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Tomotherapy and brain metastases: towards the neuroanatomical target theory

Abstract

Lung, breast cancer and melanoma are the most frequent malignancies that develop brain metastases. Its incidence is growing due to advances in imaging technologies and treatment of the primary tumors. The most important prognostic factors are age, performance status, control of the primary and the number of metastatic brain lesions. Whole Brain Radiation Therapy (WBRT) is the mainstay of treatment for multiple metastatic lesions, but Stereotactic Radiotherapy in addition to WBRT is a valid option for oligometastatic patients. Recently some authors underlined the importance of neurocognitive function preservation in this subgroup of patients by reducing the dose of radiation to hippocampus based upon the "neuroanatomical target" theory. We conducted a study of feasibility and safety adopting Tomo-Therapy to treat oligometastatic brain patients with a maximum of 4 lesions. Advantage of Tomo-Therapy is to perform WBRT with concomitant Stereotactic Radiotherapy to the visible lesions while at the same time sparing the hippocampus. The sensitivity of the central nervous system to radiotherapy closely correlates with the volume of irradiation, the total dose and the dose per fraction. The dose to the region of the hippocampus during WBRT may delay or reduce neurocognitive deterioration. In our series did not observe radiation-related acute or early-delayed toxicity. We argue that the use of Thomo Therapy to avoid selective brain areas, such as the hippocampus, together with lower doses to whole brain may be associated with a low incidence of neurocognitive toxicity. At the same time high doses to the visible lesions may results in best local control.

Keywords: radiotherapy, brain cancer, tomotherapy, radiation induced toxicity, brain metastases, stereotactic radiotherapy, neurocognitive function, hippocampus sparing

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Abbreviations: WBRT: Whole Brain Radiotherapy; WBRT-HS: Whole Brain Radiotherapy- Hippocampus Sparing; LINAC: Linear Accelerator; IMRT: Intensity Modulated Radiation Therapy; IGRT: Image Guided Radiation Therapy; MRI: Magnetic Resonance Imaging; CT: Computed Tomography; RPA: Recursive Partitioning Analysis; RTOG: Radiation Therapy Oncology Group; SIB: Simultaneous Boost

Introduction

Brain metastases represent an important issue in oncology due to its high incidence in many malignancies; about 20 to 40 % of patients with cancer develops brain metastases.[1,2] Its incidence is growing due to advances in imaging technologies and treatment of primary[3] and depends in part on the primary cancer: lung, breast cancer and melanoma being the most frequent primary sites that metastasize to that organ. Cerebral hemispheres (80%), followed by the cerebellum (15%) and the brainstem (5%). Palliative Whole Brain Radiation Therapy (WBRT) has been the historical standard of care for these patients,[4] but median overall survival typically is very low with this modality (4-6 months).[5] It has long been demonstrated that patients with limited brain involvement, especially those with only one metastasis, represent a relatively favorable subgroup. Surgical resection followed by WBRT has proven to be a superior treatment modality than WBRT alone or surgical resection alone.[6] However, not all the patients are suitable for surgical resection, so Stereotactic Radio Surgery (SRS) followed by WBRT has become a treatment option for both single[7,8] and oligo-metastatic patients.[9,10]

Classically radiation induced toxicity classified:

a. Acute, expressed in days to weeks after irradiation, with intense , nausea and vomiting;

b. Early delayed that occurs 1-6 months post-irradiation and can involve transient demyelination with somnolence;

c. Late delayed usually observed > 6 months post-irradiation these late delayed injuries have been viewed as irreversible and progressive.

