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Original article

Hippocampal sparing in stereotactic radiotherapy for brain metastases: To contour or not contour the hippocampus?

Épargne de l'hippocampe lors de la radiothérapie en conditions stéréotaxiques des métastases cérébrales : faut-il délinéer ou non l'hippocampe ?

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ABSTRACT

Purpose. – The aim of our study was to evaluate hippocampal irradiation in patients treated with fractionated stereotactic brain radiotherapy.
Patients and methods. – Retrospective hippocampal dosimetric analysis performed on 22 patients with one to four brain metastases treated with fractionated stereotactic radiotherapy using volumetric intensity-modulated arc therapy. Original plans did not include hippocampus as avoidance structure in optimization criteria; hippocampus was retrospectively delineated on magnetic resonance coregistered with planning CT and using as reference the RTOG 0933 atlas. Hippocampus was defined both as a single and as pair organ. Constraints analysed were: Dmax < 16 Gy, D40% < 7.3 Gy, D100% = Dmin < 9 Gy. Assuming a α/β ratio of 2 Gy, biologically equivalent dose in 2 Gy fractions was calculated. Hippocampal-sparing plans were developed in cases where hippocampal constraints were not respected in the original plan.
Results. – Among constraints analysed Dmax and D40% have been exceeded in ten out of 22 cases. The constraints were not respected in patients with more than one metastatic lesion and in three patients with only one lesion. Considering all exceeded constraints values in non-hippocampal sparing plans, the 50% of them was respected after replanning. No significant differences were found among conformity and homogeneity index between non-hippocampal sparing and hippocampal sparing plans.
Conclusion. – Volumetric intensity-modulated arc therapy hippocampal sparing plans significantly decreases dose to hippocampus assuring an equal target coverage and organs at risk avoiding.

Mots clés :
Métastases cérébrales
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RÉSUMÉ

Objectif de l'étude. – Évaluer l'irradiation de l'hippocampe chez les patients traités par irradiation fractionnée cérébrale en conditions stéréotaxiques.
Patients et méthodes. – Analyse dosimétrique rétrospective de l'hippocampe conduite chez 22 patients atteints d'une à quatre métastases cérébrales traitées par une irradiation fractionnée en conditions stéréotaxiques en utilisant l'arcthérapie volumétrique modulée. Les plans de traitement originaux ne comprenaient pas l'hippocampe dans les critères d'optimisation ; l'hippocampe a été rétrospectivement délinéé sur l'imagerie par résonance magnétique co-enregistrée avec la scanographie de planification, en utilisant comme référence l'atlas du Radiation Therapy Oncology Group (RTOG) 0933. L'hippocampe a été défini à la fois comme un seul et comme un organe pair.

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Résultats. – Les contraintes analysées étaient : dose maximale inférieure à 16 Gy, dose dans 40 % du volume (V40 %) inférieure à 7,3 Gy, dose dans 100 % du volume (D100 %) égale à la dose minimale (Dmin) inférieure à 9 Gy. En supposant un rapport α/β de 2 Gy, une dose biologiquement équivalente en fractions de 2 Gy a été calculée. Des plans d'épargne de l'hippocampe ont été élaborés dans les cas où les contraintes n'étaient pas respectées dans le plan initial. Parmi les contraintes analysées, les dose maximale et dose dans 40 % du volume ont été dépassées dans dix des 22 cas. Les contraintes n'ont pas été respectées chez les patients atteints de plus d'une lésion métastatique et chez trois atteints de lésion unique. En considérant les contraintes dépassées dans les plans d'épargne de l'hippocampe, 50 % d'entre elles ont été respectées après une nouvelle planification. Aucune différence significative n'a été observée en termes d'indices de conformité et d'homogénéité entre les plans avec et sans épargne de l'hippocampe.
Conclusion. – Les plans d'épargne de l'hippocampe par arcthérapie volumétrique modulée réduisent significativement la dose dans l'hippocampe, en assurant la couverture du volume cible et l'épargne des organes à risque.

1. Introduction

Radiation-induced cognitive impairment is a well-known sequel of cranial irradiation and some studies suggest the role of radiation-induced hippocampus injury [1–3].

Several patient populations have been used to study this adverse effect, including children undergone prophylactic irradiation for non-central nervous system malignancies, patients with nasopharyngeal cancer, low-grade gliomas, benign non-parenchymal brain tumours, and patients affected by primary or metastatic brain tumour [4,5].

