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Randomised trial

Stereotactic radiotherapy of the tumor bed compared to whole brain radiotherapy after surgery of single brain metastasis: Results from a randomized trial

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ABSTRACT

Purpose: To evaluate if neurological/cognitive function outcomes in patients with resected single brain metastasis (BM) after stereotactic radiotherapy of the tumor bed (SRT-TB) are not inferior compared to those achieved with whole-brain radiotherapy (WBRT).
Methods: Patients with total/subtotal resection of single BM were randomly assigned either to SRT-TB ($n = 29$) or WBRT ($n = 30$). SRT-TB arm consisted of 15 Gy/1 fraction, or 5×5 Gy. WBRT consisted of 30 Gy/10 fractions. Neurological/cognitive failure was defined as a decrease of neurological score by one point or more, or a worsening of the MiniMental test by at least 3 points, or neurological death. Cumulative incidence of neurological/cognitive failure (CINCF), neurological death (CIND), and overall survival (OS) were compared.
Results: Median follow-up was 29 months (range: 8–45) for 15 patients still alive. The difference in the probability of CINCF at 6 months (primary endpoint) was −8% in favor of WBRT (95% confidence interval: +17% −35%; non-inferiority margin: −20%). In the intention-to-treat analysis, two-year CIND rates were 66% vs. 31%, for SRT-TB and WBRT arm, respectively, $p = .015$. The corresponding figures for OS were 10% vs. 37%, $p = .046$.
Conclusions: Non-inferiority of SRT-TB was not demonstrated in our underpowered study. More data from randomized studies are needed for confirmation of the value of this method.
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The treatment of brain metastases includes whole-brain radiotherapy (WBRT), stereotactic radiotherapy (SRT), surgery, or their combinations. Addition of WBRT to SRT or surgery of 1–4 metastases has not improved overall survival in any randomized trial [1–3]. However, the use of WBRT was associated with improved local control and reduction of neurological deaths in prospective and retrospective studies [2–4]. This beneficial effect of WBRT on local control led to the implementation of this method into treatment of brain metastases. Delayed white matter toxicity, detected by magnetic resonance imaging (MRI), occurs more often after WBRT than after SRT [5]. Even if neurotoxicity of WBRT is multifactorial and not severe in most patients, this constitutes a rationale for not using it. The neurotoxicity of WBRT, together with no demonstrated survival benefit, and even suggestions of the detrimental effect on survival [6], has led many centers to gradually abandon up-front WBRT and to use only local treatment such as surgery or SRT as a primary treatment for up to 3–4 brain metastases [7].

Surgery only of brain metastases resulted in unacceptably high relapse rates in the surgical bed (59%) and/or at new sites in the brain (42%) [3]. This has led to a new treatment paradigm, namely to perform SRT of the tumor bed (SRT-TB) to improve local control with deferring WBRT in order to spare neurotoxicity. A review of 21 retrospective series, including 1011 patients, showed promising results after such management; the crude one-year control rate in the tumor bed was 79% with 51% of patients developing new brain metastases [8]. Nevertheless, some series had incomplete data on tumor control and in two series WBRT was used as a part of the treatment strategy. In addition, the high rate of brain recurrences outside the tumor bed gives rise to concern on its impact on neu-

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rocognitive functioning after SRT-TB compared to that observed after WBRT. We think that preserving good/adequate neurocognitive function after SRT-TB remains to be demonstrated. WBRT may worsen such functioning because of toxicity [5,6]; on the other hand, WBRT may maintain good neuro-cognition by reducing the risk of relapse [9,10]. Thus, in terms of neurocognitive functioning, a beneficial effect of WBRT on tumor control may outweigh its neurotoxicity.

The evidence from prospective studies on the impact of the excess of brain recurrences resulting from omission of WBRT on the neurocognitive functioning is conflicting [3,6,9]. The EORTC 22952–26001 phase III randomized trial demonstrated that patients treated with omission of WBRT after surgery or radiosurgery of up to three brain metastases have the duration of functional independence, defined as no deterioration of WHO performance status (PS), not shorter than patients treated with WBRT [3]. However, PS deterioration in cancer patients may reflect not only brain tumor control or brain treatment toxicity but may be influenced by extracranial disease progression and/or treatment of such progression. Therefore, neurocognitive functioning is a better measure of the effect of brain metastases treatment than duration of functional independence. Thus, a notion that the omission of WBRT does not affect neurocognitive functioning remains to be proven, especially in patients with a resected single brain metastasis. In these patients, the bias of the competing risks from extracranial disease progression and treatment is relatively low. Patients with resected single brain metastasis have a priori a better prognosis than whole population of patients with brain metastasis. Additionally, patients receiving SRT-TB for a single brain metastasis may be a distinct population of patients with brain metastases due to treatment given, because we have not yet comparison of their outcome with patients treated by WBRT in the controlled trial. Thus a prospective evaluation of whether the SRT-TB only in patients with resected single brain metastasis is not inferior to WBRT in terms of neurocognitive functioning is justified. The results of such evaluation are reported herein.

