Neuropsychological Evaluation of Patients with Intrinsic Brain Tumors

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This chapter begins with a discussion of the primary purposes of neuropsychological assessment in patients with intrinsic brain tumors and is followed by an overview of the most important tumor characteristics as well as patient status factors that need to be considered when using neuropsychological tests to assess these patients. The cognitive domains that comprise a comprehensive battery of neuropsychological tests are reviewed, along with some representative tests from each domain. In addition, personality testing, assessment of mood, and measures of health-related quality of life designed specifically for patients with brain cancer are briefly covered. Next, a short, standardized battery of neuropsychological tests that have been used internationally in multisite brain cancer clinical trials is described. The chapter concludes with a summary of the salient results of neuropsychological assessments before and after treatment with resective surgery, cranial irradiation, and chemotherapy and the primary cognitive deficits associated with each of these treatment modalities. Finally, there is a brief discussion weighing the clinical decision making trade-offs using health utility measures when there are conflicts between the quantity (survival) and quality (cognition and quality of life).

7.1 Introduction

The neuropsychological assessment of patients with brain tumors has become more common in recent years because it has been more widely appreciated that cognitive impairments can have significant impacts on medical treatment compliance, self-care, and vocational, educational, and social functioning. Consequently, cognition can directly affect the overall quality of life of patients living with brain cancer [1]. Since many intrinsic brain tumors cannot be cured, palliation of symptoms and maintenance or improvement in quality of life are important goals of treatment. Because improvements in treatment in recent years have extended life expectancy considerably, evaluation of treatment outcome needs to be expanded beyond the traditional measures of time to progression of disease and survival. Neuropsychological evaluation is a useful method to measure the direct effects of tumor progression and treatment and is an important estimate of outcome, since even mild cognitive deficits can negatively impact the quality of life [2]. Up to 75% of cancer patients will experience cognitive impairment during or after treatment of their cancer, and in many cases this will persist for years [3, 4].

Many different factors may contribute to the cognitive dysfunction seen in patients with brain tumors, including the direct effects of the tumor on the brain, effects of treatment (i.e., radiotherapy or chemotherapy), adjunctive medical treatment (e.g., steroids, antiepileptic drugs), and patient status factors (e.g., premorbid cognitive capacity, psychological distress, symptomatic epilepsy, tumor grade, size and rate of growth, and tumor lateralization and localization). Most if not all of these factors need to be considered in the individual case when attempting to interpret cognitive test results in patients with brain cancer. When interpreted correctly, neuropsychological testing can identify and diagnose specific neurobehavioral disorders and provide guidance for rehabilitative or psychological intervention. Testing can also serve as an early indicator of disease recurrence and progression, even before signs of disease are apparent on CT or MRI, and this information may be used to help guide clinical decision-making [5–8].

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K. Fountas, E. Z. Kapsalaki (eds.), *Epilepsy Surgery and Intrinsic Brain Tumor Surgery*,
https://doi.org/10.1007/978-3-319-95918-4_7

7.2 Purposes of Neuropsychological Assessment in Patients with Brain Tumors

Neuropsychology combines the knowledge base of established brain-behavior relationships with standardized psychometric measures (tests) to assess and diagnose disturbances of mentation and behavior and relates these findings to their neurologic implications and to issues of clinical treatment and prognosis. Standardized measures that assess a broad range of established cognitive domains (such as attention or memory) are compared with normative performance levels of healthy individuals, and negative deviation from these normal population levels may suggest impairment in a given cognitive domain. Focal or multifocal disease in various regions of the brain may result in characteristic patterns of deficit. These patterns are used to generate descriptions of cognitive, psychological-emotional, and functional competence.

7.2.1 Clinical Characterization of Deficits

In patients with brain tumors, one of the primary uses of neuropsychological assessment is to provide a quantitative characterization of the patient's cognitive and behavioral impairments to assist in treatment planning and provide guidance for rehabilitation efforts [9]. The cognitive impairments caused by the direct effects of tumors or to circumscribed resective surgery may be restricted to a single cognitive domain (such as new verbal learning), where the most important determinant of such deficit patterns is the location of the tumor (e.g., in the language dominant [usually left] temporal lobe in the case of new verbal learning). For example, orbitofrontal lobe tumors may result in alterations of emotional control and changes in personality, while dorsolateral prefrontal locations will often cause executive cognitive dysfunction (e.g., poor organization and planning, difficulty switching mental sets). Formal testing can provide clinical characterization and monitoring of cognitive and behavioral disorders that may affect patients' abilities to maintain their occupational, academic, family, or social roles.

7.2.2 Identification of Tumor Recurrence or Disease Progression

Neuropsychological assessment can detect signs of tumor recurrence and disease progression even before signs of disease are present on neuroimaging. Detailed testing of cognitive functioning of patients with high-grade gliomas is more sensitive in gauging the extent of damage to the brain resulting from tumor infiltration than is the structural information provided by CT or MRI [10]. Tests of memory and attentional set-shifting have been shown to predict tumor recurrence in patients with glioblastoma multiforme [8]. Hence, a second purpose of testing is to measure change. Repeat assessments can be valuable in charting progress (e.g., recovery after surgery or radiotherapy) as well as for detecting any decline in cognitive capacity (e.g., from tumor regrowth). Thus, in addition to the clinical value provided by cognitive testing from delineation of the pattern of cognitive and behavioral deficits, neuropsychological assessment also has prognostic value and may serve as an early indicator of disease progression.

7.2.3 Diagnosis of Psychological-Emotional Disorders

In confusing or complex cases, neuropsychological assessment can be useful for teasing out the relative contributions of neurologic conditions (e.g., cellular degeneration, neurochemical disruption), emotional states (e.g., anxiety, depression), and psychiatric illnesses (e.g., personality disorder, psychoses). Abnormal psychological states may be caused by the direct effects of the tumor, secondary effects of treatment (including medications), adjustment reactions to the illness and subsequent alterations in life circumstances, or by some combination of these factors. For example, frontal lobe tumors often cause alterations in personality, emotional control, and comportment. A comprehensive neuropsychological examination will include assessment of mood and personality as well as other aspects of emotional functioning when indicated. This is to ensure that patients' psychological problems are properly identified and addressed through appropriate targeted treatments. Furthermore, the potential contributions of emotional factors in producing spurious abnormal cognitive test results must be considered in test interpretation.

