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A PATIENT-CENTRED APPROACH IN NEURO-ONCOLOGY: DEFINITION AND MEASUREMENT OF CLINICAL OUTCOME IN BRAIN TUMOR PATIENT

S.S.D. MED/27 NEUROCHIRURGIA

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SOMMARIO

I tumori cerebrali, indipendentemente dal tipo istologico, condividono un modello di crescita che spesso richiede l'avvicendarsi di diverse modalità di trattamento.

Spesso i pazienti vengono sottoposti a chirurgia, radioterapia e chemioterapia in un arco di tempo molto ravvicinato, o a volte queste procedure vengono eseguite in contemporanea. Tutto questo rende estremamente difficile valutare l'efficacia del singolo trattamento.

Sebbene i tumori cerebrali siano molto rari, vengono considerati tra i tumori più devastanti e segnano nel profondo chi ne soffre.

Oltre al prolungamento degli anni di vita, il miglioramento della qualità di vita dei pazienti e il posizionamento di questi ultimi al centro della terapia dovrebbero diventare il gold-standard per tutti i professionisti che si occupano della patologia.

Un'ipotetica soluzione per affrontare il problema è quella di adottare un approccio centrato sul paziente in cui la completa valutazione di quest'ultimo viene inclusa nell'outcome set.

Tradizionalmente, i trials clinici sull'efficacia dei trattamenti per i gliomi sono stati basati su misure come la riduzione della dimensione del tumore o su misure dipendenti dal tempo, tra cui la sopravvivenza libera da progressione di malattia e la sopravvivenza complessiva.

La valutazione degli effetti dei trattamenti che usano queste misure può essere completata inserendo anche la valutazione degli outcome clinici come, ad esempio, la misurazione degli effetti a livello sia funzionale che sintomatologico della patologia sulla persona.

Purtroppo, le misure di outcome più comunemente riportate non sono necessariamente le più appropriate. Il loro uso è spesso giustificato dal fatto che sono gli strumenti di misura più citati in letteratura; questo approccio è scientificamente scorretto e comporta il rischio che strumenti non vengano presi in considerazione.

Gli strumenti maggiormente utilizzati in neuro-oncologia sono influenzati da nozioni ancorate al tipo di trattamento (come la chemioterapia o la radioterapia) piuttosto che al tumore e alle caratteristiche del paziente.

L'utilità di avere dati riferiti direttamente dal paziente può essere massimizzata con la standardizzazione di metodi per valutare, analizzare e interpretare i risultati.

Tuttavia, le linee guida neuro-oncologiche non menzionano strumenti specifici e si limitano a indicare genericamente un "monitoraggio neurologico".

Il paradosso è che, mentre nuove terapie e nuove tecniche diagnostiche migliorano progressivamente i tassi di sopravvivenza, le condizioni cliniche e le prestazioni dei pazienti restano tuttora per lo più sconosciute.

Negli ultimi anni, è stato osservato un crescente interesse nei confronti della valutazione cognitiva nei trials clinici e le abilità cognitive sono sempre di più considerate un importante outcome correlato al paziente per valutare la risposta al trattamento.

Il monitoraggio dei sintomi e delle funzioni cognitive del paziente è diventato un grande vantaggio per la ricerca in campo neuro-oncologico in quanto utile a ricavare informazioni sull'efficacia del trattamento in termini di benefici o di effetti avversi per i pazienti.

A tal proposito, è opportuno sottolineare che i pazienti desiderano certamente vivere più a lungo. ma allo stesso tempo aspirano a conservare le migliori condizioni possibili.

Da queste considerazioni è scaturito l'interesse che ha portato alla realizzazione di questa tesi di dottorato il cui obiettivo è di fornire una panoramica della valutazione dell'outcome clinico dei pazienti con tumori cerebrali.

In particolare, il lavoro analizza diversi aspetti della valutazione dell'outcome nella patologia neuro-oncologica e si basa sul presupposto che essa permette sia di raccogliere informazioni sull'impatto della lesione neoplastica sulle funzioni cognitive e sulla qualità di vita sia di monitorare gli effetti delle terapie nel tempo. A tale scopo vengono analizzati diversi aspetti dell'assessment di pazienti sottoposti ad asportazione di tumore cerebrale in cui le funzioni cognitive vengono valutate tramite prove specifiche prima e dopo il trattamento.

La tesi è suddivisa in tre diversi studi.

Il primo studio descrive le caratteristiche dei trials clinici sui gliomi e il profilo di outcome (obiettivi, endpoints, domini, categorie e strumenti), dal 1990 (nascita della medicina basata sulle evidenze) al 2019.

Il secondo studio fornisce una descrizione dei test neuropsicologici principalmente utilizzati nei trial clinici sui tumori cerebrali pubblicati negli ultimi 30 anni e propone una valutazione della qualità metodologica degli studi sulle proprietà di misura di tali strumenti mediante la checklist COSMIN.

Infine, il terzo studio si focalizza sulla valutazione neuropsicologica del linguaggio nelle condizioni di multilinguismo. Si tratta di un aspetto che, in neuro-oncologia, a causa della sempre più diffusa integrazione, è diventato un punto cruciale nella valutazione perioperatoria dei pazienti sottoposti a trattamento chirurgico per tumore cerebrale. L'obiettivo è di verificare come sono state tenute in considerazione le diverse variabili che influenzano l'elaborazione linguistica nelle persone multilingue durante la pianificazione di interventi di rimozione del tumore in chirurgia da sveglio.

ABSTRACT

Brain tumors, independently from histology, share a similar progressive growth pattern that often requires multiple treatment modalities.

Surgery, radiotherapy, chemotherapy and medications are often administered in close proximity to one another or, sometimes, contemporaneously. For that reason, the assessment of the effectiveness of any single treatment is extremely difficult.

Brain tumors are a rare cancer but they are among the most devastating forms of cancer and afflict the very core of the person.

Optimizing the life style of patients should become essential and on a par with the life prolongation goal of anti-cancer therapy.

A potential solution to this problem is a patient-centered approach to different tumor types and treatments in which the comprehensive patient assessment is included in the outcome set.

