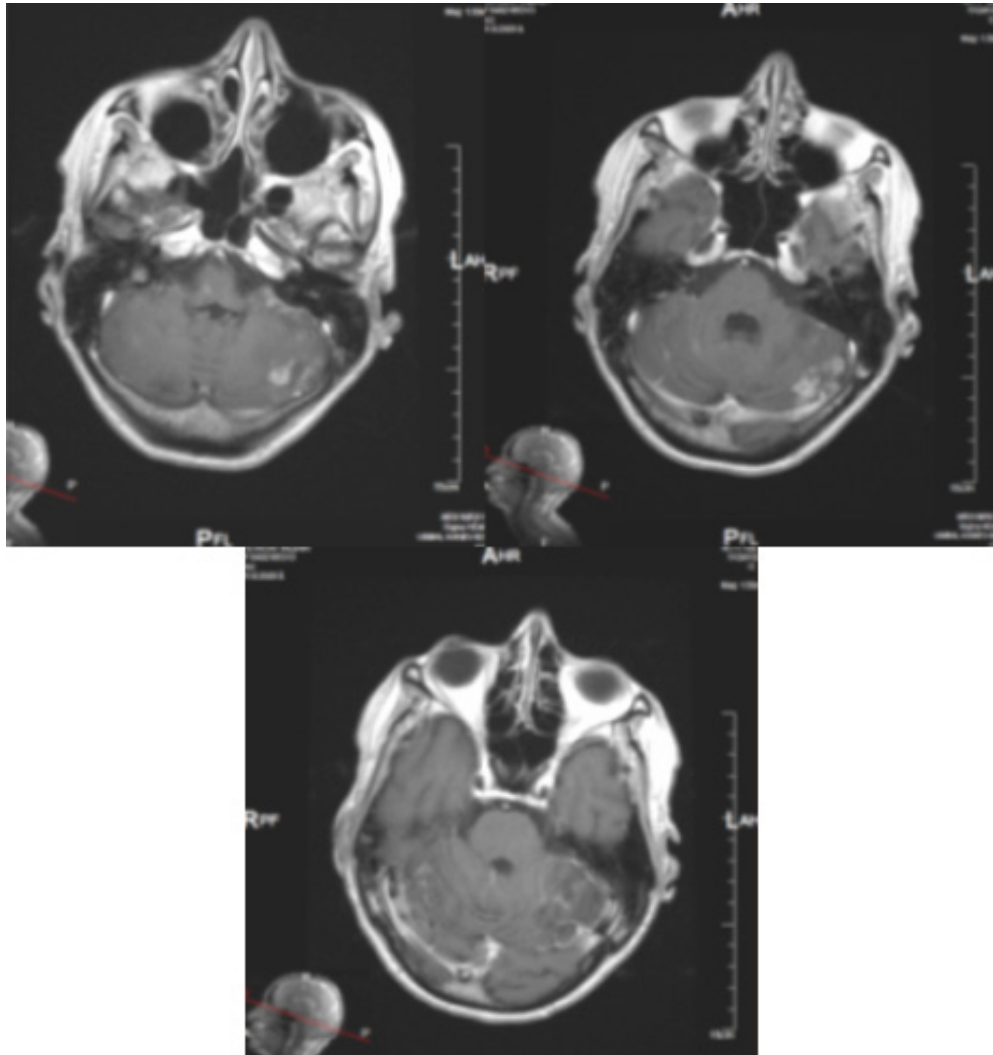
Figure 13: AX T1 FLAIR MRI after 4 months of RT and 3 months of targeted therapy alone.
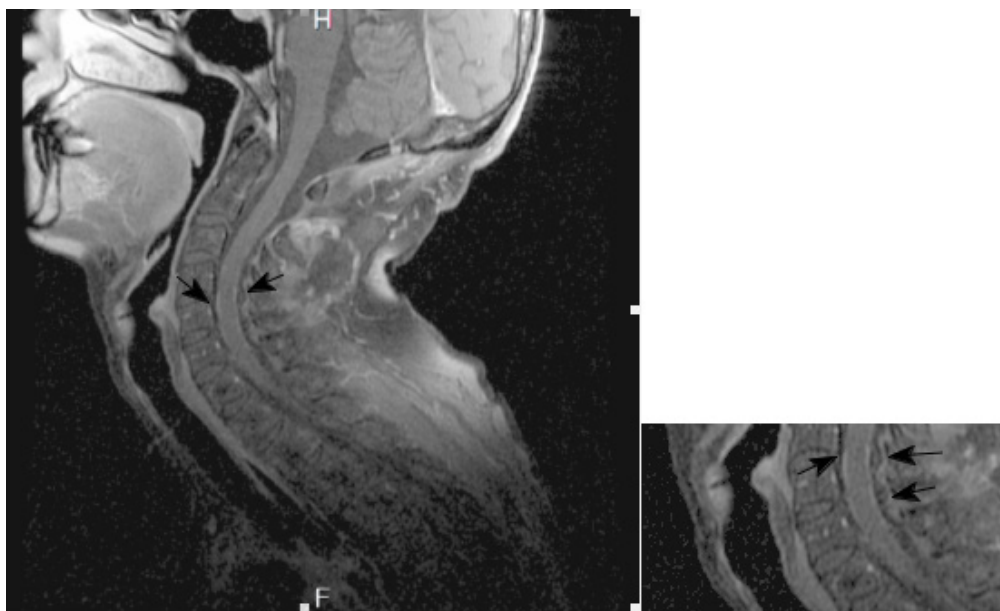
Figure 14: A/SAG T1 FLAIR MRI of cervical spinal axis after 4 months of RT and 3 months of targeted therapy alone.
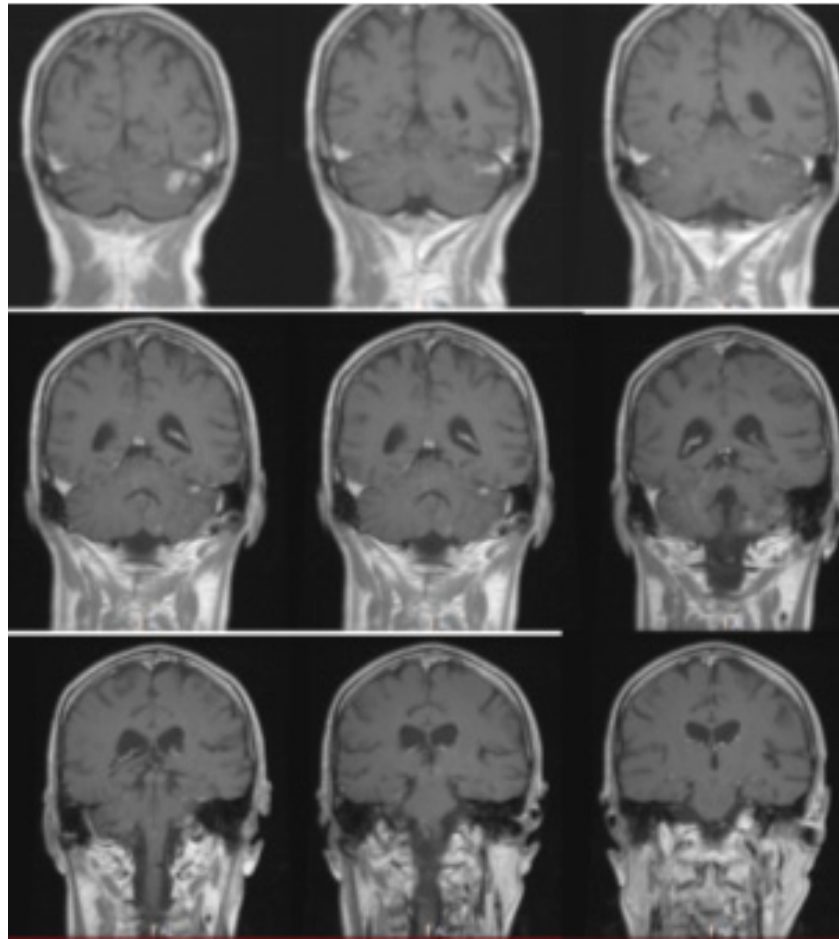