Radiation-induced cognitive impairment, the most important late-delayed toxicity, is reported to occur in up to 50-90% of adult brain tumor patients who survive >6 months post-irradiation. WBRT is a powerful way to control the neurological symptoms and quality of life, there has been some recent controversy about whether WBRT affects neurocognitive function;[11,12] the dose of radiation therapy WBRT is 30Gy in 10 patients with neurological symptoms due to metastasis, this treatment improves quality of life, but in asymptomatic patients may instead lead to a deterioration of cognitive function. The Brain damage has several pathogenetic hypotheses:[13]

i. Theory of vascular damage,

ii. Theory of parenchymal damage, and more recently

iii. Theory of neuroanatomical target.[14,15]

Peiffer et al.,[15] indicates that it is not the dose to the whole brain, but rather the dose to the hippocampus and temporal lobes that predicts the subsequent radiation-induced cognitive impairment. These authors proposed a "neuroanatomical target theory", which suggests that selective damage to certain brain structures may be the cause of cognitive impairment after radiotherapy. This hypothesis has therefore prompted several researchers to investigate the selective avoidance of certain brain areas. The impairment of learning, memory, and motor coordination seem to be linked to irradiation of the hippocampus.[16-20] Despite the fact that these functions are located in different brain

areas, the pathogenetic hypothesis of these changes can be attributed to radiation damage suffered by the progenitor cells that are in the sub-granular zone of the hippocampus. This area is in fact one of the most active in the process of neurogenesis.

Originally, Stereotactic Radio Surgery a specialized gamma radiation unit called Gamma Knife (GK). In GK devices from a large number of 60Co sources (30 to 201 sources) arranged in a hemisphere helmet within a shielded source body, are focused on the target. The patient undergoes placement of a stereotactic frame to the head fixed with screws after local anesthesia. With the technological development of Linear Accelerator (LINAC), commonly used to treat almost all kind of cancer, has become possible to perform both radiosurgical treatment in a single fraction with fixed skull helmets (as in the case of the Gamma Knife), fractionated stereotactic treatment (more than 1 session) using non-invasive thermoplastic masks. Helical Tomotherapy consists of a special LINAC with a built-in Computed Tomography (CT) that verify the correct patient positioning (by performing a CT scan before each session of radiation therapy) and administer the radiation dose helically, distribute the around the hippocampus, sparing it almost completely. The advantage of TomoTherapy, compared to Gamma Knife (GK) e.g., is to deliver a WBRT (not possible with GK), sparing the hippocampus, at the same time to administer higher doses (Stereotactic Radiotherapy) to individual metastases. Its best use is in those treatments that require avoiding critical anatomical structures. The central nervous system is therefore one of the fields of greatest interest for Tomotherapy application. We report our experience using this technique in patients with brain metastases with a more favorable prognosis (1-4 metastases) taking into account the new evidence on the radio-induced toxicity.

Materials and methods

We introduced a new treatment approach for oligometastatic brain patients supported by the previously cited theory. Our treatment approach consists of 10 fractions (5 Fr/Week) using this scheme: 2.5 Gy x 10 to whole brain sparing the hippocampus (WBRT-HS) and 4.4 Gy x 10 Simultaneous Boost (SIB) to the visible lesions (max 4). All patients were assigned to Recursive Partitioning Analysis (RPA) by RTOG for brain metastases[21] and only patients in Class 1 were enrolled: Karnovsky Performance Status (PS) ≥70, primary cancer controlled. Patients also had to meet the following requirements: Histologically proven of primary malignancy; no more than 4 brain metastases by CT and/or MRI3 cm. Before radiation treatment all patients were subjected to: complete blood count, routine blood chemistry, total body CT and brain MRI. Contrast-enhanced MRI is the diagnostic modality of choice to distinguish between solitary and multiple metastases.[22] An initial assessment of neurocognitive function using the Mini Mental State Examination was performed. The late neurological toxicity evaluation was performed according to the parameters of the Common Toxicity Criteria v.4.0. The neurocognitive function assessment will be carried out in parallel with the determination of late toxicity using the Mini Mental State Examination. The CT simulation was performed for all patients with a Toshiba Aquilon® at 0.3 mm step and personalized thermoplastic mask ("frame less"). MRI/CT image fusion was performed using Treatment Planning System of TomoTherapy.