Traditionally, clinical trials of treatments for gliomas have relied on measures such as the reduction in tumor size, or on time-dependent metrics including the progression-free survival and the overall survival.

The procedure used to evaluate of treatment effects by means of these measures can be complemented by the assessment of clinical outcomes such as measurements of the functional or symptomatic effects of the condition on the person.

Unfortunately, the most commonly reported outcome measures are not necessarily the most appropriate. They are often selected and motivated since they are widely cited in the literature; this is an incorrect approach on a scientific ground and also precludes new and more effective instruments to be introduced and accepted.

The instruments currently used in neuro-oncology are influenced by notions anchored to the type of treatment (such as chemotherapy or radiotherapy) rather than to tumor and, particularly, to patient characteristics.

The utility of patient-reported outcome data can be maximized with standardization of methods to assess, analyze, interpret and report results.

Nevertheless, neuro-oncological guidelines do not mention instruments and parameters but rather generically prescribe “neurological monitoring”.

A paradox is that, while new therapies and diagnostics are improving survival rates, much remains unknown about the patient clinical conditions and performance at an instrumental level.

However, in the last years, a growing interest on cognitive response in clinical trials has been observed and the cognitive performance is now considered as an important patient-related outcome to assess response to treatments.

Tracking symptoms and function can inform clinicians about whether a treatment results in measurable benefits or adverse effects to patients.

We should not forget that patients want to live longer, but they also want to continue to function as well as possible for as long as possible.

This research. arose from the considerations set forth above.

The aim of the thesis is to provide an overview of the clinical outcome assessment of patients with brain tumors. The thesis analyzes the role of the assessment in collecting information about the direct impact of neoplastic invasion of the cerebral parenchyma and in monitoring the effects of therapies.

This thesis is composed of three different studies.

The first study describes the characteristics of clinical trials on gliomas and the outcome profile (objective, endpoints, domains, categories and instruments), since the 1990 (the advent of evidence based medicine) to 2019.

The second study describes the neuropsychological tests mainly used in the brain tumor clinical trials published over the last 30 years and tries to evaluate the methodological quality of studies on measurement properties by means of the COSMIN checklist.

Finally, the third study focuses on the neuropsychological assessment of language in multilingual people. Due to the increasingly widespread integration, this has become a crucial issue in neuro-oncology, especially in the perioperative evaluation of patients undergoing surgical treatment for brain cancer. The aim is to verify to what extent the variables that affect linguistic processing in multilingual speakers have been considered during planning and decision making in awake surgery for brain tumors.

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I. Study 1 - A SYSTEMATIC REVIEW OF PATIENT ORIENTED OUTCOMES IN NEURO-ONCOLOGY OVER 30 YEARS PERIOD

1. Introduction

Although brain tumors are a rare cancer, they are among the most devastating of cancers and afflict the very core of the person. Optimizing the life style of patients is essential and on a par with the life prolongation goal of anti-cancer therapy (NICE, 2009; Chang et al, 2005).

In 1977, experts gathered in Turin (Italy), at a meeting held under the auspices of the World Health Organization (WHO), to discuss the standardization of reporting the results of cancer treatment. Since then, tumor-related outcome criteria (disease progression, complete response, partial response, etc.) have become a widely applied yardstick in clinical trials and treatments (surgery, chemotherapy and radiotherapy) have become increasingly effective in controlling disease in clinical practice (MacDonald et al., 1990). These criteria were renewed and published in 2000 and, thereafter, through Response Evaluation Criteria in Solid Tumors (RECIST) and Response assessment in neuro-oncology (RANO) guidelines (Therasse et al., 2000; Wen et al., 2010a; Wen et al., 2010b; van den Bent et al., 2011).

The big picture of patient-oriented assessment was described in all its details by the WHO again in 2001 and, to date, it remains the international standard to describe any disease (WHO, 2001). It encompasses organ-measurable dysfunction, symptoms, and functional performance, which are the categories used to describe patient-oriented outcome.

As a consequence, we can expect that a first shared statement is that signs, symptoms and performance status reflect the category (tool kit) of instruments to be necessarily used in order to measure health-related factors. Nevertheless, neuro-oncological guidelines do not mention instruments and parameters but rather generically prescribe "neurological monitoring" (Chang et al., 2005; Chang et al., 2007). This approach is ordinarily used in the assessment of many functional domains (consciousness, motor function, vision, cranial nerves, and other brain function) preventing a detailed picture.

Therefore, a paradox of this sophisticated area is that while new therapies and diagnostics are improving survival rates, much remains unknown about the patient clinical conditions and performance at an instrumental level (Cheng et al., 2009). This fact calls for a re-evaluation of typical trials design, complemented with objectives to be prepared with robust outcome measures.

The aim of this chapter is to describe the characteristics of the clinical trials and the outcome profile over time (both objective and end-points on one side, and domains, categories and instruments on the other side), since the formal origin of the evidence-based medicine (1990).

2. Method

2.1 Search strategy

This systematic review of the literature aimed at extracting data from the studies. In outcome research the systematic review aims to extract construct, methods, instruments and criteria chosen to give significant results.

A systematic literature search was performed on the electronic databases PubMed/Medline, Cochrane Controlled Trials Register, PsycINFO, and PsycARTICLES from January 1990 to December 2019. Relevant studies listed as references were also considered. No restriction in the search field description was performed, and only English-language articles were considered. Experts in the field were also contacted in order to identify possible articles not retrieved in the electronic search. Details on the search strategy and selection process were documented according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines (Moher et al., 2009).
Clinical trials published between 1990 and 2017 with intervention for gliomas were reviewed. The review was restricted to randomized clinical trials in order to ensure that homogeneous studies were analyzed, (Moher et al., 2012).

