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Review

Whole brain radiotherapy: Consequences for personalized medicine

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ABSTRACT

Several studies focusing on brain irradiation are in progress. Reflecting updates of relevant outcomes in palliative treatment of patients suffering from brain metastases, the primary objective of these studies is the evaluation of neurocognitive function and quality of life. Improvements of technology in radiation oncology allows us to spare the hippocampal region while appropriately irradiating other parts of brain tissue. Irradiation of the hippocampus region is likely to lead to manifestations of adverse events with a subsequent impact on patient's quality of life, which is in fact an improper approach in palliative medicine. Ongoing studies evaluate results of hippocampus avoiding radiotherapy compared to standard whole brain radiotherapy. Incorporation of neurocognitive function assessment may result in the confirmation of superiority of sparing the region of hippocampus and thus change current style of providing brain irradiation.

1. Background

Approximately 30% of patients develop brain metastases (BM) as a part of their cancer disease.[1] This number is expected to grow due to an increasing number of registered preparations from targeted therapy drugs, improvement of surgical and radiotherapy methods and an increased availability of better palliative and supportive care. Increasing incidence of BM is also due to improvements in imaging technologies and their higher availability.[2] Brain metastases are considered to be one of the most serious complications of cancer disease, which dramatically increase the morbidity and mortality. Their optimal treatment remains controversial, mainly with respect to the aim of provided medical care.[3] In most cases of patients with metastases (MTS) of any location, the treatment aim is not to destroy all cancer cells and cure the patient, but to reduce actual difficulties and prolong the overall survival with good quality of remaining life by achieving an appropriate reduction of symptoms and prevention of its further

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impairment.[4] Besides the reduction of symptoms, the goal of a good palliation is to minimize its side effects. In order to achieve this aim, it is important to determine appropriate end-points not only in relation to an individual patient, but also in relation to the ongoing randomized clinical trials (RCT) as resources for future treatment guidelines. Recently, more attention has been paid to symptom-related outcomes of care, especially to neurocognitive functions (NCF) and quality of life as the most frequently mentioned issues.[5]

One of the standard therapeutic methods of brain metastases is radiotherapy (RT), which offers several possibilities to influence further progression of disease. Apart from the basic technique, i.e. radiation of the whole brain (WBRT – whole brain radiotherapy), new treatment methods are being put into practice, such as stereotactic methods of intracranial radiosurgery or radiotherapy. These novel methods allow delivering higher doses of radiation into a small amount of tissue. However, these techniques remain available only for a small group of patients.[6] Recently, a lot of trials have been conducted to compare different radiotherapy techniques as separate methods of treatment to their combinations. Other studies deal with a combination of radiotherapy and neurosurgery.

In most patients the radiation of the whole brain is indicated because of numerous brain metastases present or because of unmanageable extracranial illness. Thus, attention must also be paid to the development of further improvements in providing WBRT, especially in the light of new knowledge about radiation brain injury mechanisms and in respect to the personalized palliative approach to each patient. In this article, we focus mainly on the whole brain radiotherapy.

In general, one of the main future directions in the treatment of cancer patients is the implementation of so called tailor-made personalized medicine into clinical practice. That means optimization of drug prescription based on patient's individual gene profile in a narrower sense. Although this concept applies particularly to systemic treatment with chemotherapeutic agents, some principles of this philosophy could be implemented into other areas of care for cancer patients, meaning the pursuit of individualized approach to the treatment. One of the basic principles of tailor-made personalized medicine is the usage of a specific procedure for the specific patient, in order to maximize, if possible, the therapeutic effect while avoiding side effects.

In relation to the facts mentioned above, it is necessary to take into account some patient-specific variables while making decisions about indications to cranial irradiation. At first, the question is if patient can realistically benefit from being provided such irradiation. In practice it is about responsible life expectancy estimation (for example expressed by the Karnofsky Performance Scale) and about considering all consequences relating to the actual possibilities to provide the care. If RT is indicated, the next question is what part of brain should be irradiated and how. Choosing the right procedure is important in relation to the assessment of all benefits and risks of our intervention. We summarize some recent recommendations in the use of WBRT and mention some future directions related to this issue.

2. Indications for WBRT

In daily radiotherapy practice, one of the most important factors in decision-making is the level of technical equipment in a particular radiotherapy department. Not all departments are able to provide their patients with the most advanced care, e.g. precise stereotactic radiosurgery (SRS), or WBRT with simultaneous integrated boost (SIB) to BM using volumetric modulated arc therapy delivered by helical tomotherapy or by linear accelerators (Rapid Arc, IMAT/VMAT therapy).[7] Thus, also because of this technical limitation, WBRT remains the most commonly radiotherapy method used in the treatment of patients with brain metastases.

When considering the best specific type of treatment it is important to compare all its pros and cons. In general, palliative treatment should be as undemanding as possible in order not to burden patients with long complex treatment. Cost of this care should be low or at least weighed against potential benefits in comparison with other lower or more expensive alternatives.[3]

Before starting treatment it is useful to recognize the number of BM – single lesion, oligometastatic (2–3) or multiple impairments. It is also very important to properly assess the general performance status and consider other specific clinical situations (presence or absence of extracranial metastases). These are the most common prognostic/predictive factors mentioned in recent guidelines. Karnofsky Performance Scale (KPS) is the most useful tool to estimate patient's ability to profit from any kind of treatment. Indeed, KPS is a part of all tools for stratification of patients into prognostic groups – Recursive Partitioning Analysis and Graded Prognostic Index (RPA and GPI score).[8,9] Patients with KPS of less than 70% (RPA group III) will benefit from WBRT compared to other type of brain radiotherapy regardless of the type of brain impairment.

Several studies have been performed to assess the importance of the implementation WBRT in combination with local treatment of brain metastases.[10–13] Abe et al.[14] reviewed these findings and concluded, that initial local brain radiotherapy without its whole irradiation does not influence overall survival, but results in a significant increase in brain tumor recurrence (BTR), while the inclusion of WBRT into the primary treatment prolongs time to recurrence and prevents neurologic death.[14]

Brain tumor recurrence means the clinical progression resulting in severe impact on patient's quality of life. BTR is the most important cause of additional deterioration of NCF. It seems that it is useful to stratify patients into the low and high risk group of BTR and hence determine the indication for WBRT.[11] Aoyama also evaluated the risk of developing brain metastases in breast cancer patients after up-front WBRT according to the risk of BTR. Patients in high BTR risk group (2 or more BM, presence of extracranial metastases) who underwent WBRT developed BTR in other site of brain in 21% at 6 months compared to 57% of patients without WBRT. Patients in the low BTR risk group (single BM, no extracranial metastases) with and without WBRT developed BTR at 6 months in 9%, vs. 31%, respectively.[15]