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Overview

Neurocognitive Effects Following Cranial Irradiation for Brain Metastases

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Abstract

About 90% of patients with brain metastases have impaired neurocognitive function at diagnosis and up to two-thirds will show further declines within 2–6 months of whole brain radiotherapy. Distinguishing treatment effects from progressive disease can be challenging because the prognosis remains poor in many patients. Omitting whole brain radiotherapy after local therapy in good prognosis patients improves verbal memory at 4 months, but the effect of higher intracranial recurrence and salvage therapy rates on neurocognitive function beyond this time point is unknown. Hippocampal-sparing whole brain radiotherapy and postoperative stereotactic radiosurgery are investigational techniques intended to reduce toxicity. Here we describe the changes that can occur and review technological, pharmacological and practical approaches used to mitigate their effect in clinical practice.

Key words: Brain metastases; hippocampus; neurocognitive function; quality of life; radiotherapy; stereotactic radiosurgery

Statement of Search Strategies Used and Sources of Information

Searches for original and review articles were conducted on Pubmed and Google Scholar databases. Search terms included ‘neurocognitive’, ‘cognitive’, ‘brain metastases’, ‘whole brain radiotherapy’, ‘stereotactic radiosurgery’ and ‘quality of life’. Individual bibliographies were reviewed for additional relevant references.

Introduction

Brain metastases occur in around 25% of patients with a malignancy originating outside the central nervous system (CNS) [1,2]. Deficits in neurocognitive function (NCF) may relate to intracranial disease progression or toxicity from treatment. Whole brain radiotherapy (WBRT) is a standard therapy [3,4] expected to improve neurological signs and symptoms in about 50% of patients [5–7].

Treatment for patients with brain metastases is individualised because WBRT may be associated with both declines [8–10] and improvements [11] in NCF depending on the clinical circumstances. Declining NCF increases caregiver burden [12] and impairs financial, work and social activities [13,14] in those who are able to remain independent. Changes in NCF precede and predict for changes in quality of life (QoL) and functional independence [15], but a causal relationship has not yet been proven.

As systemic therapies continue to improve, the potential sequelae of cranial irradiation in this population become increasingly relevant. Here we describe changes in NCF that can occur, summarise how they are assessed and review technological, pharmacological and practical approaches used to mitigate their effect in clinical practice.

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Characterising Neurocognitive Changes after Cranial Radiotherapy

The functional organisation of major cognitive domains within the brain is illustrated in Figure 1. NCF in patients with brain metastases is influenced by multiple interdependent factors (Table 1). Neurocognitive dysfunction is characterised by diminished learning and memory, attention, executive function, processing speed and motor dexterity [16]. However, defining the incidence of these deficits is challenging because of the way NCF is assessed and the timing of assessments has varied between studies.

A number of expert groups recommend a core battery of sensitive, validated tests to assess NCF in brain metastases trials [17–19]. These include Hopkins Verbal Learning Test-Revised (HVLT-R), Trail Making Test (TMT) parts A and B and the Controlled Oral Word Association (COWA) test (Table 2). Together these tests should take no longer than 30 minutes to complete, facilitating compliance [19].

The Mini-Mental State Examination (MMSE) is a dementia screening tool that has been used in older studies of cranial irradiation to measure NCF. However, it lacks sensitivity to detect changes relevant to many patients with brain tumours [19,20]. For example after cranial irradiation, HVLT-R [21] and TMT part B [22] scores show changes in NCF that MMSE does not.

Impaired performance in at least one NCF test is apparent in up to 90% of self-caring adults at diagnosis of brain metastases, with verbal memory and fine motor deficits the most common [8]. Severity of impairment correlates with volume but not number of intracranial metastases [8,22,23]. Using sensitive neurocognitive tests, further reductions in NCF are detectable in up to 65% of patients within 2–6 months of WBRT [8,9,24–26]. The proportion attributable to treatment-induced neurotoxicity is unclear because progressive disease and pre-terminal decline are also common events during this interval and are confounding factors. In some patients, NCF stabilises or improves after WBRT due to regression of disease [8,11] and/or reduced rates of intracranial recurrence [23,27]. Benefits are greatest in terms of executive function and fine motor co-ordination rather than memory [8].