2.2 Criteria for considering studies

Eligibility of the trials included the content of the outcome and was limited to patient-oriented measures: technological tools (i.e., audiometry for evaluating acoustic function), testing (i.e., neuropsychological tests for evaluating memory), clinical evaluation (i.e., neurologic examination for evaluating motor coordination) and questionnaires (i.e., patient-reported outcome for patients' perceived disturbances).
The experimental treatment included Radiotherapy alone (RT), Radiotherapy and Chemotherapy (CT), Chemotherapy alone, including biological therapy, and Surgery, with or without other treatments.
The aim was to list the outcome measures used in the studies, to group them by the research question (objective) and endpoints and then to analyze the outcome at objective level and at instruments level.
The studies were grouped in 6 epoch of 5-year each since 1990 in order to reveal how the same purpose evolved over time an to search for incongruences or innovation.
Overall, the first part of the present work examines the study phase, the duration, the number of enrolled patients, the study origin, the histology and the treatment.
In the second part the outcome profile was analyzed: how often the single objective was reported in each epoch during this 30-years period (prevalence of objective), which was the prevalence of primary objective among them and which were the cluster of objectives (outcome set). Objectives included the overall survival (OS), the progression free survival (PFS), the response to treatment (RTT) and the toxicity (TOX).
The OS was defined as the time from treatment to death; the PFS was the length of time after the treatment before the disease gets worse; the RTT provided information about changes induced by the treatment; the TOX referred to side effects such as adverse events, safety and complications.
In the third part patient-oriented outcomes were further investigated at instrument level by category, symptoms, neurologic signs and performance status. Along the time, a measure of heterogeneity was given by the number of instruments used for different purposes within the same category or different category for the same purpose.

2.3 Methods of study evaluation

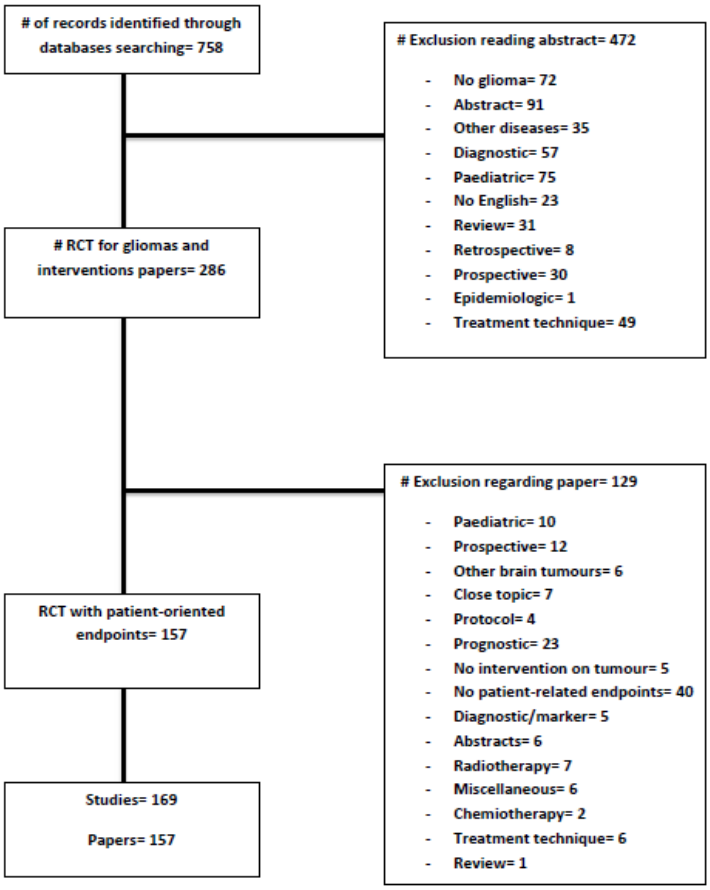
Two reviewers (A.M. and A.T.) independently reviewed all identified studies, and a third reviewer (M.T.) was consulted in case of disagreement. Each reviewer had an access password to the online system and completed a predefined electronic data-extraction form (DEF) for each RCT meeting the study criteria. When disagreements occurred in the DEF, the reviewers revisited the paper to reconcile any difference until consensus was achieved, and a final DEF was validated and used for data analysis. Some trials had multiple publications: here, the relevant data from all the papers were combined.

3. *Results*

3.1 Characteristics of the studies

The search strategy resulted in a total of 758 records selected on the basis of their title and their abstract. The abstracts were evaluated and 472 articles were excluded. This selection resulted in 286 articles and their full text were carefully read. Then, 129 articles were rejected. The remaining 157 articles were examined by 2 reviewers for data extraction. Overall, the number of the studies was 169 (Fig. 1).

Fig.1 Selection of studies



Overall, between 1990-1994, 25 studies (16% of the total number), 10 phase II and 15 phase III, have been found; between 1995-1999, 18 studies (11% of the total number), 11 phase II and 7 phase III; between 2000-2004, 32 studies (19% of the total number) 9 phase II and 23 phase III; between 2005-2009, 30 studies (20% of the total number) 13 phase II and 17 phase III; between 2010-2014, 24 studies (16% of the total number), 8 phase II and 16 phase III; between 2015-2019, 28 trials (18% of the total number), 17 phase II and 11 phase III (Fig. 2.1).
The mean of patients enrolled in phase III trials was greater than the mean of patients enrolled in phase II trials and steadily increased to date (Fig. 2.2).