Most of these studies describe cognitive impairment after whole brain irradiation in patients affected by brain metastases; in fact, brain metastases represent the most frequent intracranial tumour and they occur up ten times more frequently than primary tumours [6].

Despite whole brain radiotherapy longer represented the mainstay treatment for brain metastases, in the modern radiotherapy era stereotactic brain radiotherapy and radiosurgery achieved a central role in treatment of patients with brain metastases. These techniques allow a better sparing of organs at risk and an improved outcome due to a minimal invasive approach, highly conformal dose distributions and high ablative doses; therefore, a longer survival can be expected and late neurological sequels could be relevant in these patients.

However, to date, hippocampus is not routinely considered among organs at risk in fractionated stereotactic brain radiotherapy for brain metastases. Furthermore, there are few of clinical data to suggest that radiation dose to the hippocampus during stereotactic brain radiotherapy leads to memory and cognitive effects.

The summation of these clinical observations provides a rationale for exploring the hypothesis that, without conformal avoidance during stereotactic brain radiotherapy, hippocampus can be over-irradiated and that conformal hippocampus avoidance may spare some patients of the cognitive sequels of cranial irradiation.

We sought to address this hypothesis conducting a retrospective study of adult patients with 1–4 brain metastases treated with fractionated stereotactic brain radiotherapy. We evaluated hippocampal dose–volume histograms on hippocampi retrospectively delineated, in order to define the advantage of hippocampal sparing techniques in limited brain metastatic setting where longer survival and better quality of life could be expected.

2. Methods

From January 2015 to July 2016 a total of 22 patients with one to four brain metastases, treated in our radiotherapy institute with fractionated stereotactic brain radiotherapy, were retrospectively evaluated.

All patients underwent a simulation-computed tomography (CT) without contrast medium, with 2 mm slice thickness and acquired from the vertex to the lower border of C2. A thermoplastic mask equipped of 3 fixation points was used as head immobilization system.

Diagnostic magnetic resonance (MRI) using a 3 T scanner with 2 mm slice thickness and gadolinium contrast- enhancement was acquired for all patients.

Before contouring, CT simulation and diagnostic MRI were fused on Oncentra MasterPlan 4.3 version using a rigid registration algorithm.

Hippocampus was retrospectively delineated on gadolinium contrast-enhancement T1 weighted MRI. Delineation was performed on axial images using as reference RTOG 0933 atlas, then neuroradiologist, with an expertise over 5 years, in sagittal, coronal and axial projections revised contours [7].

Hippocampus was defined both as a single (H_u) and a pair organ (H_{dx}, H_{sn}). Hippocampal avoidance zone was generated adding an isotropic 5 mm margin.

Constraints analysed were: Dmax < 16 Gy, D40% < 7.3 Gy, D100% = Dmin < 9 Gy both for single hippocampus and pair organ. Assuming a α/β ratio of 2 Gy, biologically equivalent dose in 2 Gy fractions (EQD2) was calculated [4,6,8].

Patients were treated with volumetric intensity-modulated arc therapy using 6 or 10 MV photons; 11 patients received a total dose of 20 Gy (four fractions delivering 5 Gy) and 11 received 24 Gy (three fractions delivering 8 Gy).

Subsequently, hippocampal sparing plans were developed, using the same technique and prescription dose, in cases where hippocampal constraints were not respected in the original plan.

All plans were normalized in such that at least 95% of the planning target volume was covered by prescribed dose. Lens, eyes, optic nerves, optic chiasm, spinal cord, cochleae and brain stem were also considered as organs at risk.

Conformity index and homogeneity index were considered to compare hippocampal sparing and non hippocampal-sparing plans.

The conformity index, in Paddick's version, was defined as $\frac{TV_{PIV}}{PIV} \times \frac{TV_{PIV}}{TV}$, where TV was the target volume, TV_{PIV} was the volume of the target receiving the prescription dose and PIV was the prescription isodose volume [9,10].

The homogeneity index was defined, according to RTOG, as $\frac{I_{max}}{RI}$, where I_{max} was the maximum isodose around the target and RI was the reference isodose [11,12]. Conformity index and homogeneity index values near 1 correspond to more homogenous and conformity irradiation of the target volume.