7.2.4 Determining Competency Issues

Cognitive and emotional status both play a role in determining a patient's overall competency. Questions typically involve a patient's ability to exercise rational judgment, make competent decisions, and live in an independent fashion. In addition to cognitive status, assessment of the patients' awareness of their limitations is also important in establishing their ability for independent functioning. Although there is some overlap between neuropsychological test results and inferences about decision-making capacity in cancer patients, additional information must be obtained to make informed

clinical judgments about mental competence. Specific assessment methods that help determine decision-making capacity include formal tests (e.g., MacArthur Competence Assessment Tool for Clinical Research [MCAT-CR]) [11], structured interviews (e.g., Independent Living Scales) [12], or a simple standard clinical interview covering the necessary areas. Complicating this issue is the fact that decision-making capacity is not an all or none phenomenon. As noted by Rodin and Mohile [13], there are gradations of capacity that may not remain stable over time. In many countries, determination of degree of competency has legal consequences, and valid, reliable measures should be used to make such judgments. Most cancer patients will be asked to make crucial life-altering decisions at some point during the course of treatment, and neuropsychology can assist in determining their capacity to make such decisions.

7.2.5 Assist in Formulation of Rehabilitation Strategies and Research

Most patients treated for primary brain tumors will experience some form of cognitive impairment or emotional disturbance, and many of these problems will be present for years to come. Rehabilitation therapies are typically tailored to the specific pattern of deficits for each individual, and a comprehensive neuropsychological assessment may be used to assist with planning targeted rehabilitation interventions.

7.3 Factors Complicating Interpretation of Neuropsychological Results

Cognitive dysfunction is a common complaint among cancer survivors. This is most often caused by the tumor itself or by the effect of cancer-related treatments such as chemotherapy, endocrine treatment, or radiation. Cognitive difficulties seem to be heightened in survivors with primary central nervous system cancers or in those with brain metastases. It has been reported that even survivors who never had primary brain involvement may display cognitive changes [14]. Although there is limited evidence about the mechanisms involved in increasing the risk for chemotherapy-induced cognitive complaints, studies have reported elevated levels of cytokines or DNA damage as possible causes [15]. Additional studies have suggested that neurocognitive impairments from chemotherapy agents are associated with neurotoxicity [16]. Furthermore, emotional distress, fatigue, and psychosomatic effects can influence cognition as well, and patient expectations may also affect test results. For instance, it has been shown that those treated with chemotherapy who were informed in advance of possible cognitive changes were more likely to complain of cognitive difficulties and to produce lower scores on neuropsychological testing than those who were uninformed [17].

7.3.1 Timing of Testing and Location of Tumor

In some cases cognitive impairment is not evident immediately after therapeutic intervention, and as a result assessments in the acute stages are not always informative. However, it has been suggested that children diagnosed with brain tumors may exhibit cognitive changes prior to tumor resection or chemotherapy. Children with cerebellar tumors who underwent neuropsychological testing 3–4 days prior to surgery performed worse on verbal memory testing than healthy controls [18]. When comparing children with brain tumors to those with non–central nervous system cancer before therapeutic intervention, performances in the areas of verbal learning, attention, and working memory were commonly impaired in children with brain tumors. In addition, such children have demonstrated impaired performances (<1 SD) on at least four different cognitive tests compared to those without central nervous system involvement [19]. It appears that performances of those with primary tumors may be affected by compromised brain connectivity, whereas in children without central nervous system involvement cancer-induced mechanisms, such as aberrant immunologic processes, are more likely responsible for reduced cognitive performance [20].

Another concern involved in the neuropsychological assessment of patients with brain tumors is whether damage to brain regions is focal or multifocal. The location of the tumor(s) is the most important factor determining the type of cognitive deficit obtained, while tumor dimension seems to exert a smaller effect [21]. When assessing long-term brain structure and cognitive outcome following cerebellar tumor resections in children, reduced cognitive function, increased gray matter density, and white matter microstructural abnormalities were observed and thought to be related to hydrocephalus [22]. In addition, cerebellar tumors may particularly affect the patient's attention capacity because of their proximity to the ascending reticular activating system, which regulates attention and arousal.

Supratentorial hemispheric tumors appear to be related to lower intelligence quotients (IQs) in children tested before surgery. In addition, factors such as epilepsy and symptom duration are the main issues affecting cognition at the time of diagnosis, whereas age, gender, and neurologic findings seem to be less prominent. Children with supratentorial midline neoplasms have demonstrated deficient memory abilities probably caused by disruption of diencephalic structures

and connections. Linguistic abilities and cortical left-sided tumors have been correlated. Visual-motor integration and planning capabilities have been associated with cortical right-sided tumors [23].

7.3.2 Effects of Treatment Interventions, Comorbidities, and Medications

Neuropsychological deficits may be secondary to a variety of factors, including the focal destructive effects of the tumor, secondary mass effects, acute or late neurotoxic effects of chemotherapy or radiation treatment (type and dosage), or the effects of resective neurosurgery. In addition, some of the medications typically prescribed for patients with primary brain tumors, such as glucocorticosteroids, anticonvulsants, and psychoactive medications, can negatively affect cognition [24]. High-grade glioma patients prescribed corticosteroids have been found to have worse baseline cognition [25]. Radiation-induced cognitive deficits have been found in up to 50% of long-term brain tumor survivors [26]. In addition, those treated with stereotactic radiosurgery and whole-brain radiation therapy experience more severe learning and memory impairments compared to patients with stereotaxic radiosurgery alone [27].