Fig. 2.1 Number of trials by phase and epoch

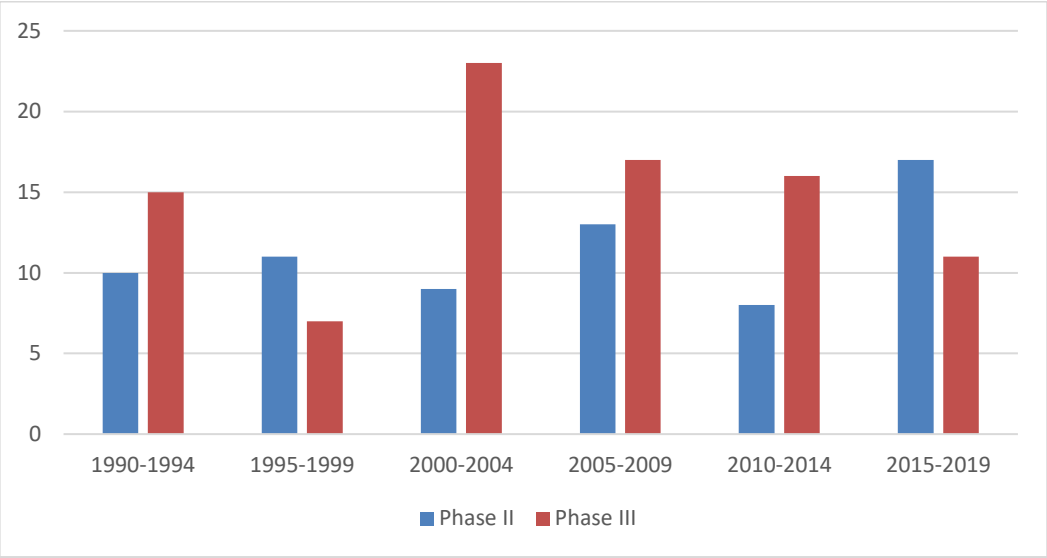
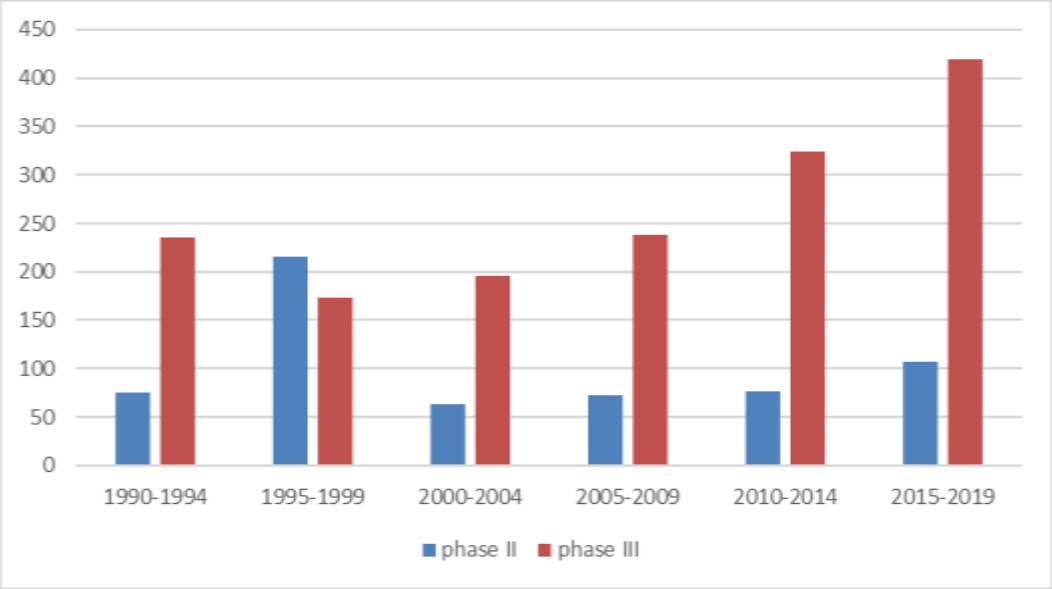


Fig. 2.2 Number of patients enrolled by phase and by epoches



At study site level, the USA have been recognized as the country most involved in national and international studies, 42% and 41% respectively.
In detail, regarding national studies, the USA were the leading country followed by Italy (9%), Germany (8%) and the others (18%). On the other hand, for international studies, the USA were followed by Germany (17%), the Netherlands (11%) and the others (18%) (Fig. 2.3, 2.4).

Fig. 2.3 Geographical distribution – National site

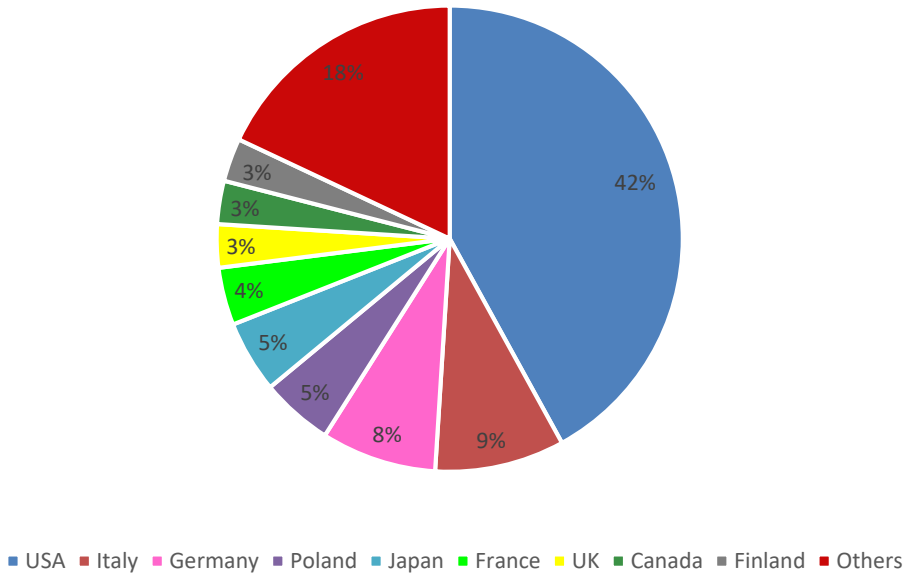
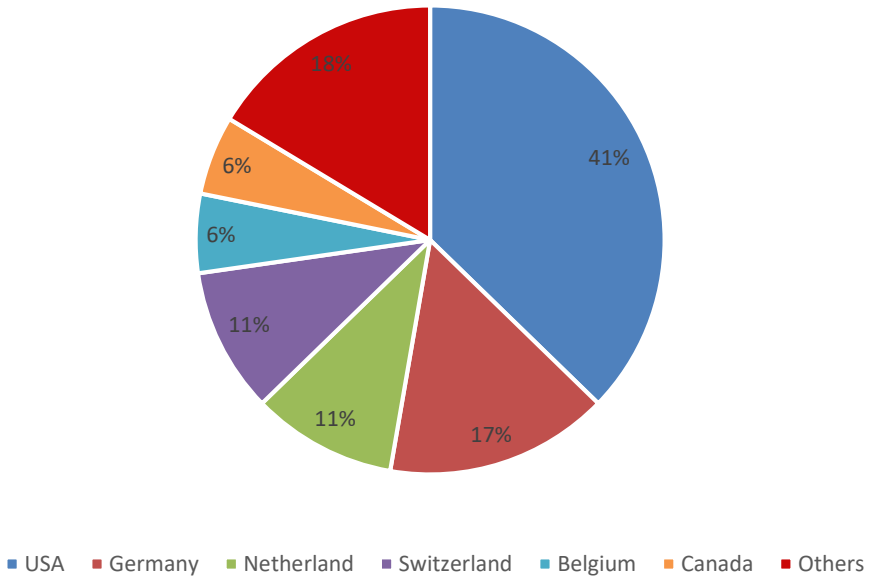