Figure 15: COR T1 FLAIR MRI after 4 months of RT and 3 months of targeted therapy alone.
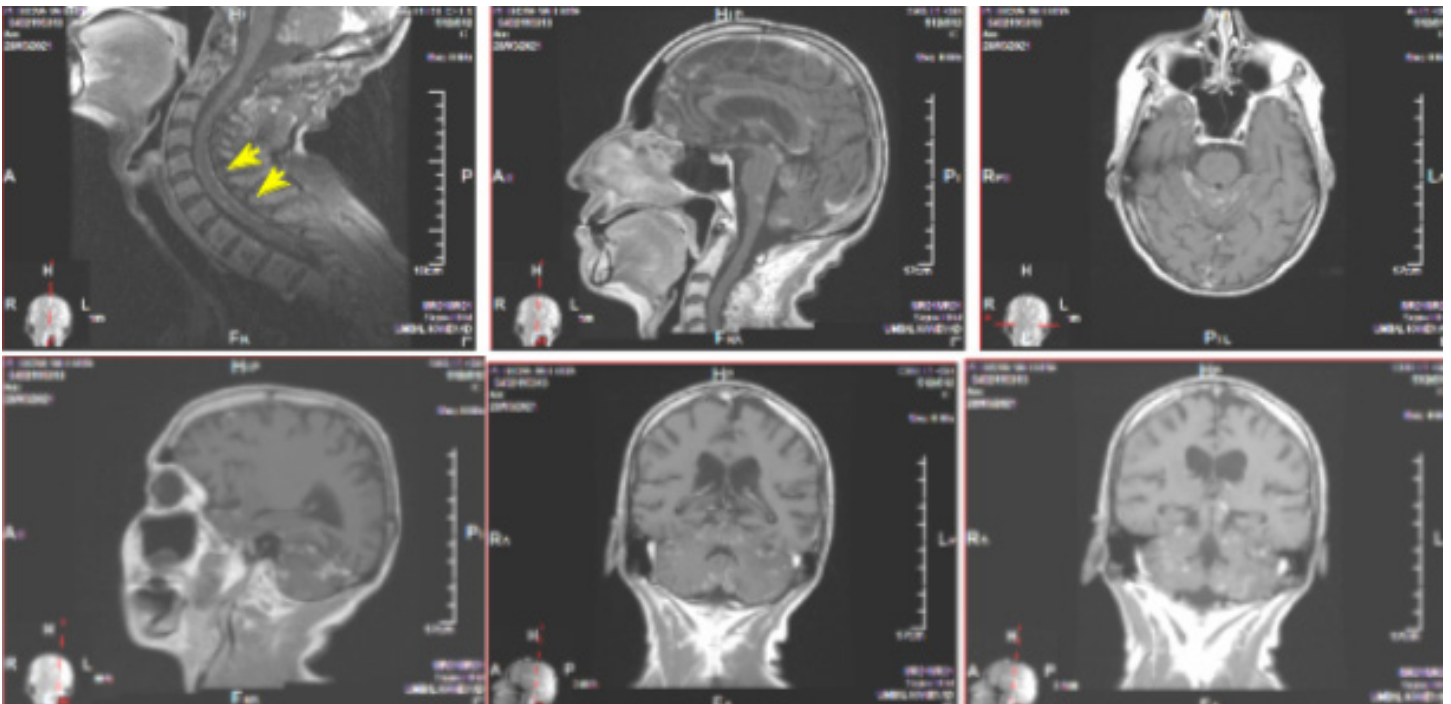
Figure 16: One year after radiotherapy SAG T1 FLAIR MRI, AX T1 FLAIR MRI and COR T1 FLAIR MRI visualized progression of LMD in cerebellum and in cervical part of spinal axis.