Patients and methods

Patients

The protocol was approved by the ethics committees from the participating institutions. The study was registered with ClinicalTrails.gov under number NCT01535209 and was conducted according to the Declaration of Helsinki. Eligibility criteria were as follows: single brain metastasis found by preoperative MRI of the brain, pathologically confirmed metastasis from the solid tumor in the resected brain tumor, total or subtotal resection in the surgeon's operative report, Karnofsky performance status (KPS) $\geqslant$ 70, life expectancy > 6 months, no obstacle to perform MRI in the follow-up period, and signed informed consent. Exclusion criteria were as follows: brain metastasis from small-cell lung cancer and hematological malignancies, dementia syndromes, and previous brain irradiation.

Procedures/treatment

Patients meeting eligibility criteria were randomized after surgery either to WBRT (control arm) or SRT-TB (experimental arm). Postoperative MRI before randomization was not mandatory. Radiotherapy had to start up to six weeks after surgery. There were no specific requirements for staging procedures before the randomization. At baseline we recorded KPS, neurological status using the Medical Research Council (MRC) scale [11], Mini-Mental State Examination (MMSE) test results, and the extent of extracranial disease.

SRT-TB was linac based. Patients had post-gadolinium enhanced T1-weighted MRI (1.5 mm slices) and CT with intravenous contrast performed for planning. Both sets of images were fused for target delineation. The clinical target volume was defined as the contrast-enhancing surgical cavity with exclusion of the surgical tract, postoperative changes and surrounding edema. Contouring was performed with the aid of a neuro-radiologist whenever necessary. A three millimeter margin was added to create the planned target volume. A dose of 15–18 Gy was prescribed at the isodose line (IDL) encompassing the PTV (no lower than 80% IDL, usually 90% IDL). For surgical cavities larger than 5 cm, or those of irregular complex shape, or in the proximity of critical structures for which dose limits with a single fraction would be exceeded, the prescribed dose was 25 Gy given in 5 fractions over 5 days. The dose limit for brainstem and chiasma/optic nerves was 8 Gy in a single fraction. Patients were immobilized for SRT-TB in stereotactic masks system and at the beginning of the study positioned for treatment using a localizing stereotactic frame. During a study conduction, the conventional frame-based radiosurgery was replaced by a frameless image-guided radiosurgery with verification done by a stereoscopic kilovoltage X-ray system combined with infrared position tracking or MV cone beam CT. Radiotherapy technique consisted of multiple (eight or more) non coplanar micro-multileaf collimator beams (Brain-LAB, Germany) or volumetric modulated arc therapy (RapidArc®). Patients in the WBRT arm had no MRI done for planning; additionally, CT for planning was done without intravenous contrast. The WBRT dose was 30 Gy in 10 fractions, delivered 5 times weekly at the linear accelerator. At the beginning of the study treatment plans were discussed with a main study investigator (LK) and a workshop was organized for one institution participating in the study.

Follow-up

Treatment and diagnostic procedures of extracranial disease were left to the discretion of the attending physician. Eight weeks after radiotherapy and every three months thereafter, patients had follow-up visits that consisted of the brain MRI, physical examination, KPS, neurological status evaluation according to the MRC scale and MMSE test. Radiotherapy side-effects, treatment, steroids dose, and extracranial disease status and treatment were recorded. In all cases of suspicion of radionecrosis, patients were presented at the multidisciplinary meeting where additional imaging (PET-CT or MR spectroscopy) or watchful waiting policy were decided.

Treatment of relapses in the brain was left at the discretion of attending physician and patients' preferences.

Study design and statistics

The study was designed as a non-inferiority multicenter randomized trial. Our null hypothesis was that there is a worsening of neurological and/or cognitive functioning in patients with resected single brain metastasis who had undergone SRT-TB compared to up-front WBRT. The alternative hypothesis was that patients treated with SRT-TB had neurocognitive function not inferior compared to those who have upfront WBRT.

The primary end-point of the study was the cumulative incidence of neurological/cognitive failure (CINCF) at 6 months. Neurological/cognitive failure was defined as a worsening of neurological status by one point or more within the five-point MRC scale [11], or a worsening of the MMSE test score by three or more points compared to the baseline score, or neurological death; whichever occurred first. Neurological death was defined as death from progression of metastatic disease in the brain, toxicity from treating brain metastases, and death from undetermined cause(s). We assumed 20% of non-inferiority margin in CINCF at 6 months. Thus,