Fig. 2.4 Geographical distribution – International site



Phase III studies had a longer duration than phase II studies, with a little exception

during the epoch 1990-1994 and 2010-2014 where both phases had similar duration (Fig. 2.5).
Regarding the histology, the most analyzed brain tumor was glioblastoma (GBM) with a percentage of 62% (n=96), followed by high grade (HG) glioma (n=46, 29%), grade III glioma (n=6, 4%) and low grade (LG) glioma (n=5, 3%). Only 4 studies (2%) have focused on low grade combined with high grade brain tumors (Fig. 2.6). In detail, analyzing the GBM, the brain tumor most frequently included in these trials in the 5 different epochs, the results were the following: 7 clinical trials in the epoch 1990-1994; 5 in 1995-1999; 18 in 2000-2004; 19 in 2005-2009; 21 in 2010-2014; 26 in 2015-2019.
As regards treatments, the peak of prevalence of surgery for brain tumors was between 2000 and 2004; later on, chemotherapy blew up. Probably due to the recognized value of surgery, the prevalent treatment along all the periods was radiotherapy (RT) combined with chemotherapy (CT), with a little exception between 2010-2014 where only CT had the highest prevalence. It is worth to note that RT alone disappeared in the last epoch (Fig. 2.7).

Fig. 2.5 Study duration

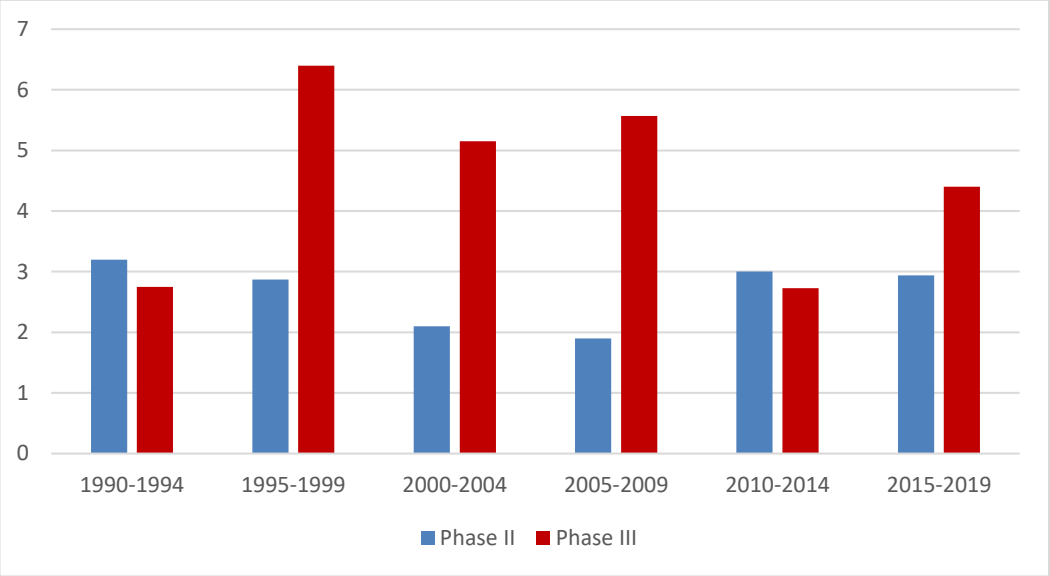


Fig. 2.6 Type of tumors

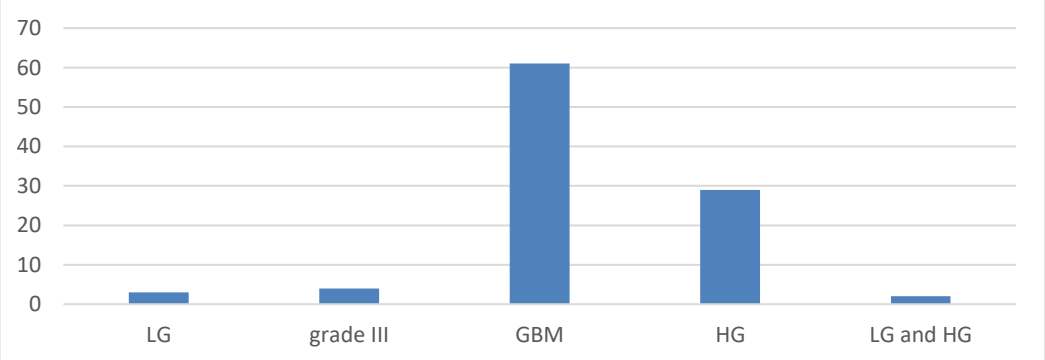
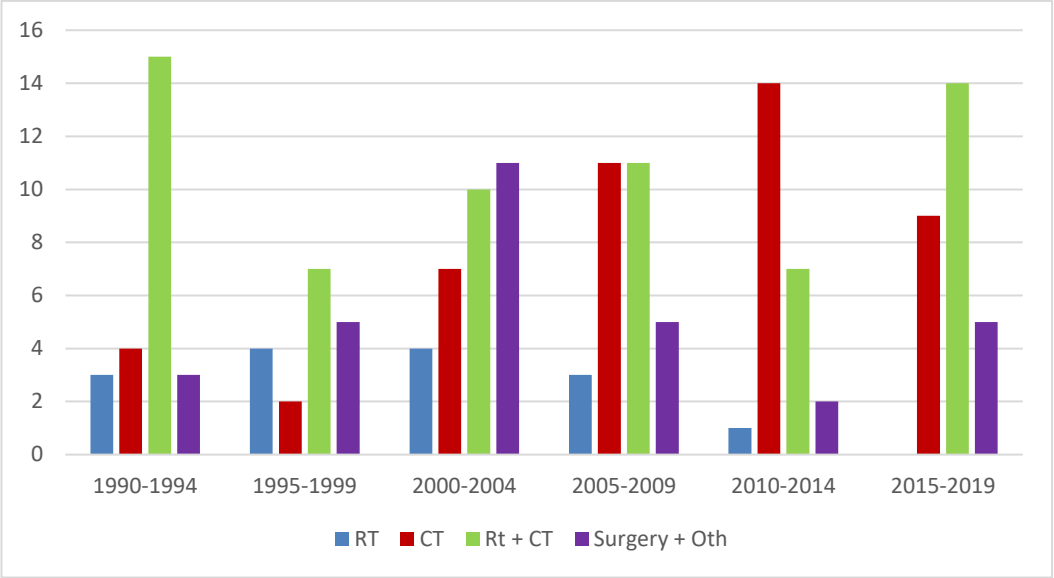