Neuropsychological tests are sensitive to the neurotoxic effects of treatment as well as to the resection of eloquent brain regions. It is estimated that up to half of those who receive cranial irradiation with a longer than 6-month survival rate will experience some type of cognitive impairment [28]. In brain metastases trials, a 4-month post-irradiation neuropsychological assessment was found to assist in establishing the early effects of radiation therapy because the deterioration at this point was reproducible [29]. Some of the cognitive deficits seen in children with acute lymphoblastic leukemia (ALL) treated with cranial irradiation and chemotherapy may only be detected by using specific sensitive neuropsychological tests. For example, in one recent childhood ALL study, 50% of children with white matter abnormalities showed deficits on a test of visual-motor integration [30, 31]. Furthermore, intracerebral calcifications were correlated with the number of intrathecal methotrexate doses and with low performance IQ and significant impairment in attention and visual-spatial-construction. Girls were more vulnerable to the effects of CNS prophylaxis than boys [31]. Thus, neuropsychological assessment can identify specific areas of cognitive dysfunction in brain tumor patients treated with radiation, chemotherapy, or neurosurgical resective treatment.

7.4 Demographic Background and Normative Considerations

Neuropsychological assessment consists of a variety of behavioral measures and tests that are administered in a standardized, controlled fashion, and the results are used to infer a patient's underlying ability and current functioning across a number of broad cognitive domains. The major cognitive domains typically assessed include attention, memory, intelligence, language, visual-perceptual and visual-spatial thinking, psychosensory and motor abilities, personality-emotional functions, and, when indicated, health-related quality of life.

Patient performance on cognitive and psychological-emotional tests are compared with normative performance levels of the general population. Significant negative deviation from these normal population levels may suggest impairment in a given cognitive domain. Major tests have norms that are usually stratified by important moderating demographic variables such as age, gender, education, ethnicity/race, and socioeconomic status. In general, normative comparisons should be made with subgroups that most closely approximate a patient's particular demographic group. Almost all tests provide age-based normative scores, but the availability of norms based on education, ethnicity, race, and culture are less common. Nevertheless, normative comparisons should take these important demographic variables into account whenever possible.

7.4.1 Medical History Considerations

Primary tumors affecting various regions of the brain may result in characteristic patterns of deficit. The pattern of neuropsychological impairment depends upon a number of factors, including the tumor type, size, rate of growth, degree of infiltration, and the specific brain region affected. There are four primary biological mechanisms through which brain tumors can affect brain functions. Brain tumors may cause: (1) increased intracranial pressure that results in generalized symptoms such as headache, nausea and vomiting, and reduced attention capacity; (2) invasion or displacement of brain tissue focally, which in turn may cause isolated sensorimotor or focal cognitive deficits; (3) induction of seizures, usually localization-related complex partial epilepsy; or (4) secretion of hormones or alteration of endocrine patterns, which in turn may affect many different bodily, including brain, functions [32].

After headaches, neurobehavioral changes are the most common presenting symptoms of primary brain tumors [33]. Rapidly growing tumors such as glioblastoma multiforme often cause acute increased intracranial pressure, which will result in widespread neurobehavioral and neurologic effects. In contrast, slow growing, lower grade tumors may produce few or no obvious neurobehavioral or neurologic effects by enabling brain structures to accommodate to surrounding shifting tissue or even reorganize their behavioral functions [34].

From a neurobehavioral perspective, tumors may present in a way similar to other localized lesions and result in behavioral changes in the same way that other discrete brain lesions do. Thus, temporal lobe lesions often result in mem-

ory impairments or psychiatric symptoms. If the tumor invades the temporal lobe language zones, patients typically show deficits in understanding spoken or written language or in their ability to name objects. Frontal lobe tumors affecting the dorsolateral prefrontal regions may cause executive dysfunction with impairments in cognitive flexibility, planning, organization, and generativity as examples. Dominant frontal lobe lesions affecting Broca's area may present conspicuous problems with speech output and fluency. Orbitofrontal tumors, often meningiomas or craniopharyngiomas, can cause disorders of restraint, such as disinhibition of emotional expressiveness or difficulties in the inhibition of socially inappropriate behaviors. Lesions affecting the mesial frontal areas result in apathy, lack of drive, initiative, and motivation and an absence of spontaneity. Brain tumors often disrupt the dopaminergic pathways from the brainstem to the frontal lobe (mesocortical system) or from the brainstem to the limbic regions (mesolimbic pathways) and result in deficits in mental processing speed and attention/concentration and working memory.

Localized tumors in the diencephalon have characteristic neurobehavioral consequences. Tumors that affect the midline limbic structures, such as the dorsomedial nucleus of the thalamus, fornix, and mammillary bodies can result in an anterograde amnesia that may be differentiated from hippocampal memory disorders by neuropsychological testing. Tumors originating in the hypothalamus typically result in disruption of some hypothalamic functions, such as temperature dysregulation, hyperphagia or anorexia, endocrine abnormalities, or hypersomnolence. Thalamic tumors can produce attentional deficits, mental dullness, and memory loss [35].

In addition to the possibility of producing cognitive deficits, brain tumors may also cause behavioral changes, mood disorders, or problems in adaptive behavior. It can be difficult to determine if these psychiatric issues are related to the primary organic effects of the tumor itself (presumably from disruption of corticolimbic interconnections) or to secondary reactive adjustments to the cancer diagnosis and its life-altering consequences. Depression and anxiety reactions are particularly common in tumor patients after diagnosis and treatment. Regardless of the etiology of psychological problems, neuropsychological assessment can identify patients who need psychiatric pharmacotherapy, psychotherapy, or counseling.

7.5 Neuropsychological Assessment

When assessing brain tumor patients, the administration of a comprehensive battery of tests remains standard practice for neuropsychologists. Because the neurocognitive dysfunction caused by tumors and treatments is unpredictable, it is reasonable to establish a testing battery that samples an extensive range of cognitive abilities. Moreover, the severity of cognitive impairments found may be influenced by the rate of tumor growth. Slow tumor growth allows for compensatory plasticity of cognitive functions, which may be associated with only mild or even no deficits. A neuropsychological evaluation should (1) assess several domains found to be most sensitive to tumor and treatment effects, (2) use standardized materials and administration procedures, (3) have published normative data, (4) have moderate to high test-retest reliability, and (5) have alternate forms or be relatively insensitive to practice effects and therefore suitable to monitor changes in neurocognitive function over time. Tests that have been translated into several languages or only primarily require translation of test directions are also useful [5].

