Abstract

Analysis of the possibility of hippocampal sparing during brain radiotherapy with the VMAT technique (Volumetric Modulated Arc Therapy) at the Bialystok Oncology Center

Radiotherapy (RT) is one of principal method for treating brain cancer. The annual number of new diagnoses primary brain tumors (PBT) in Poland is approx. 3,000, which accounts for approx. 2% of all tumors in both sexes with average age of diagnosis between 50 and 60 years of age. Brain metastases (BM) are more common than PBT and occur in about 15-20% of adult .

Over recent years, a neurocognitive function decline in oncological patients has increasingly been observed after brain irradiation. The hippocampus is a paired limbic structure located in the medial temporal lobes of the telencephalon. Preliminary findings suggest that irradiation may damage neural stem cells in the hippocampus and as a consequence apoptosis, with result in deteriorating cognitive function. Hippocampal sparing RT may results in low neurocognitive impact treatment in cancer patients undergoing brain RT and provides improvement in their quality of life (QoL).

The aim of the study was to analyse the possibility of hippocampus avoiding (HA) during brain RT using the modern RT technique used in the Department of Radiotherapy (ZR) at the Bialystok Oncology Center (BCO.

The specific aim was to analyse the discrepancies of hippocampus localisation on magnetic resonance imaging (MRI) scans for the planning of brain RT with HA procedure and analyse the possibility of using HA procedure during brain RT in ZR BCO in three selected clinical situations:

a) in patients with small cell lung cancer (SCLC) undergoing prophylactic brain irradiation (PCI)

b) in patients with PBT

c) in patients with diagnosed BM.

The first part of the doctoral dissertation describes difficulties in hippocampal contouring on 10 patients' virtual axial images of computed tomography (CT) brain fusion with T1- enhanced magnetic resonance MRI (every 1 mm) according to the RTOG 0933 atlas

recommendations in the *Oncentra Masterplan* by Elekta. This study describes in detail discrepancies on delineated the left and right hippocampus (LH and RH, respectively) by ten doctors, which concerned: the three-dimensional localization, shape, volume and size of the hippocampus. The largest differences were observed in the first three delineated cases, which characterized by larger hippocampal volumes than in the other seven cases. The volume of LH of more than half hippocampi contours was slightly bigger than the RH. Most differences in delineation of the hippocampus were observed in the area of the posterior horn of the lateral ventricle. Conversely, a large number of hippocampal contours overlapped near the brainstem and the anterior horn of the lateral ventricle.

The second part of the doctoral dissertation describes possibility of hippocampus sparing in three clinical groups:

1. 15 limited SCLC patients received prophylactic cranial irradiation (PCI) with bilateral HA procedure with the Volumetric Modulated Arc Therapy (VMAT) technique up to total dose of 25 Gy in 10 fractions. This study evaluate the possibility of reducing the irradiating dose on bilateral hippocampi by VMAT technique compared to 3D conformal RT (3D CRT). PCI with HA procedure provided comparable target coverage and dose distribution for all VMAT plans. Statistically significant differences was noted by even 40% ($p<0.00001$) in the mean dose (D mean) delivered to the hippocampi during PCI using VMAT technique comparing to 3D-CRT technique.
2. 16 patients with PBT had received hippocampal sparing partial brain irradiation with megavoltage VMAT technique to a total dose of 54-60 Gy in 30 fractions. The possibility of sparing the contralateral or bilateral hippocampus was analyzed depending on the clinical situation of the patient, tumor localization, the distance of the hippocampus or peritumor edema. Apparently, patients with tumour or oedema closer to hippocampus (on average up to 1cm - 2 cm) required more sophisticated RT planning to achieve an acceptable compromise between PTV coverage and hippocampal sparing. A significant correlation was found beetwen tumour localisation, especially on the temporal or temporo-parietal lobe, which increase of D mean on sparing hippocampus (p-value < 0.005).
3. 10 patients with diagnosed BM had received whole brain radiotherapy (WBRT) to total dose of 30 Gy in 10 fractions with simultaneous infield boost (SIB) to 1 – 3 individual BM up to a total dose of 60 Gy in 10 fractions with one or bilateral hippocampus sparing with use the VMAT technique. This study had evaluated of possibility of avoidance one

or both hippocampi depending on the clinical situation of the patient and the localization, number of BM with maintaining plan prescription doses to the brain and BM while keeping acceptable dose limits to critical structures.

There was no significant difference in D mean and maximum (D max) to sparing hippocampi in patients with one BM compared to patients with two or three BM. Moreover, lower D max (but not statistically significant) has been achieved to sparing hippocampus in patients with BM located outside the temporal lobe.

On the doctoral dissertation, the following conclusions were drawn:

1. The correct of graphical delineation of the hippocampus on MRI brain scans with HA improved with each subsequent contoured case, which indicates the need of hippocampus delineation training before implementing the HA procedure by doctors.
2. In our study, the greatest discrepancies in graphical localization of hippocampus were observed in the area of the posterior horn of the lateral ventricle, which indicates that particular attention of training in contouring this structure should be paid to defining this area of the hippocampus.
3. The VMAT technique with HA procedure during PCI allows for reduce the D mean and D max per hippocampus by about 40% compared to 3D CRT technique, which indicates that VMAT technique should be used in ZR BCO to planning PCI with HA procedure.
4. The analysis of the implementation HA procedure during PBT RT planning showed, that VMAT technique allows for coverage of ionizing radiation a much lower D mean in the protected hippocampus while maintaining therapeutic doses in the target, which indicates the possibility of RT planning with HA in patients with PBT.
5. PBT located in the temporal or temporo-parietal lobe and extensive peritumor oedema worsen the possibility of the HA procedure during RT brain planning, which indicates, that the qualification of patients for implementation the HA procedure should take place before qualification for RT in the brain.
6. The analysis of the possibility of use the HA procedure during brain RT in patients with BM planned for SIB-WBRT showed, that VMAT technique enables to keep dosimetric criteria in relation to therapeutic doses of the brain and BM while maintaining tolerance doses to OaRs, including the hippocampus, which indicates the possibility of implementation HA procedure with VMAT technique in ZR BCO in patients with BM.

7. BM located in the temporal lobe constitute an impediment in perform the HA procedure (without possibility of maintaining therapeutic doses to target volumes), which should be account for qualifying patients with BM for planning SIB-WBRT with HA.
8. The implementation of HA procedure into RT planning requires the use of a highly specialized RT technique, i.e. VMAT, which extends the RT planning time. This fact should be taken into account in the work organization at ZR BCO.

A sophisticated RT planning with VMAT technique allows for achieve a lower radiation dose in the centrally brain located hippocampus, while maintaining dosimetric restrictions on RT targets. Compared to 3D CRT, VMAT technique requires more complex RT planning process, involving more workload by qualified teams of doctors and physicists.