EJC SUPPLEMENTS 12 (2014) 29–40

Available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Monitoring and optimising cognitive function in cancer patients: Present knowledge and future directions

S.B. Schagen [a,1,*], M. Klein [b,1], J.C. Reijneveld [c,1], E. Brain [d,1], S. Deprez [e,f,1], F. Joly [g,1], A. Scherwath [h,1], W. Schrauwen [i], J.S. Wefel [j,1]

[a] Division of Psychosocial Research and Epidemiology, Netherlands Cancer Institute, Amsterdam, The Netherlands
[b] Department of Medical Psychology, VU University Medical Center, Amsterdam, The Netherlands
[c] Department of Neurology, VU University Medical Center, Amsterdam, The Netherlands
[d] Department of Medical Oncology, Institut Curie – Hôpital René Huguenin, Saint-Cloud, France
[e] Department of Radiology, University Hospital Leuven, KU Leuven, Leuven, Belgium
[f] Department of Imaging and Pathology, KU Leuven, Leuven, Belgium
[g] Department of Medical Oncology, Centre François Baclesse – CHU Côte de Nacre, Caen, France
[h] Department and Outpatient Clinic of Medical Psychology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[i] Department of Medical Oncology and Palliative Care, University Hospital Ghent, Gent, Belgium
[j] Department of Neuro-Oncology, Section of Neuropsychology, University of Texas M.D. Anderson Cancer Center, Houston, TX, USA

ARTICLE INFO

Article history:
Received 26 March 2014
Accepted 26 March 2014

Keywords:
Cognitive function
Cancer

ABSTRACT

The potentially detrimental effects of cancer and related treatments on cognitive functioning are emerging as a key focus of cancer survivorship research. Many patients with central nervous system (CNS) or non-CNS tumours develop cognitive problems during the course of their disease that can result in diminished functional independence. We review the state of knowledge on the cognitive functioning of patients with primary and secondary brain tumours at diagnosis, during and after therapy, and discuss current initiatives to diminish cognitive decline in these patients. Similarly, attention is paid to the cognitive sequelae of cancer and cancer therapies in patients without CNS disease. Disease and treatment effects on cognition are discussed, as well as current insights into the neural substrates and the mechanisms underlying cognitive dysfunction in these patients. In addition, rehabilitation strategies for patients with non-CNS disease confronted with cognitive dysfunction are described. Special attention is given to knowledge gaps in the area of cancer and cognition, in CNS and non-CNS diseases. Finally, we point to the important role for cooperative groups to include cognitive endpoints in clinical trials in order to accelerate our understanding and treatment of cognitive dysfunction related to cancer and cancer therapies.

* *Corresponding author:* Address: Division of Psychosocial Research and Epidemiology, Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands. Tel.: +31 205122480; fax: +31 205122322.
E-mail address: s.schagen@nki.nl (S.B. Schagen).
[1] All authors contributed equally to this work.
http://dx.doi.org/10.1016/j.ejcsup.2014.03.003

1. Introduction

Compared to classical oncological outcome measures such as time to progression and survival, the importance of cognitive functioning in cancer patients has only recently been recognised. In patients with tumours either inside or outside the central nervous system (CNS), cognitive functioning is a critical outcome measure because cognitive dysfunction can have a large impact on the daily life of patients [1,2]. Even mild cognitive difficulties can have functional and psychiatric consequences – especially when persistent and left untreated. Deficits in specific cognitive domains such as memory, attention, executive function and processing speed may profoundly affect quality of life. For example, cognitive impairment negatively affects professional reintegration, interpersonal relationships and leisure activities. In addition, fear of future cognitive decline may also negatively affect quality of life.