The cognitive domains that should be included are general verbal and nonverbal intellectual functions, language, attention, orientation, verbal and nonverbal learning and memory, visual-spatial skills, frontal-executive functions, psychosensory and motor abilities, mood, and health-related quality of life.

7.5.1 General Intellectual Functions

A valuable testing battery will assist in determining an individual's verbal and nonverbal general cognitive abilities through the use of intellectual functioning tests (e.g.,, Wechsler Adult Intelligence Scale, 4th edition [WAIS-IV], Wechsler Intelligence Scale for Children, 5th edition [WISC-V]). Through the use of these composite tests, verbal abilities including verbal concept formation, verbal reasoning skills, and fund of general information can be assessed. Perceptual organization skills include nonverbal reasoning, visuospatial information processing, and visual-motor coordination. The Wechsler scales also include subtests designed to measure attention, concentration, and working memory (digit span and mental arithmetic) and mental processing speed (coding/digit symbol and symbol search).

7.5.2 Language

Language may be affected in cases where the tumor invades eloquent cortical regions that mediate various language functions. The most prominent disorders of verbal functions are the aphasias with associated difficulties in expressive or receptive verbal abilities [36]. Tests that assess language should provide a comprehensive assessment of oral and written language and aural comprehension and reading and may include formal evaluation of spontaneous speech (fluency), naming of objects, auditory comprehension, speech repetition, phonemic associative (letter) fluency, paraphasic errors in speech, and the ability to produce over-learned phrases. A thorough language evaluation often includes testing-associated functions such as oral reading, reading comprehension, written and oral spelling, and speech articulation.

When testing for anomia, the Boston Naming Test requires patients to provide the names of object line drawings. Phonemic (letter) fluency can be measured by asking the examinee to generate words beginning with a specific letter, such as F, A, or S, allowing 1 min for each letter. Semantic fluency assesses the ability to produce words belonging to a specified category (e.g., animals, fruits, or vegetables) in 1 min.

7.5.3 Attention

Neuropsychologists may assess verbal or visual attention. A common measure of auditory attention is the Digit Span subtest from the WAIS-IV and WISC-V. There are many different types of attention, such as sustained attention, selective attention, alternating attention, divided attention, and vigilance, and there are a variety of neuropsychological tasks that may be used to measure these different aspects of attention. Tests of repetition of digits forwards or backwards, sentence repetition, block tapping sequence span, complex mental tracking, mental arithmetic, visual search, cancellation tasks, and continuous performance tasks can all measure different features of attentional capacity.

7.5.4 Orientation

Some commonly used bedside mental status examinations such as the Mini-Mental Status Exam (MMSE) [37] or the Montreal Cognitive Assessment (MoCA) [38] include assessment of orientation to time and place. Orientation requires consistent and reliable integration of attention, perception, and memory and is evaluated by inquiring about the person's knowledge of time, place, and personal information, such as their name, age, and date of birth. Orientation questions are typically part of all mental status examinations and are included in most memory test batteries. It should be noted that mild orientation difficulties may be experienced in individuals with no cognitive impairment, especially in situations such as unemployment, retirement, or when they are hospitalized [39].

7.5.5 Learning and Memory

When examining verbal and nonverbal (visual-spatial) memory, a comprehensive evaluation should include: (1) recall to assess learning and retention of meaningful information (such as stories), which resembles what the examinee has heard in a conversation; (2) rote learning ability across three or more trials, which yields a learning curve and is subsequently tested for both free recall and recognition; (3) visual-spatial memory, which could include copying a complex figure followed by a recognition trial; (4) remote memory, such as fund of information; and (5) personal autobiographical memory [39]. One commonly used memory test battery that contains these necessary memory testing procedures is the Wechsler Memory Scale, 4th edition (WMS-IV), which includes story memory, paired-associates learning, and visual-spatial recall of geometric figures. Some stand-alone measures of visual memory that are not part of a memory test battery include the Rey-Osterrieth Complex Figure Test (ROCFT), and the Brief Visual Memory Test, revised (BVMT-R).

7.5.6 Visual-Spatial-Perceptual Skills

Visual-spatial skills refer to the ability to analyze, discriminate, and synthesize visual stimuli, including visual perception, spatial judgment, and organization of visual materials. Impairments of analysis of visual information can be measured by tests requiring the assembling of objects, drawing, judging the directional orientation of lines, position discrimination, and stimulus orientation [39]. One disorder of visual-spatial processing is hemispatial neglect, which is a deficit in awareness of stimuli contralateral to a lesion [40]. Tests involving line bisection, Judgment of Line Orientation, cancellation, double simultaneous stimulation, and drawing tasks assist in identifying contralateral multimodal neglect in an affected individual. In addition, the Clock Drawing test, Rey-Osterrieth Complex Figure Test, and the RBANS-Figure Copy or the WAIS-IV Block Design subtest may also be useful to assess visual spatial competence.

7.5.7 Executive Functions

Executive cognitive functions are involved in the control and direction of thought and behavior and include such abilities as planning, monitoring, initiating, switching sets, and inhibiting extraneous responses. These cognitive functions are mediated by the prefrontal cortical regions and allow an individual to engage successfully in independent, purposive, self-directed, and self-serving behavior. A standard battery of tests that evaluate these verbal and nonverbal higher cognitive abilities is the Delis-Kaplan Executive Function Scale (D-KEFS). When frontal-executive functions are impaired, both cognition (e.g., planning) and behavior (e.g., impulsivity) may be affected, and completion of activities of self-care, employment, and socialization may not be possible [36]. As a result, a caregiver-rated questionnaire, such as the Frontal Systems Behavioral Scale (FrSBe), may be helpful in capturing both the executive cognitive deficits and personality changes seen with frontal lobe damage and determining

the severity of impairment. The most commonly used executive function test, the Wisconsin Card Sorting Test, assesses higher reasoning skills and requires the patient to form abstract concepts, switch mental sets, and inhibit responses with the use of feedback. Other examples of executive function measures include the Stroop Color Word Test, Trailmaking Test Part B, phonemic fluency, alternating fluency, and the Frontal Assessment Battery [36, 39].