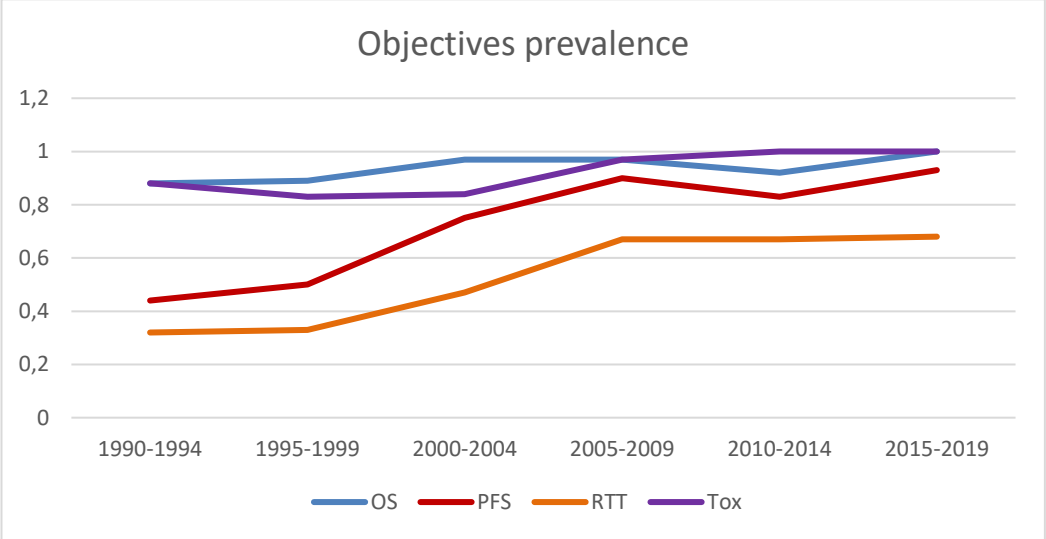
Fig. 2.7 Type of treatments



3.2 Profiling of the outcome set

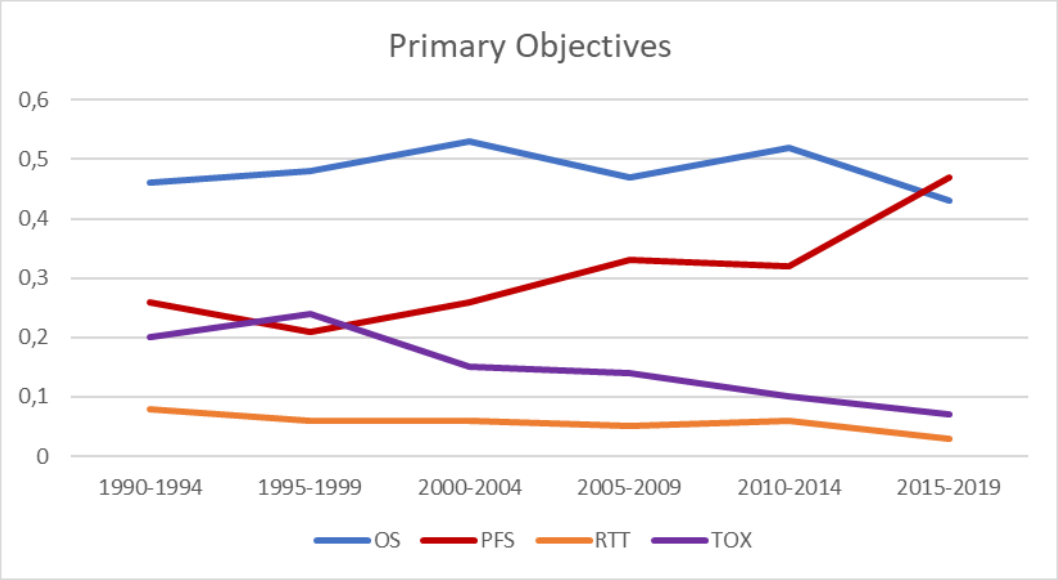
In general, the number of objectives increased over time and showed a trend towards a comprehensive approach to satisfy different expectations.
The TOX and the OS appeared to be the most analyzed objectives, always above 85%, whereas RTT had a steadily increase, starting at 32% in the 1990- 1994 till 68% in the last epoch, while PFS started at 44% but then increased till 93% between 2015- 2019 (Fig. 3.1).