Figure 17: A Re- irradiation with VMAT technique in the cerebellum up to TD 20 Gy with DD 2Gy and **B**/ RT in the LM-infiltrated cervical part of spinal axis up to TD 45Gy with DD 1, 8Gy.

Figure 18: Brain CT with intravenous contrast - in the left –sided cerebral hemisphere is recorded cystic brain metastasis with perifocal edema and 27/16 mm dimensions, as well as second periventricular to left frontal ventricular horn with dimensions up to 14 mm (indicated with the yellow arrow).

Figure 19: Radiosurgery with VMAT technique in the field of the two brain metastases with one fraction 15 Gy.

Figure 20: COR T1 FLAIR MRI; SAG T1 FLAIR MRI; AX T1 FLAIR MRI 2 months after radiosurgery - multiple sub- and supratentorial leptomeningeal metastases.
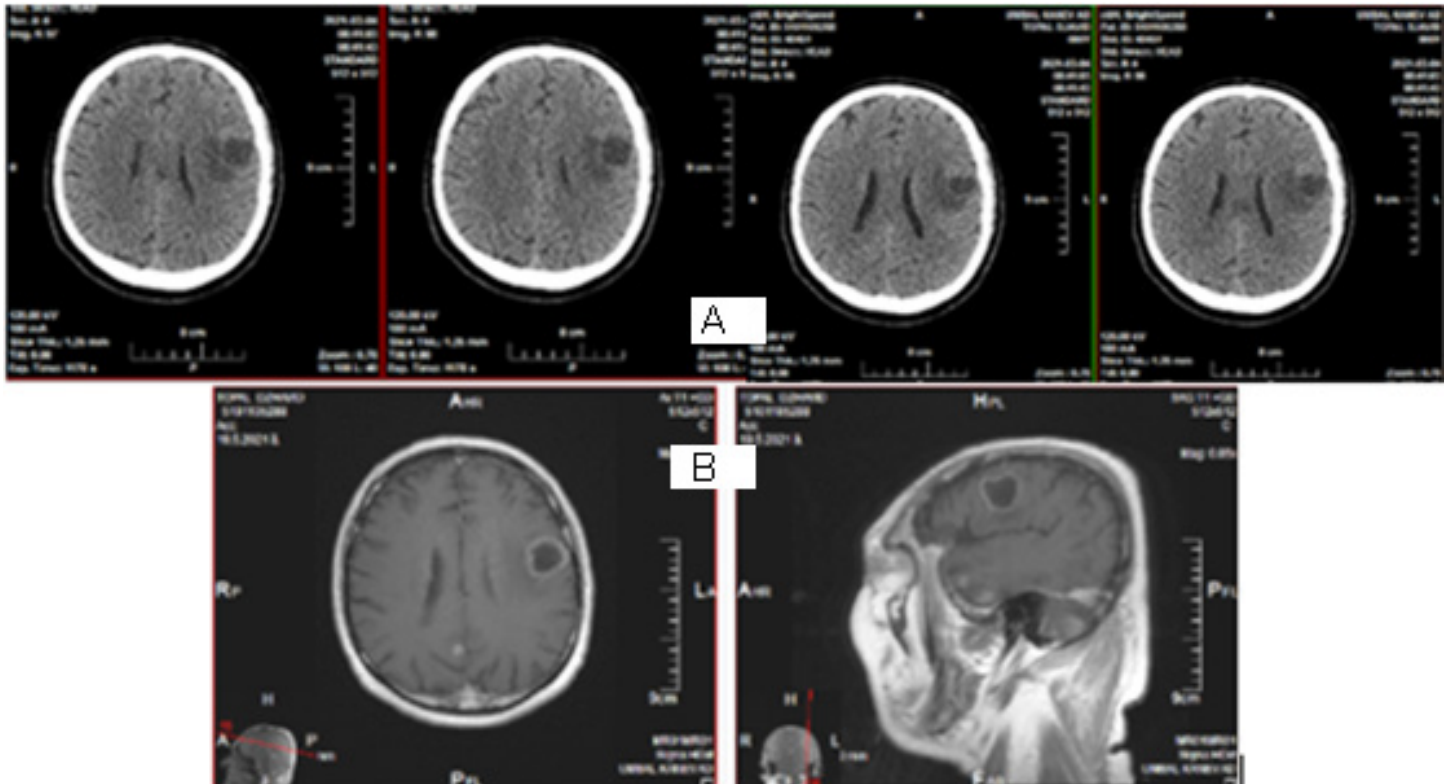
Figure 21: A/B CT and MRT image of the brain metastasis in left brain hemisphere after radiosurgery with 15 Gy.
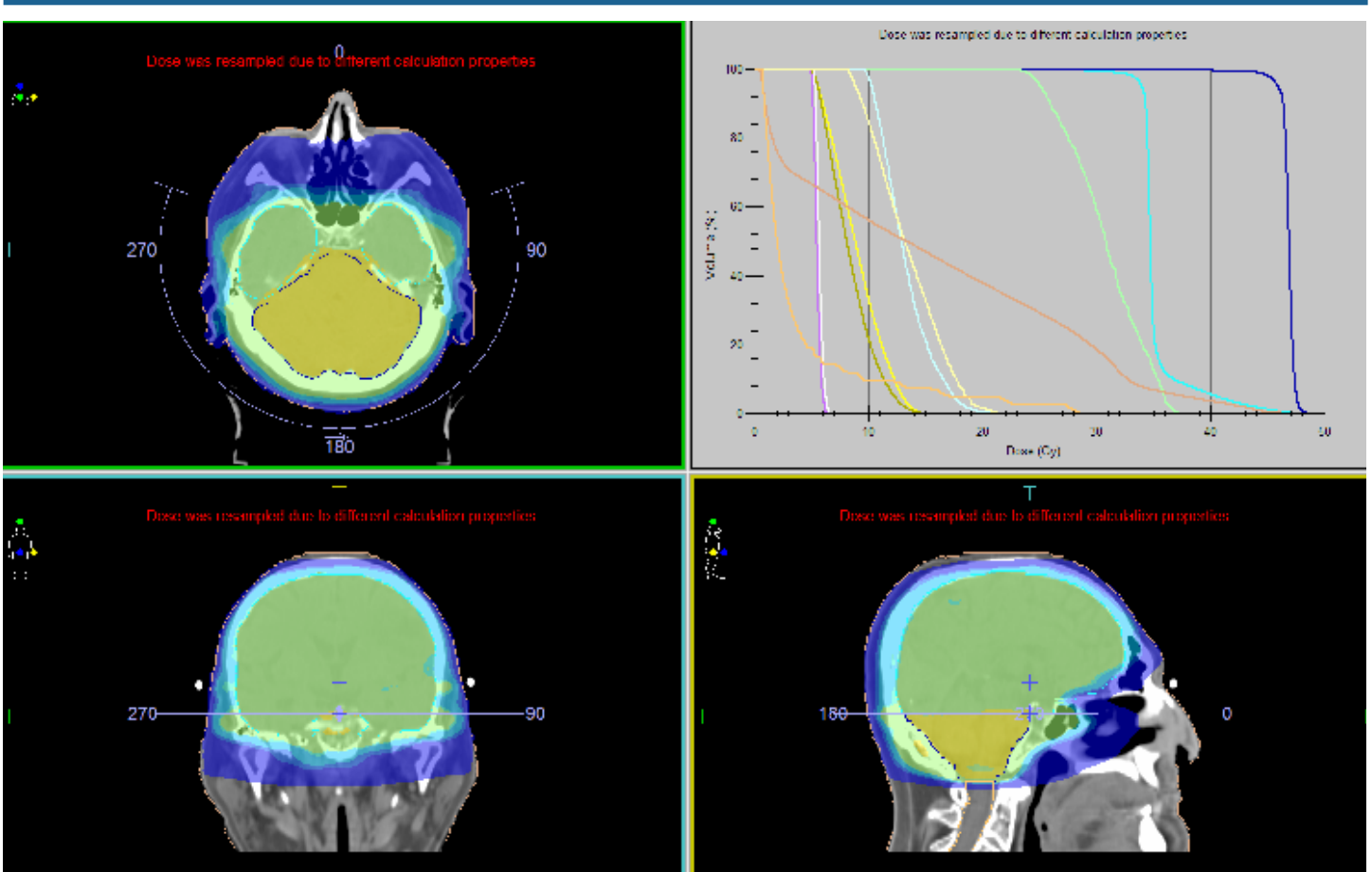
Figure 22: Whole brain Re-irradiation with VMAT technique in the area of two brain hemispheres up to TD 34 Gy and in the cerebellum up to TD 46Gy with DD 2Gy.