7.5.8 Psychosensory and Motor

Sensorimotor abilities involve receiving and transmitting information to and from the central nervous system. These abilities are usually involved in visually guided behaviors such as hand-eye coordination. Psychosensory disorders include agraphesthesia (inability to recognize symbols drawn on the surface of the skin), astereognosis (inability to recognize an object by touch alone), finger agnosia (inability to identify by touch alone which finger is being stimulated), and right-left disorientation. Disorders of motor functions include apraxia (inability to follow a motor command when this inability is not caused by a primary motor deficit or a language impairment). Ideomotor apraxia can be tested by asking the individual to perform complex pantomimed commands, such as "pretend to comb your hair" [41]. Manual dexterity, fine motor skills, and strength can be assessed by speeded tests of manipulative agility using finger-tapping devices, pegboards, or hand dynamometers [36].

7.5.9 Mood and Personality

Cognitive dysfunction affects physical, psychological, social, and vocational functioning. Many patients with primary brain tumors encounter behavioral, emotional, and intellectual challenges that affect their ability to perform activities of daily living [42]. Personality changes may be attributed to orbital and medial frontal disease or limbic involvement. In addition, mood and anxiety disorders may be primary organic or secondarily reactive. As a result, tests measuring personal adjustment and emotional functioning through the use of questionnaires, such as the Beck series (Beck Depression Inventory, Beck Anxiety Inventory) and objective personality inventories (e.g., Minnesota Multiphasic Personality Inventory) can contribute valuable information to a neuropsychological battery. Objective tests are self-report instruments (such as inventories or scales) in which patients or their informants describe symptoms and emotions by selecting items they claim to be true. Commonly used objective personality tests include the Minnesota Multiphasic Personality Inventory (MMPI-2, MMPI-RF) and the Personality Assessment Inventory (PAI) [36].

7.5.10 A Brief Neuropsychological Battery for Use in Cancer Research

A test battery that meets many of the criteria discussed earlier that has been used in a number of clinical trials, such as the ones conducted by the European Organization for Research and Treatment of Cancer (EORTC), North Central Cancer Treatment Group (NCCTG), National Cancer Institute (NCI-C), Radiation Therapy Oncology Group (RTOG), and the Medical Research Council (MRC), has been described by Klein and colleagues [5]. This brief universal research battery assesses: (1) *memory* using the Hopkins Verbal Learning Test [43], which is a verbal learning and memory test consisting of a list of 12 words in three semantic categories that assesses immediate recall across three trials, recognition of the words from distractors, and delayed free recall; (2) *verbal (phonemic) fluency* using the Controlled Oral Word Association test from the Multilingual Aphasia Examination [44], which requires the production of words beginning with a specific letter for three 1-minute trials; (3) *visual-motor scanning speed* using the Trailmaking Test, Part A [45], which entails connecting dots in numerical order in a timely manner; and (4) *executive function*, using the Trailmaking Test, Part B [45], in which the subject connects dots with alternating numbers and letters as rapidly as possible.

7.5.11 Health-Related Quality of Life

Owing to the effects that a brain tumor and its treatment may have on individuals, Health-Related Quality of Life (HRQoL) or simply Quality of Life (QOL) measures are frequently administered to assist with management of disease. QOL has become an important factor to track when treating brain tumor patients because treatment is not only aimed at maximizing survival but also at improving quality of life throughout the entire course of the disease. There is no universally agreed-upon QOL instrument for use with brain tumor patients, but there are several instruments that have been designed specifically for use with brain cancer patients.

7.5.12 European Organization for Research and Treatment of Cancer (EORTC) Questionnaire

One commonly used instrument, the EORTC QLQ-C30 questionnaire [46], was developed by the European Organization for Research and Treatment of Cancer (EORTC). This measure takes into account five functional scales (physical, role, emotional, cognitive, and social), three symptom scales (fatigue, pain, nausea and vomiting), "global

health status" and overall "quality of life" items, and six single items for remaining symptoms and problem areas (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). This questionnaire yields a total of 30 QOL items [2]. For a more relevant questionnaire designed specifically for patients with brain cancer (as opposed to tumors elsewhere in the body), the EORTC QLQ-BN20 questionnaire was developed [47]. The brain tumor-specific EORTC QLQ-BN20 questionnaire consists of 20 questions covering four scales (future uncertainty, visual disorders, motor dysfunction, and communication deficit) and seven single items (headache, seizures, drowsiness, hair loss, itchy skin, weakness of legs, and bladder control). Both EORTC inventories require patients to rate their symptoms and problems over a seven-day recall period. With the exception of the "global health" and "overall quality of life" items of the QLQ-C30, all items of both the EORTC QLQ-C30 and the EORTC QLQ-BN20 are rated on a four-point Likert scale ranging from "not at all" to "very much." Answers to the items "global health" and "overall quality of life" are provided on a seven-point Likert scale, ranging from "very poor" to "excellent." Scores of all single item and multi-item scales of the EORTC questionnaires are linearly transformed to a 0–100 scale [48].

7.5.13 Functional Assessment of Cancer Therapy: General (FACT-G) Questionnaire

Another widely used measure to evaluate HRQoL based on a 7 day recall period is the Functional Assessment of Cancer Therapy, General (FACT-G) questionnaire. The FACT-G (version four) includes four domains (physical, social/family, emotional, and functional well-being) and covers a total of 27 items [49]. Additionally, this questionnaire can be used alongside a brain-specific module such as the FACT-Br, which measures specific concerns commonly seen in brain tumor patients [50]. The main difference between the EORTC and the FACT questionnaires is that the latter emphasizes the psychosocial aspects of the disease and its treatment, while the EORTC focuses more on physical functioning and current symptoms [2].