Fig. 3.1 Prevalence of objectives



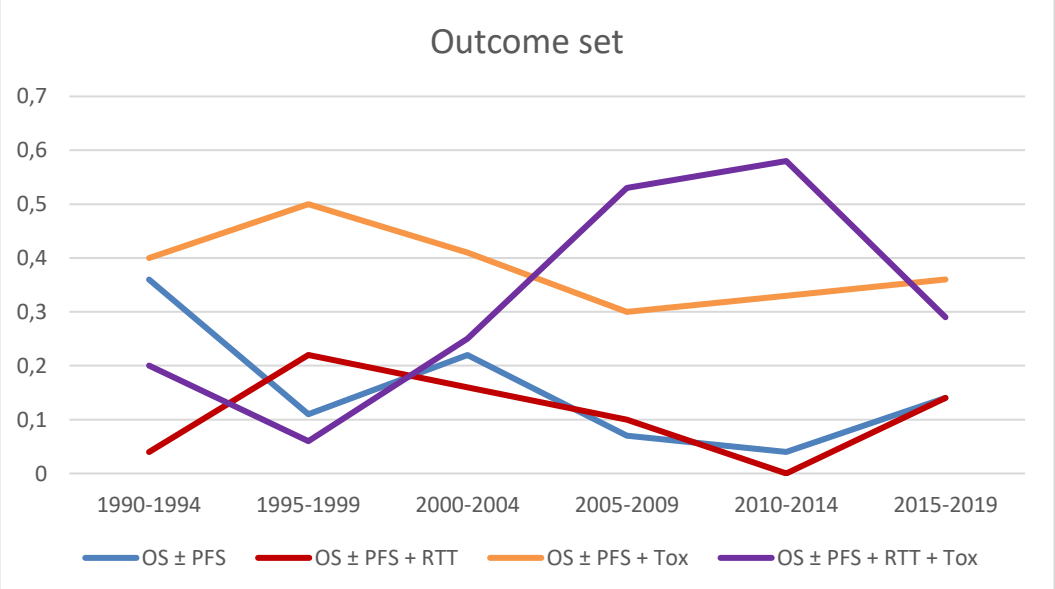
The primary objectives of a study, single or multiple, represented the measure used to evaluate the efficacy of the experimental treatment.
The OS appeared to be the most analyzed in brain tumors clinical trials since the beginning, stable above 40% for each decade. PFS gradually increased stepwise; in the last analysed period increased from 26% to 47%.
On the contrary, TOX and RTT were primary objectives in a minority of cases and Toxicity showed a slow and steady fall over time (Fig. 3.2).

Fig. 3.2 Primary objectives



The outcome set is the cluster of objectives designed to answer the study questions. It regards the broad framework of the outcome in brain tumor clinical trials. What appears to be relevant was that it changed over time. From studies with few and standardized objectives, namely OS and TOX or OS and PFS, to an increasing attention to the RTT, starting since 2000. In fact, while in the first ten years (1990-2000), OS±PFS+TOX and OS±PFS prevailed, OS±PFS combined with RTT and TOX, which rated 20% and less at the beginning, raised steadily from 25% to 58% between 2000 to 2014, and was comparable with OS±PFS+TOX to date. Actually, there is still a considerable heterogeneity of outcome set, even at objective level, which should be considered fundamental for comparative studies (Fig. 3.3).

Fig. 3.3 Outcome set



3.3 Analyzing patient-related instruments

Finally, instruments and criteria used to develop the aims of the studies related to the patient, namely PFS, RTT and TOX were considered. For every epoch, we classified the category of patient-related instruments as symptoms, signs and performance status. Disease-related instruments, usually analyzed with MRI according to different criteria, were beyond the scope of the present paper. However, the trials with patient-related instruments combined with disease-related instruments were included and described.

Among all the trials, 118 (75%) assessed the PFS. Three trials (2,5%) used patient-related instrument only. The others used both patient and disease-related instruments, and neurologic exam in all but one case. Overall, patient-related instruments alone or used with instruments related to disease were 45% in 1990-1994, in 55% in 1995-1999, in 46% in 2000-2004, in 37% in 2005-2009, in 35% in 2010-2014, in 22% in 2015-2019. In six trials (5%) multiple instruments were used to evaluate the patient, performance scale in all cases (Tab. 1.1; the number of reference is reported in the Appendix).

Eighty-four trials (53%) assessing the RTT in order to examine the type of instrument used for specific domain related to the end-points were analyzed. This objective was presumed to be a measure of treatment efficacy (Tab. 1.2; the number of reference is reported in the Appendix).

For every epoch, we classified the categories of instruments and the domains of interest (general (neurologic), cognitive and quality of life).

Overall, patient-related outcome measures occurred for 75% in 1990-1994, 100% in 1995-1999, 87% in 2000-2004, 70% in 2005-2009, 47% in 2010-2014 and 57% in 2015-2019, but, interestingly, its trend was different from the ascending prevalence of RTT. As mentioned above, from 1990 to 2000, the number of trials that focused on this objective was low and grew thereafter. In particular, RTT significantly grew up in the epoch 2005-2009 (67%) and remained stable to date.

However, innovation was not enough in this field. For the neurological domain, the instrument used to assess the signs of the disease is the neurological exam, not driven by any quantitative preselected scale of assessment, followed by Mini Mental State Examination (MMSE), sometimes used in combination. The most used instrument to evaluate the performance status was the Karnofsky Performance Scale (KPS). In addition, regarding the neurological domain, the symptoms were assessed through the evaluation of the neurological functions, not a unique scale used in the past, developed by different authors, before the introduction of patient-reported outcome.

The cognitive domain per se was only reported in 6 trials and results as the least studied. The instruments used were the MMSE, the Mattis Dementia Rating Scale (MDRS) and, between 2000 and 2010, ad hoc built neuropsychological batteries.

Quality of life assessed by patient-reported outcome (PRO) emerged as a new area of interest since 2000. The instrument most frequently used to assess the symptoms and functioning is the Quality of life Questionnaire-Core 30 (QLQ-C30) and its brain cancer version (Quality of Life Questionnaire Brain Cancer Module (BN20)). Sometimes, the KPS was used, alone or in combination with the PRO, or eventually with the cognitive assessment by a neuropsychological battery or the MMSE.