A Radiation Oncologist manually contours all the Volumes of Interest (VOI). The Gross Tumor Volume (GTV): Corresponds to the clinically evident metastases on T1 weighted MRI/CT planning imaging fusion. The Planning Target Volume for the lesions (PTV-SIB) was obtained by performing three-dimensional expansion of 2 mm around the GTV. Clinical Target Volume (CTV): corresponds to the brain parenchyma (whole brain). The PTV for whole brain was obtained by subtracting to the CTV the PTV of metastases and the hippocampus. The organs at Risk were also: hippocampus, optic chiasm, eye, lens, optic nerve, brainstem and cochlea. For the hippocampus contouring, with assistance of neuroradiologist, we now adopting the on-line RTOG contouring atlas guidelines (www.rtog.org/corelab/counturingatlases/hippocampalsparing.aspx).

Results and discussion

At "St. Camillo-Forlanini" Hospital 6% of all patients treated at Department of Radiation Oncology are affected by brain metastases. We treated 75 patients: 41 (55%) had multiple brain metastases (>4); 15 (20%) single metastases; and 19 (25%) oligometastases (>1 not >4). We treated 10 patients from the oligometastatic group and 7 from the single metastases group (17 patients) with the WBRT-HS/SIB Treatment. The other patients were managed with standard WBRT. Median age was 65 years (range 32-84). The median follow up was 4.5 months.

A complete response, defined as complete disappearance of all the lesions on MRI imaging, was observed in 3 patients with single metastases (43%) and in 2 oligometastatic patients (20%). 5 oligometastatic patients with stable disease (50%), defined as a reduction >50% of total volume, experienced a complete response some lesions. Three patients with single metastasis showed stable disease (43%) and only one had recurrence and is now retreated. Two oligometastatic patients (20%) developed new lesions number but no increase in the size of treated lesions. In our series, although limited, we had no acute or early delayed radiation induced toxicity. We did not observe disorders related to verbal and visual memory in any patients.

Patients with brain metastases have a poor prognosis and most of them have no chance of cure; 50% will die. WBRT is the standard treatment for patients with multiple brain metastases but in the 30-40% of patients with oligometastases that have a better prognosis,[23] WBRT may over treat the normal brain parenchyma while at the same time the under treating the macroscopic lesions. We believe, therefore, that in order to obtain a good local control the dose to the macroscopic lesions must be higher (in Stereotactic Treatment) while the dose to healthy parenchyma must be kept as low as possible: 30 Gy delivered in 10 fractions are not enough for macro lesions and are too much for normal tissue. The commonly used standard fractionation schedules for WBRT are 30 Gy in 10 fractions or 20 Gy in 5 fractions. There are no data demonstrating the superiority of one over the other[24] but several authors suggest administering a lower dose per fraction in patients with more favorable prognosis because a dose per fraction >2 Gy and total dose > 45 Gy are associated with dementia.[25,26]

The schedule used in our study for WBRT is the same of Prophylactic Cranial Irradiation (2.5Gy x 10 fr.). The concept of Prophylactic Cranial Irradiation (PCI), commonly used in patient with Small Cell Lung Cancer (SCLC) is to eliminate microscopic deposit of metastatic tumor cells within the brain before they come macroscopically evident. Recently PCI was investigated even in patients with Non-Small Cell Lung Cancer (NSCLC) with a reduction in the incidence of brain metastases from 18% to 8%.[27] We argue that the use of TomoTherapy to avoid selective brain areas, such as the hippocampus, lower doses to whole brain (like in PCI: 2.5Gy x 10fr.) may be associated with a lower incidence of acute, early late and neurocognitive toxicity without a reduction in the control of

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microscopic disease. At the same time macroscopic lesions have received the same dose they would have received with a stereotactic treatment (4.4Gy x 10fr.).[28,29]

Conclusion

The dose to the region of the hippocampus may delay or reduce neurocognitive deterioration,[16,18] giving higher doses to the macroscopic metastases should progression of intracranial disease. We think this goal is achievable adopting Tomo-Therapy with WBRT-HS/SIB (our proposed schedule).We started a Phase II randomized trial of comparison between WBRT and WBRT-HS/SIB in oligometastatic patients to elucidate the real benefit of the new technique in this setting.

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None.

Conflicts of interest

Authors declare that there is no conflict of interest.

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