Morbidity after treatment for brain tumours

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Abstract

Radiotherapy (RT) is an important element in the therapy of brain tumours. Unfortunately, RT on brain tumours involves irradiation of larger volumes of the brain or the whole brain and severe morbidity and cognitive impairment have been reported after RT to the brain with a negative impact in quality of life for the patients. Cognitive dysfunction is one of the most concerning complications among long-term cancer survivors and given the prolonged survival of these patients, it makes them more likely to experience neurocognitive impairment after RT. The general objective of the research program is to establish methods to assess neurocognitive function following RT on brain tumours. The study will have a specific focus on the radiation tolerance of the hippocampus, which is believed to be highly important for the development of radiation induced neurocognitive dysfunction. Information on the hippocampal radiation tolerance is needed for optimal selection of patients who may benefit from particle therapy with protons.

Most patients with brain tumours experience neurocognitive dysfunction and decline in quality of life after RT. At this stage, there is no consensus on how to assess cognitive function in these patients. In this project we wish to explore which cognitive domains are affected, and to which extent. In response to this, a test-battery for testing of post-RT changes will be developed. The test-battery will include specific tests related to important cognitive domains.

Previous studies indicate that RT related damage of the hippocampus plays an important role in neurocognitive decline. Hippocampus plays a significant role in learning and memory, and injury of the hippocampus causes decline in these functions. There is very modest knowledge of the dose-response relationship for development of radiation-induced damage to the hippocampus. Equally, there is very little knowledge about dose-volume factor of hippocampus. We wish to investigate the correlation between scores from neurocognitive tests and of dose-volume parameters for hippocampus, and estimate the steepness of the dose-response curve and the volume effect of the hippocampus. These estimates for hippocampus are important input factors when using a model called Normal Tissue Complication Probability (NTCP). The model is believed useful to distinguish which patients will benefit from use of protons. Protons have a favourable physical dose-debt characteristics and may reduce the risk of morbidity related to radiation exposure to the normal brain tissue.

<u>The PhD-program includes three studies constructed to test neurotoxicity after RT:</u>

1. ***Development of methods for assessment of neurocognitive disorders after brain RT***

The first study is a cross-sectional study that will include patients treated with RT for specified brain tumours in the period 2006-2016. These patients will be tested by the described test-battery. The correlation between scores from the tests, and dose-volume parameters for hippocampal exposure, will be studied. An age- and gender- matched control cohort of patients with brain tumours who have not undergone radiation therapy will be included in the study. The study will provide a comprehensive tool for assessment of neurocognitive function in patients treated with RT for brain tumour. The results will be basis for selection of tests in study II and III.

2. Longitudinal investigation of neurocognitive changes following RT for **specified brain tumours** *in a national cohort study.*

The second study will enrol patients with specified brain tumours from the four Neuro-Oncology Centres in Denmark. Patients will undergo neurocognitive testing before RT and at 6 and 12 months. In addition, patients will fill in the same questionnaire as in study I. Endpoints from neurocognitive testing will be extracted from study I. The scores will be correlated with socio-demographic characteristics, extend of surgery, gross tumour volume (GTV), tumour-involvement of temporal lobes, tumour-involvement of the hippocampus, planned target volume (PTV) involvement of the temporal lobes and hippocampus and additional chemotherapy. For comparison and assessment of test-retest factor, the untreated control cohort from study I will be tested twice with 6 months intervals and will serve as a control group. The study can provide valuable information of RT effects on neurocognitive function and to uncover which domains are primarily affected. In addition, we will assess the influence of a number of predictive factors on the development of neurocognitive dysfunction.

3. Establishment of a NTCP model for assessment of the radiation sensitivity and volume effects of the brain.

The third study will employ the patients from study II and use the same control group. Doses and volumes of the brain receiving radiotherapy, especially the hippocampus and the temporal lobes, will be retrieved form the treatment planning (computer) system. The score from the neurocognitive tests will be correlated to dose-volume parameters. The study will provide important information on neurotoxicity related to RT for brain tumours. Additionally, it will provide input parameters to be used in model-based treatment planning selection of patients to proton therapy for brain tumours as well as developing the model-based model.

With these three projects we wish to establish methods to assess neurocognitive functions following RT on brain tumours, and create a valid test-battery to be routinely used on all Danish patients suffering from brain tumours. In addition, we will investigate if hippocampus has

volume-factor and estimate the steepness of the dose-response curve to Hippocampus. These results should help us in the selection of patients who will benefit from proton therapy. It is hoped the use of proton therapy will benefit patients with brain tumours, to reduce neurocognitive deficits after RT.