Figure 23: Control CT /17.05.21 -Brain leptomeningeal metastases sub-and supratenerially with dimensions up to 10mm (Figure 23).

Figure 24: The Intensity modulated whole-brain radiotherapy (WBRT) with DD 3 Gy up to TD 30 Gy.

brain hemispheres up to TD 34 Gy and in the cerebellum up to TD 46Gy with DD 2Gy (Figure 22). Currently, the patient conducts this second irradiation, covered with antiedematous and anti-inflammatory therapy.
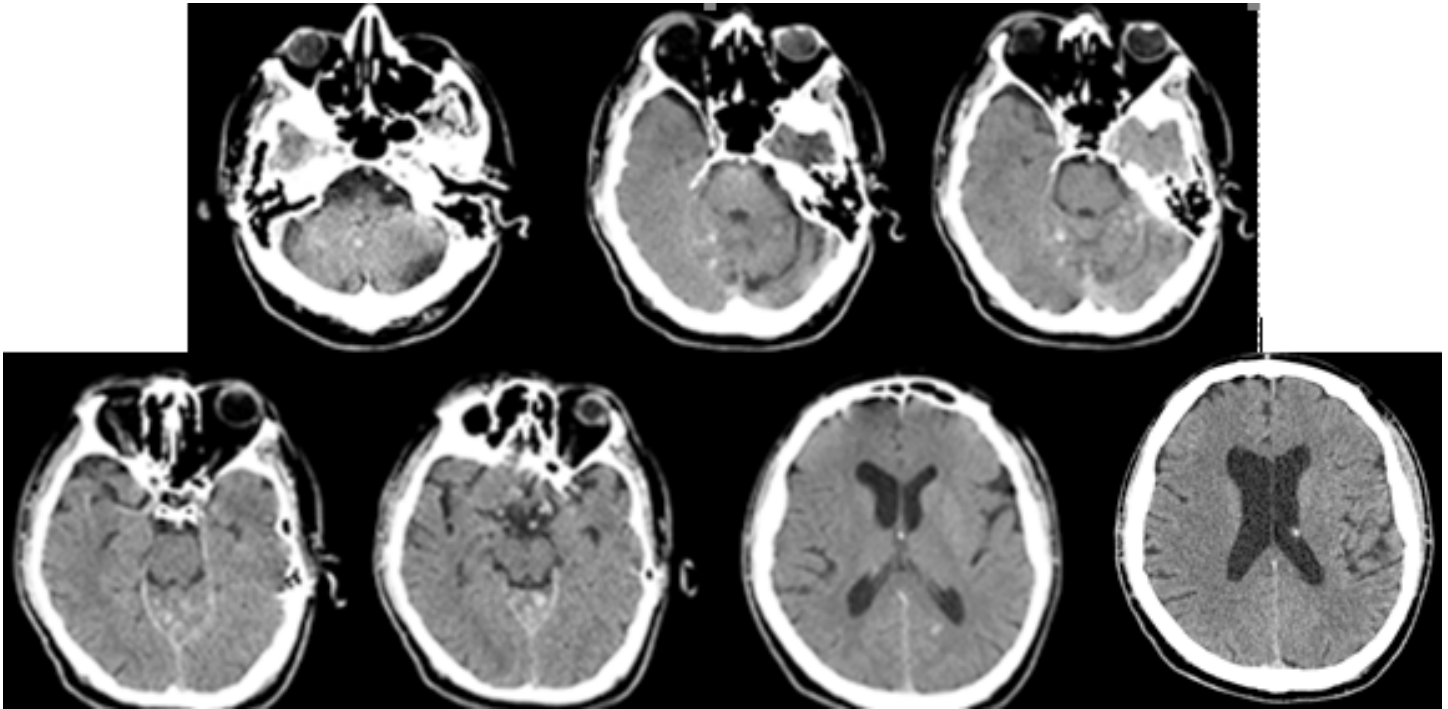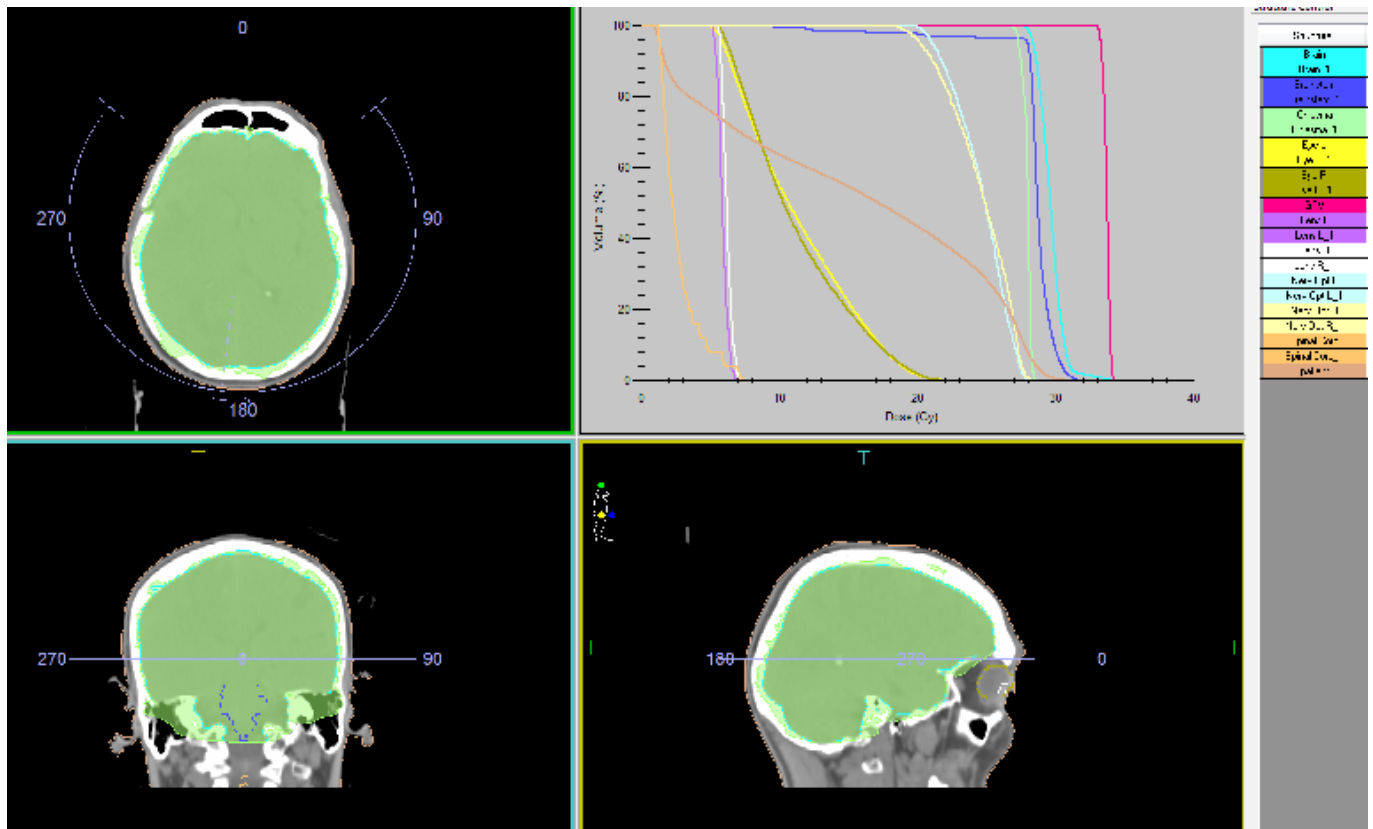
Clinical case № 5

Concerned for a patient at the age of 56. In September 2020, radical excision with clean resection edges of a pigmented skin lesion was performed. The histological study proves nodular malignant melanoma / Breslau 4, Clark 4, and the genetic study lacks a mutation in Cordon 600 of the BRAF gene. No additional treatment with target therapy has been performed. PET/CT - there is no data on a metabolic active lesion in the field of operation and in nearby lymphatic groups as well as distant dissemination. The whole body CT with intravenous contrast in May 2021 visualizes pathologically increased lymph nodes in right axilla with dimensions up to 40mm with necrosis, diffuse liver lesions up to 10 mm, as well as brain leptomeningeal metastases sub-and supratenerially with dimensions up to 10mm (Figure 23).