7.5.14 MD Anderson Symptom Inventory – Brain Tumor (MDASI-BT)

For those patients requiring a shorter questionnaire, the HRQoL 24-hour recall, the MD Anderson Symptom Inventory (MDASI) was developed [51]. This inventory measures severity of 13 symptoms as well as the interrelation of these activities with daily living (6 items). A specific brain tumor module, MDASI-Brain Tumor, is available as well [52]. This module focuses primarily on symptoms and includes nine items (weakness, difficulty understanding, difficulty speaking, seizures, difficulty concentrating, vision, change in appearance, change in bowel pattern, and irritability). Items on the MDASI and the MDASI-BT are scored on a numeric rating scale ranging from 1 to 10, where 0 indicates "not present" and 10 is "as bad as you can imagine." Scores are then calculated by averaging the sum of the items in the subscale and for the total questionnaire [53].

Because of the neurologic impairments, cognitive changes, and mood disorders experienced by patients with brain tumors, the validity of the scores on self-rated questionnaires may be questionable at times. Severity of depression has commonly been associated with poorer QOL ratings by patients. In these situations, the inventories should be completed with the assistance of a proxy, family member, or another reliable source. However, the clinician must take into account that the level of agreement between the patient and the proxy may vary. Despite these confounding influences on self-rating inventories, HRQoL questionnaires may nevertheless be valuable in determining the effects of the disease and its treatment on patients' quality of life [2]. Common neuropsychogical, mood, and quality of life tests are listed by cognitive domain in Table 7.1.

Table 7.1 Commonly used neuropsychological tests by cognitive domain

Cognitive domain	Test
Intellectual Functioning	Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV), Wechsler Intelligence Scale for Children, 5th ed. (WISC-V)
Orientation	Montreal Cognitive Assessment (MoCA), Mini Mental Status Exam (MMSE)
Attention	Digit Span; WAIS-IV
Verbal Memory	Rey Auditory Verbal Learning Test, California Verbal Learning Test, Logical Memory & Paired Associates Learning - Wechsler Memory Scale, 4th ed. (WMS-IV)
Visual Memory	Rey-Osterrieth Complex Figure, Brief Visual Memory Test-Revised, WMS-IV Visual Reproduction
Language	Boston Naming Test, Token Test, phonemic (letter) fluency
Executive Functions	Wisconsin Card Sorting Test, Stroop Color-Word Test, Trailmaking Test Part-B, Frontal Assessment Battery, Delis-Kaplan Executive Function System (D-KEFS)
Visuospatial	Clock Drawing, Judgment of Line Orientation, Rey-Osterrieth Complex Figure Test, WAIS-IV Block Design
Sensorimotor	Finger Tapping, Grooved Pegboard, Hand Dynamometer
Mood	Beck Depression Inventory-II, Beck Anxiety Inventory, Beck Scale for Suicide Ideation
Functional Status	European Organization for Research and Treatment of Cancer (EORTC QLQ-C30 or QLQ-BN20), Functional Assessment of Cancer Therapy-General (FACT-G), MD Anderson Symptom Inventory-Brain Tumor (MDASI-BT)

7.6 Neuropsychological Assessment Following Treatment

Patients with primary brain tumors will usually be treated with some combination of neurosurgery, radiation, and chemotherapy. Although neuropsychological assessment is useful for monitoring the effects of these treatments, it is often difficult to identify the separate contribution of each individual treatment because they interact to either produce cognitive deficits or to improve existing deficits. Furthermore, the timing of the neuropsychological testing also matters because the acute effects of surgery and the short-term consequences of irradiation and chemotherapy are often different from their long-term effects.

7.6.1 Neurosurgery

After diagnosis, resective surgery is usually the first treatment undertaken in patients with brain tumors. Resective surgery planning needs to balance the risks of cognitive decline (and medical morbidity) against the benefits of improved survival. The major factors determining cognitive outcome are the location of the brain tumor and the extent of resection. Cognitive deficits may arise from compression of normal brain tissue or through invasion into functional brain tissue, or by disconnecting related functional nodes. Although there is extensive literature about the impact of surgery on neurologic outcome for a variety of brain lesions, there are fewer studies of neuropsychological outcome after neurosurgery for brain tumors [54]. That said, much of the literature on focal neurosurgical resection of noncancerous brain lesions is applicable to neurosurgery for brain tumors.

7.6.2 Cognitive Impairment After Surgery

Much of the literature on focal excisions in epilepsy surgery are generally applicable to brain tumor surgery outcome. Thus, resective surgery in the dominant (left) temporal lobe can result in verbal memory deficits and some language decline, such as anomia, while nondominant (right) temporal lobe resections may be associated with visuospatial memory decline [55, 56]. Orbitofrontal lobe tumors may result in alterations of emotional control and changes in personality. Dorsolateral prefrontal excisions may result in executive cognitive dysfunction. Mesial frontal lobe resections often produce reduced motivation and initiation or apraxia when the supplemental motor area is affected [57]. Parietal and posterior temporal lobe resections may lead to impairments in a variety of higher cognitive functions, including language (e.g., anomia, aphasia, alexia, agraphia), intellectual functions, or visuospatial cognition, as examples [45].

7.6.3 Cognitive Improvement After Surgery

Equally important in this context is the fact that neurosurgical excision of brain tumors may also improve cognitive functioning or leave it unchanged. For example, reduction of compression effects through surgical excision of noninvasive lesions has been shown to improve attentional functioning in patients with frontal meningiomas [58], and long-term improvement in verbal working memory has been reported after removal of low-grade gliomas in frontal premotor and anterior temporal lobe regions (often after transient postoperative worsening) [59]. Patients with high-grade gliomas may also show improvement. Talacchi and coworkers [60] found that approximately one quarter of patients evidenced cognitive decline after surgery, while the majority of patients (~75%) either improved or showed no significant change after surgery. Verbal memory, visuospatial memory, and word (phonemic) fluency were the most frequent negatively affected functions. Moreover, extent of tumor removal did not affect outcome, and postoperative cognitive improvement was correlated with high-grade tumors. Preoperatively, many patients with tumors of the third ventricle have impairments in memory, executive functions, and fine motor speed that are not significantly improved after tumor removal [61]. Similarly, craniopharyngiomas are often successfully treated surgically with limited postoperative cognitive or quality of life consequences as long as nearby hypothalamic structures are not harmed [62].