Long-term cancer survivors are steadily increasing and many patients may develop cognitive dysfunction that can result in diminished functional independence. In this paper that focuses on cognitive functioning in cancer patients, we summarise the knowledge on the incidence and determinants of cognitive dysfunction in both patients with CNS and non-CNS cancers, the neuropsychological pattern and structural brain changes associated with various anti-cancer treatments, risk factors for developing neurotoxicity, as well as current treatment options to prevent or diminish adverse effects on cognition. Important knowledge gaps are discussed and future directions are presented. Specific attention is paid to the key role research cooperative groups hold to advance our understanding of cancer and cancer therapy-associated cognitive dysfunction – an understanding that forms the basis of preserving and enhancing cognitive function.

2. Cognition in primary and metastatic brain tumour patients

2.1. *Primary brain tumours*

The most commonly occurring primary brain tumours are gliomas (originating from the supportive cells of the CNS) and meningiomas (originating from the dural coverings of the brain), with annual incidence rates of approximately 7 and 9 per 100,000 per year respectively [3]. The incidence is low in absolute numbers when compared to the major cancer groups, but considerable when their impact on the health care system and the informal caregivers is concerned. Treatment usually consists of a combination of surgery, irradiation and chemotherapy, the choice depending on histological subtype and malignancy grade according to the World Health Organisation (WHO) classification [4,5]. The median survival ranges from approximately 14 months for glioblastoma (GBM, WHO grade IV) patients to more than 10 years for low-grade oligodendroglioma (WHO grade II) patients, and even longer for WHO grade I meningioma patients that have a 5-year survival of approximately 95% and are considered to be 'benign' tumours [5]. Patients with low-grade (WHO grade I and II) tumours typically present with epileptic seizures, whereas many patients with higher tumour grades (WHO grade III and IV) present with progressive neurological deficits [4].

2.2. *Metastatic brain tumours*

Approximately 20–40% of patients with a systemic malignancy will develop brain metastases during the course of their illness. Lung cancer, melanoma, renal cell carcinoma and breast cancer are the most common primary tumours that metastasise to the brain. Melanoma has the highest rate relative to other primary tumours, with 75% of patients with disseminated disease developing brain metastases. With best supportive care and depending on performance status, extent of extracranial disease, and age, the median survival time is approximately 1–2 months. Radiotherapy increases the median survival to 3–5 months, and further survival benefit might be achieved in specific subgroups through combinations of surgery, stereotactic radiotherapy, whole brain radiotherapy (WBRT) and systemic therapies [6]. The initial symptoms patients present with are similar to patients with primary brain tumours, but cognitive dysfunction, including memory problems and mood or personality changes, is already present in 90 percent of patients with brain metastases [7].

2.3. *Cognitive functioning at presentation*

Even at first presentation, many, if not all, patients with primary and metastatic brain tumours have cognitive deficits. Reijneveld et al. showed that patients with presumed low-grade glioma (WHO grade II) already suffered from cognitive deficits compared to matched healthy controls [8]. The same is true for patients with high-grade glioma prior to surgery [9] or prior to the initiation of radiotherapy [10]. Contrary to what was presumed historically, even most patients with suspected WHO grade I meningiomas show subtle cognitive deficits [11]. In patients with brain metastases [7], cognitive dysfunction is more correlated with the volume than with the number of metastases [12]. In general, cognitive deficits manifest in accordance with our traditional understanding of brain behaviour relationships – specifically, greater deficits in verbally mediated cognitive functions are seen in patients with left hemisphere tumours compared to patients with right hemisphere tumours. However, when compared to patients with stroke, more subtle and diffuse patterns of cognitive deficits are seen in patients with brain tumours [13].

2.4. *Cognitive functioning during treatment*

Virtually all patients with gliomas and metastatic brain tumours cannot be cured from their disease. Therefore, palliation of symptoms and sustained or improved quality of life are considered as equally important treatment goals as prolonged survival and postponed tumour progression. Evaluation of treatment outcome in brain tumour patients should therefore focus beyond survival endpoints, and should also aim at avoiding adverse treatment effects on the normal brain