Assessed for chemotherapy, targeted therapy and whole brain radiotherapy up to TD 30 Gy with DD 3 Gy (Figure 24). Currently, the patient conducts this WBRT on the backdrop of anti-edematous and anti-inflammatory drug therapy.

Discussion

Leptomeningeal metastases (LM) are result of metastatic infiltration of the leptomeninges by malignant cells originating from an extrameningeal primary tumor site that may be extraneural (most common) or intraneural (less common) [15]. Furthermore, there is evidence of increasing incidence rates of central nervous system (CNS) metastases, including brain parenchyma and possibly leptomeninges, in metastatic breast cancer [16,17].

Overall, leptomeningeal disease (LMD) likely comprises about 11-20% of CNS metastasis [10,11]. Today, it is known that LMD occurs in ~5% of all cancer patients [1-3]. There is currently no generally accepted standard of care in the treatment of LM. LMD remains a clinical diagnosis, based on clinical symptoms, imaging, and cerebrospinal fluid analysis [18]. T1-weighted magnetic resonance imaging (MRI) with gadolinium contrast, which has been shown to be more sensitiv compared to contrastenhanced CT [19,20]. All imaging should include the brain and the spine, as LMD can impact the entire neuraxis [21].

The anatomy of the neuroaxis consists of the brain and spinal cord, covered by the meninges, which are comprised of dura mater, arachnoid membrane, and pia mater. The leptomeninges refers to the two most inner layers, arachnoid membrane and pia matter, including the subarachnoid space, which separates these two sheets, and is the location of the cerebrospinal fluid (CSF), where circulates tumor cells in patients with LMD. The pathogenesis of LMD is multifaceted, and can include direct extension from preexisting CNS tumors or systemic tumors, that follow peripheral nerves into the subarachnoid space, as well as infiltration through hematogenous dissemination, or even seeding of the subarachnoid space during surgical procedures [2,22-25].

Although any cancer can metastasize to the leptomeninges, breast cancer (12-35%), lung cancer (10-26%), melanoma (5-25%), gastrointestinal cancer (4-14%), and cancers of unknown primary (1-7%) are the most common causes of solid-tumor-related LM [26,27]. Nonetheless prognosis of LM remains poor with a median OS of 3 months and less than 15% of all patients surviving 1 year following diagnosis [15]. The hematogenous metastatic desimination (HMD) of BC cells applies to the choroidal plexus localized in the entire ventricular system of the brain, given the relatively high cerebral inflow of blood (5 times higher than that in the brain parenchyma) and the porous endothelium of its capillaries [28,29]. One of main reasons for HMD is that the blood brain barrier (BBB) makes the CNS a perfect sanctuary for tumor cells. The BBB consisting of endothelial cells, a basement membrane, and astrocyte foot processes, is a barrier that selectively chooses molecules to enter the CNS [30].

Multimodality treatment

In patients with LMD, surgery (for hydrocephalus), radiation therapy (RT), and chemotherapy (Ch) (systemic Ch or intra-CSF Ch) may be considered [31]. With combined treatments, the median survival of patients with LM averages several months. Specific treatment of LMD typically combines systemic and intrathecal (IT) Ch and site-specific RT [15]. Patients with breast cancer (BC) LMD desperately need new treatments or drug regimens that can improve their prognosis [32]. Improving the early diagnosis of leptenderingual disease will reduce this severe carcinomoid complication. Advancements in MRI technology such as the development of postcontrast Fluid Attenuated Inversion Recovery (FLAIR) and 3-dimensional T1 weighted sequences have led to a recent increase in sensitivity rates [7,33].

Molecular therapeutic strategies are likely to play an increasingly important role in the treatment of BC with LMD. Individual case reports and case series have shown that intrathecal (IT) trastuzumab is potentially well-tolerated, and may have some activity in HER-2 positive BC LMD [15,34-37]. Although retrospective studies suggest that systemic treatment may improve the survival of BC with LMD [32,38,39], many prospective trials of systemic treatments, such as temozolomide, have not demonstrated convincing clinical efficacy [40]. Although the OS of patients with HER2-positive BC has improved substantially in the trastuzumab (T-DM1) era [41,42], the incidence of brain metastases among these patients has been increasing in recent years. A clearer understanding of the role of systemic regimens, especially BEEP, in BC with LMD is needed to improve the management and prognosis [32]. The BEEP regimen entailed a 21-day cycle of bevacizumab (15 mg/kg) on day 1, followed by cisplatin and etoposide (both 70 mg/m2) on day 2, then etoposide (70 mg/m2) only on days 3 and 4 [43]. Using a non-biased study design to evaluate systemic therapy for breast cancer LMD in a real-world clinical setting, was shown that LM is a treatable, with a median OS of 9.63 months for patients receiving BEEP regimen systemic treatment [32]. Intravenous Ch and, independently, intrathecal Ch improve survival in BC with LMD. Although IT methotrexate may alleviate neurological symptoms caused by a large tumor cell load, other studies suggest that IT cytotoxic treatment may not be as efficacious as previously supposed [44,45].