As may be seen in other chapters in this book, resective surgery for brain tumors generally has a positive impact on future time to tumor progression and survival. Along with these beneficial effects, the long-term postoperative neuropsychological profile tends to be stable when a brain tumor can be removed in its entirety. If the planned surgical resection area is presumed to include eloquent cortex, intraoperative mapping or fMRI evaluation of the at-risk cognitive function(s) may be performed under local anesthesia at the time of surgery. Results of cortical mapping may be used to tailor the extent of resection and preserve as much normal cognitive function as possible.

7.6.4 Radiation Therapy

Radiotherapy attempts to further reduce the size of any residual tumor remaining after surgical excision and to postpone future progression of tumor growth [63]. The immediate effects of radiotherapy on cognition are usually limited, although fatigue, insomnia, general malaise, and symptoms associated with increased intracranial pressure are commonly seen. Significant cognitive deficits have been documented, however, as long-term effects of whole-brain radiotherapy caused by irreversible radiation encephalopathy may occur as late as 20 years after treatment. Long-term radiotherapy cerebral abnormalities have been documented

and include spongiosis of white matter and vascular damage that appear as atrophy and white matter hyperintensities on MRI. These long-term, delayed cerebral abnormalities have been associated with a decline in cognitive functions and health-related quality of life. Although the specific deficits seen vary across patients, impairments in memory and mental processing speed are commonly encountered in patients with low-grade gliomas after radiotherapy [64, 65].

Limited field irradiation appears to cause fewer late-term cognitive impairments than whole brain radiation [66]. More recently, stereotactic radiotherapy has been utilized, and this seems to further limit the amount of radiation delivered to nearby healthy tissue, which, in turn, appears to limit the extent of cognitive impairment. Although radiotherapy-induced cognitive deficits may be expected to have a negative impact on the long-term quality of life in patients with low-grade gliomas, this has not been found in patients with high-grade tumors. Patients with high- grade recurrent tumors reportedly show little deterioration in quality of life over time following treatment with radiation despite their near universal widespread cognitive deficits [67]. This result may be sample-specific or possibly the result of these patients' lowering their expectations of what constitutes positive QOL.

7.6.5 Radiosurgery with or Without Whole-Brain Radiation Therapy

Stereotactic radiosurgery is a common and effective treatment for patients with brain metastases from cancer elsewhere in the body, but when radiosurgery is the sole method of treatment, new metastatic lesions frequently develop [68]. The use of adjuvant whole-brain radiotherapy in conjunction with stereotactic radiosurgery has been shown to improve intracranial tumor control in randomized clinical trials, but unfortunately whole-brain irradiation has also been associated with greater cognitive decline. Unexpectedly none of these clinical trials have shown any significant survival advantage of combining whole-brain radiotherapy with radiosurgery, and one clinical trial reported a survival disadvantage [27, 68, 69]. These data raise the question of whether tumor progression in the brain is more harmful to a patient's well-being than the deterioration of cognition and changes in quality of life that are associated with whole-brain irradiation.

A recent randomized clinical trial [70] examined the effects of adding whole-brain radiotherapy to stereotactic radiosurgery on cognitive functioning, QOL, tumor control, and survival in 213 adults with one to three brain metastases and found that there was significantly less cognitive deterioration (on memory, language, attention, executive function, and motor speed) 3 months after use of stereotactic radiosurgery alone (40 of 63 patients; 63.5%) than after use of radiosurgery plus whole-brain irradiation (44 of 48 patients; 91.7%). In addition, there was better quality of life (QOL) at 3 months with stereotactic radiosurgery alone, including overall QOL and functional well-being.

Although there was less cognitive deterioration and better QOL in patients who only had sterotactic radiosurgery, intracranial tumor control was worse with radiosurgery alone (79 of 105 patients; 75.3%) as compared with radiosurgery plus whole-brain radiotherapy (89 of 95 patients; 93.7%) [70]. Despite the superior intracranial tumor control associated with whole-brain radiotherapy, there was no improvement in survival rates in these doubly treated patients. Median overall survival for surgery plus whole-brain irradiation was 7.4 months, and median survival for surgery alone was 10.4 months. The authors concluded that stereotactic radiosurgery alone may be the preferred treatment strategy for patients with one to three brain metastases.

7.6.6 Chemotherapy

Chemotherapy is part of the standard regimen of treatment among patients with high-grade malignant tumors. As with surgery and radiotherapy, chemotherapy attempts to stabilize the disease and delay tumor progression [4]. It is difficult to quantify the negative cognitive consequences of chemotherapy precisely because it is almost always administered in combination with radiotherapy following surgical resection. This makes it difficult to tease out the relative contribution of chemotherapy to cognitive decline. Similar to radiotherapy, chemotherapy causes neurotoxicity within the brain, which is often reflected in white matter changes and cerebral atrophy seen on neuroimaging. Cancer patients may experience both the direct toxic effects of chemotherapy on the brain as well as indirect CNS disruption from such things as metabolic dysregulation or cerebrovascular changes. Moreover, toxicity from chemotherapy may also differ in its immediate and late-term effects. The cognitive effects of chemotherapy are well known among cancer survivors, as evidenced by their complaints of "brain fog" that causes problems when attempting to perform complex tasks or when multitasking at work or at home. These complaints have anecdotally become known as "chemobrain" by some patients and their caretakers.

Although this area of inquiry is fraught with methodologic problems, the literature in general suggests that long-term survivors of malignant gliomas who have been treated with chemotherapy in conjunction with other treatments typically have significant cognitive deficits that tend to worsen over time [9]. The most frequent cognitive domains reported to show impairment after systemic chemotherapy include memory, executive functions, attention-concentration, and processing speed [71]. After conducting a qualitative review of the literature, Ahles and Saykin [15] concluded that standard dose chemotherapy is associated with subtle decrements in concentration and memory that

can have a significant negative impact on survivors' quality of life. Systemic chemotherapy for tumors originating outside the central nervous system can also affect cognitive function. After conducting a meta-analysis of neuropsychological studies of chemotherapy in patients with non-CNS tumors, Anderson-Hanley, and coworkers [72] reported significant mild to moderate decrements in executive functions, verbal memory, and motor skills.