Data describing neurocognitive effects more than 6 months after WBRT for brain metastases are scant and limited by high dropout rates and confounding factors. An imaging study of nine long-term survivors with a median survival of 6.25 years showed acceleration in the rate of cerebral atrophy after WBRT compared with normal aging [28] but correlation with NCF was not reported. Some evidence suggests early detrimental effects may improve at later time points. In a study of 20 patients, memory function and performance in TMT part B deteriorated 4 months after WBRT but then improved by 8 months [22]. In the subgroup of nine patients surviving at least 12 months, regression of test scores back to baseline may suggest a biphasic pattern. In patients with stage III non-small cell lung cancer without brain metastases undergoing prophylactic cranial irradiation, memory impairment was greatest at 3 months and improved thereafter but did not return to baseline [21]. The proportion of patients with a deterioration in HVLT-R immediate recall score at 3, 6 and 12 months was 45, 19 and 26% patients, respectively. By contrast, the proportion of patients with deterioration at 12 months who did not receive prophylactic cranial irradiation was 7% ($P = 0.03$). Prohibitively small numbers prevented analyses comparing those who developed intracranial failure versus those who did not.

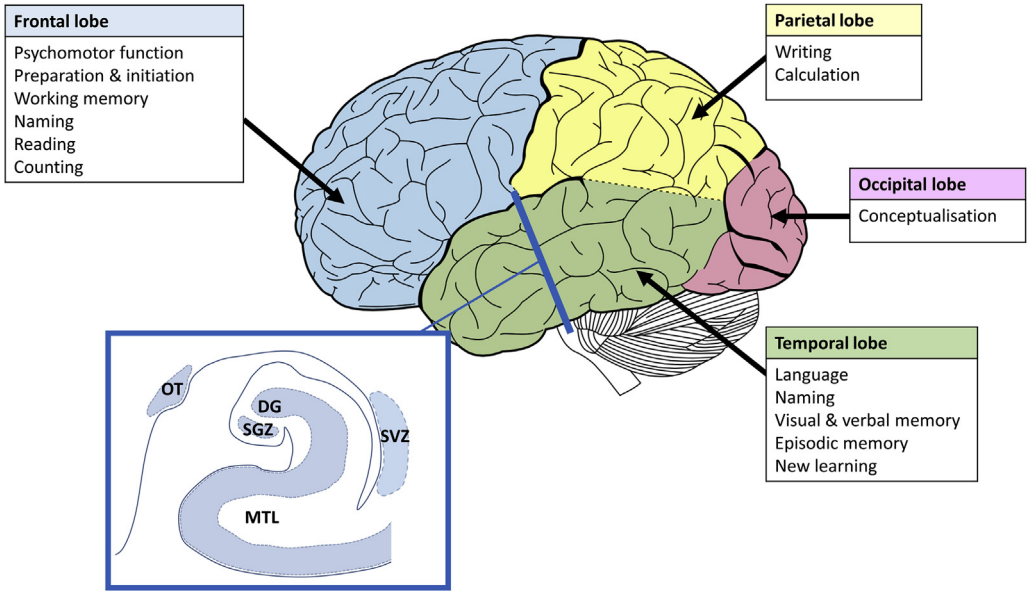

Fig 1. Organisation of major cognitive domains. The hippocampus lies in the medial temporal lobe (MTL), coronal section shown. Neurogenesis occurs within the subgranular zone (SGZ) of the dentate gyrus (DG) and just below the floor of the temporal horn of the lateral ventricle in the subventricular (SVZ) zone. OT, optic tracts.

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