Radiotherapy (RT)

In the past, before the introduction of high-tech linear accelerators and improvement of radiotherapeutic techniques with precise and accurate exposure of pathological zones, was believed that radiotherapy (RT) had a palliative role in adulthood LD. The therapeutic gains of modern RT are also due in part to the enhanced anticancer activity obtained by coadministering RT with chemotherapy (Ch), targeted molecules and currently immune checkpoints inhibitors [46]. Patients with cerebral LMD involvement typically receive whole brain radiotherapy (WBRT), which is planned to involve all neural tissue from the retro-orbit to the upper cervical vertebrae [21]. WBRT was generally administered at a dose of 30 Gy delivered in 10 fractions over 2 weeks. It provides effective relief of pain and stabilizes neurological symptoms but rarely leads to significant neurological recovery [47]. Radiotherapy was indicated to reestablish normal CSF following documentation of CSF flow blocks to permit improved efficacy and decreased toxicity of intra-CSF chemotherapy [48]. High conformal techniques, namely intensity modulated or volumetric modulated arc techniques (VMAT), ablative techniques (Stereotactic Radiotherapy and Stereotactic Radiosurgery), particle therapy (proton or carbon ion therapy) allow for success in treating irregularly shaped or critically located targets and for the sharpness of the dose fall-off outside the target [46,49]. For patients with good prognostic factors such as high KPS score, no major neurologic deficit, minimal systemic disease or reasonable systemic treatment options, involved-field radiotherapy (IF-RT), therapy was suggested by NCCN guidelines to the bulky disease and/or symptomatic sites firstly [50]. RT is especially important to consider in cases with bulky LMD, as the penetration of intrathecal (IT) Ch is poor in these instances [51]. Combination Ch and RT may be considered in breast cancer LMD, especially those without active systemic disease or concurrent brain metastasis [31]. RT has a positive impact on the quality of life, due to the alleviation of neurological symptoms [52].

Our healing results

After WBRT up to TD 40 Gy with DD 2 Gy and boost RT in the cerebral ventricle up to TD 50 Gy, in clinical case №1 we achieved 10 monthly LTC with good quality of life (Figure 2and3). After seven months of RT, a good general condition was achieved in the patient / clinical case №2, without neurological symptoms and good quality of life. Due to massive leptomeningeal metastases in the presented clinical cases (№2, №3), whole-brain radiotherapy up to TD 40 Gy with Boost RT in the areas of concentrated amount of tumor cells up to TD 50Gy-54 Gy was performed (Figure 5,6,9and10). The unfavorable in the clinical case №3 is the MRI manifestation of LMD in the cervical spinal axis after two months of WBRT with Boost RT and their asymptomatic progression after 4 months of RT (Figure 12and14). After one year of RT, there was an unstable gait with difficulty equilibrium, a consequence of LM in the cervical spinal axis, against the background of self-targeted therapy (Figure 16). This means that

the initial hematogenous overcoming of BBB is followed by the spread of tumor cells along the CSF from the cerebral ventricles to the spinal axis. In the patient, partially or entirely spinal cord RT up to TD 45 Gy should be considered (Figure 17). In clinical case №4, LM distribution from brain metastasis is observed, which is near the brain ventricles, despite the 15 Gy single dose radiosurgery (Figures 19 and 20). In Figure 21, we represent the CT и MRT image of the brain metastasis in left brain hemisphere after radiosurgery with 15 Gy. Tumor cells were distributed in the cerebral fluid and reached meninges and brain parenchyma. In the absence of contraindications in the patient, it is necessary to have WBRT with Boost RT in the brain parenchyma with massive LM (Figure 22). In clinical case №5 with the malignant melanoma, we have to carry out a whole-brain radiotherapy with DD 3Gy, as it is known, that melanoma cells are extremely radioresistant and impose high single doses (Figure 24).

Conclusions
- Leptomeningeal disease in solid tumors requires an individual radiotherapeutic approach on a different target volume and necessary radiation doses, depending on the histological characteristic of tumor cells, as well as on the volume and localization of leptomeningeal metastases.
- Brain and spinal axis MRI is required in the diagnosis of late LMD in the case of extracranial solid neoplasms. MRT imaging presents over 60% reduction of cerebral leptomeningeal metastases from BC, one year after Intensity modulated WBRT with Boost RT combined with trastuzumab or denosumab and 10 months after self-targeted therapy.
- In breast cancer leptomeningeal disease through combined with targeted therapy IM WBRT up to 40 Gy and boost- RT up to 50 Gy-54 Gy in the areas of concentrated amount of metastatic tumor cells, we achieved 10–12 months of asymptomatic survival with good quality of life.
- The progression of leptomeningeal disease from cerebrum to the spinal cord requires RT to the partially or entirely spinal axis up to TD 45 Gy.

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