7.7 Quality Versus Quantity of Life: Health Utility Evaluations

Clinical decisions about treatment options can become difficult when there are conflicts between the quantity (survival) of life versus the quality (cognition and other QOL domains) of life. Health utility measures have been developed in an attempt to quantify this dilemma across populations as well as for the individual patient. Health utility measures are related to health-related quality of life (HRQoL) measurement, and although these measures were originally designed for health economic uses (e.g., cost-effectiveness decisions, resource allocation policies), they may be used by patients and physicians to make difficult treatment decisions in the individual case. Health utility measures differ in one respect from typical QOL measures in that a single value is derived to represent an individual's health status on a scale from 0 (dead) to 1 (perfect health). Health utility measures are designed to be interval measures that reflect an individual's treatment and QOL preferences through calculation of the quality-adjusted life-year (QALY). QALY is a measure of a patient's length of life weighed by an appraisal of their health-related quality of life [73].

There are several approaches to obtain these health utilities. One commonly used direct approach is to ask individual patients to indicate which amount of lifetime they would be willing to sacrifice (number of life-years) in order to live in a better health state (less severe symptoms) across a number of QOL dimensions. Dirven and associates [2] illustrated this with the following example. Treatment A generates one additional year in a health state valued at 1 (best possible health), which results in 1 QALY (1 × 1 = 1). In contrast, Treatment B generates 1.5 additional years of life in a health state valued at 0.5 (mid-level health status), which results in 0.75 QALY (0.5 × 1.5 = 0.75). Thus, in this example, Treatment A would provide 0.25 more QALYs than Treatment B (1–0.75 = 0.25 QALYs) (see Fig. 7.1, which is derived from Dirven et al. [2]).

Several generic measures of health utility have been developed, including some for specific disease states (e.g., childhood cancer, multiple sclerosis, Alzheimer disease). These include the Health Utilities Index (HUI Mark 2 developed specifically for childhood cancer and HUI Mark 3 [samples 8 domains]) [74–78], the EuroQOL (EQ-5D [samples 5 domains]) [76–78], and the SF-6D [samples 6 domains], which was derived from the SF-36 quality of life instrument [76–78]. Although there is no agreed upon best method currently to make health utility treatment determinations in individuals with brain cancer, such approaches hold promise in assisting doctors and patients when weighing difficult treatment decisions.

7.8 Summary

The field of neuropsychology focuses on the information base of recognized brain-behavior associations with standardized psychometric measures (tests). This includes the assessment and diagnosis of impairments in cognition and behavior and relating these findings to their neurologic implications and to issues of clinical treatment and prognosis. Neuropsychological measures are sensitive to the effects of cancer treatment, including the neurotoxic effects of chemotherapy or the consequences of brain tumor resection. When assessing brain tumor patients, a comprehensive battery of tests will aid in providing accurate and precise infor-

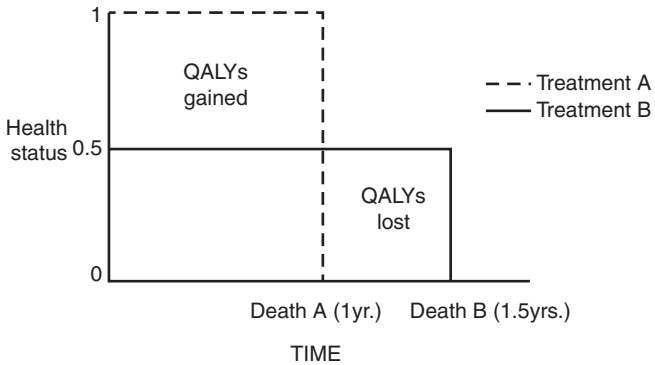

Fig. 7.1 Comparison of two treatments **A** and **B**. Treatment **A** is associated with decreased survival but better health-related QOL than treatment **B**. Quality-adjusted life-years (QALYs) are gained in the short term after treatment A (1 × 1 = 1) but lost in the long term after treatment B (1.5 × 0.5 = 0.75). Thus, treatment **A** would provide 0.25 more QALYs than treatment **B** in this example

mation about the cognitive, behavioral, and quality of life status of patients. Because of the diversity of possible deficits produced by brain cancer and its treatment, a battery capturing a wide range of cognitive abilities should be administered. The most common cognitive domains to be assessed are verbal and nonverbal intellectual functions, language, attention, orientation, verbal and nonverbal learning and memory, visual-spatial skills, executive functions, psychosensory and motor abilities, mood, and health-related quality of life information.

Thought should be given to the timing of neuropsychological testing, since the acute and long-term effects of surgery, radiation, and chemotherapy all vary. With regard to neurosurgery, the main factor determining cognitive outcome is the location of the brain tumor and the extent of resection. It's also important to recall that improvement in cognition also may be seen after surgery when the deleterious effects of the tumor, such as compression mass effects, are removed.

Radiotherapy, especially whole brain irradiation, in patients with brain tumors has been associated with both acute and long-term declines in cognitive function and health-related quality of life. Since chemotherapy is almost always administered in conjunction with radiotherapy and often with surgical resection, it has been difficult to parse out the relative contribution of each of these treatment regimens to patients' cognitive decline.

The neuropsychological assessment is an important component in determining the patient's cognitive and behavioral standing pre- and post-treatment. The patterns of impairment obtained may be used to determine cognitive, psychological-emotional, and functional competence and to assist in treatment planning and rehabilitation recommendations. As a result of the valuable information provided though a neuropsychological evaluation, comprehensive cognitive, behavioral, and quality of life assessment can contribute to the overall wellbeing of cancer patients with brain tumors throughout the course of their disease.

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