Multiple instruments for the same end-point ranged between 0 and 30%, this latter

observed in 2005-2009, followed by 12% in 2010-2014 and 24% in 2015-2019. Multiple endpoints for the same study occurred in 0- 33% of the studies in the same epoch, without relevant differences during the time course, but with prevalence in the first epoch (1995-1999).
Overall, inconsistent measures (same instrument for different purpose) occurred in neurologic and quality of life (QoL) assessment, and inadequate instruments were used for the objective of the research (KPS alone for both QoL and neurologic assessment). Furthermore, heterogeneous measures, for both domains and category or set of measures (different instrument/s for the same purpose), were encountered in the attempt to better cover the domains of interest (neurologic and cognition, neurologic and performance status, cognition and QoL).
The TOX appeared to be the most analyzed objective (n=145, 92%). For every epoch, the category of instruments was reported and the specific scale dedicated to analyze the construct of the toxicity against the domains of interest: general (systemic), general (neurologic), focal (neurologic) and cognitive. We also observed that multiple instruments were applied to evaluate the toxicity (Tab. 1.3; the number of reference reported in the Appendix).
In the domain of systemic assessment, from 1990 to 1999, there were not validated scales; since then, Common Terminology Criteria for Adverse Events (CTCAE) was introduced, sometimes associated with neurologic exam. This means that, in the majority of cases, only symptoms or observations were considered to assess positive findings. It is important to underline that the cognitive domain was the least studied, in 4 trials, and that the MMSE was the only used instrument. Overall, in 22 trials (15%). the toxicity was assessed through the use of multiple instruments.

Tab. 1.1 Progression free survival*

	1990-1994 (11/25)		1995-1999 (9/18)		2000-2004 (24/32)		2005-2009 (27/30)		2010-2014 (20/24)		2015-2019 (26/28)	
Instruments / Domains	**Neurologic exam e/o symptoms**	**Performance scale**	**Neurologic exam e/o symptoms**	**Performance scale**	**Neurologic exam e/o symptoms**	**Performance scale**	**Neurologic exam e/o symptoms**	**Performance scale**	**Neurologic exam e/o symptoms**	**Performance scale**	**Neurologic exam e/o symptoms**	**Performance scale**
Patient related	[16]					**GOS** [67]					[143]	**ECOG** [143]
Patient and disease related	[3]; [4]; [14]; [16]; [22]		[30]; [31]; [32]; [35]; [43]		[48];[49]; [50]; [51]; [52]; [61]; [62]; [70]; [73]	**FIM** [65]**;** **KPS** [70]	[76]; [82]; [88]; [91]; [95]; [96]; [99]; [100] [101]; [102]	**WHO** [96]	[107]; [109]; [113]; [117]; [123]; [124]; [125]; [127]	**ECOG** [107]**;** **WHO** [109]**;** **KPS** [123]	[145]; [147]; [149]; [150]; [154]	
Multiple instruments					**NE + KPS** [70]		**NE + WHO** [96]		**NE + ECOG** [107]**;** **NE + WHO** [109]**;** **NE + KPS** [123]		**NE + ECOG** [143]	
Disease related endpoints	[5]; [6]; [8]; [11]; [20]; [25]		[34]; [36]; [40]; [41]		[45]; [46]; [47]; [53]; [54]; [57]; [59]; [60]; [63]; [64]; [66]; [71]; [72]		[78]; [80]; [81]; [84]; [86]; [89]; [90]; [92]; [93]; [94]; [98]; [99]; [103]; [104]; [105]		[108]; [111]; [112]; [114]; [115]; [116]; [119]; [120]; [121]; [122]; [128]; [129]; [130]		[131]; [144]; [146]; [148]; [151]; [152];[153]; [155]; [156]; [157]	

* Abbreviations: GOS: Glasgow outcome scale; ECOG: Eastern Cooperative Oncology Group Scale; FIM: Functional Independence Measure; KPS: Karnofsky Performance Scale; WHO: WHO Performance Scale; NE: Neurological Exam

Tab. 1.2 Response to Treatment*

	1990-1994 (8/25)			1995-1999 (6/18)			2000-2004 (15/32)			2005-2009 (20/30)			2010-2014 (16/24)			2015-2019 (19/28)		
Instruments / Domains	signs	ps	symptoms	signs	ps	symptoms	signs	ps	symptoms	signs	ps	symptoms	signs	ps	symptoms	signs	ps	symptoms
General (neurologic)	**NE** [7]; [12] [16]; [17]; **MMSE** [16]	**KPS** [1]	**4 grade FNS** [1]	**NE** [32]	**KPS** [36]; [39]; [43]		**NE** [49]; [50]; [75]; **MMSE** [75]	**KPS** [66]; [68] **WHO** [51]	**NF** [51]	**MMSE** [89]	**KPS** [83]; [85]; [94]	**NPS** [85]	**CTB-Comp** [124]; [128]	**KPS** [127]		**NPB** [142] **NE** [138]; [153] **MMSE** [138]		
Cognitive							**MMSE** [57] ; **CTB-Comp LV** [65]			**NPI** [99] **SB** [92]								
QoL						**QAS** [29] ; **NR** [31]; **Toronto** [36] [39];	**NPB** [72]	**KPS** [74]	**C30-BCM20** [50]; [70] **FACT** [65]; [74] **NR** [64] **Spitzer** [75]	**MMSE** [90] [102]; [104]	**KPS** [81]	**C30-BN20-BCM20** [79]; [80]; [89]; [92]; [96]; [102]; [104] **FACT** [81]; [93] **NR** [90]		**KPS** [116]	**C30-BN20-BCM20** [109]; [118]; [120]; [121]; [124]; [127]; [128]; [129] **FACT [108]** **MDASI** [128]; [124]	**MMSE** [132]: [141]	**KPS** [141]	**C30-BN20** [131]; [132]; [136]; [138]; [139]; [141]; [143]; [147]; [148]; [149] **MDASI** [142]; [149]
Multiple endpoint				[39]; [36]			[50]; [65]; [75]			[92]; [93]; [99]			[124]; [127]; [128]			[136]; [146]; [148]		
Multiple instruments	**KPS+NF** [1]; **NE+MMSE** [16]			**KPS + Toronto** [36]; [39]			**NE + C30-BCM20** [50]; **WHO+NF** [51]; **NPB + FACT** [65]; **KPS+FACT**			**KPS+FACT** [81]; **KPS+NF** [85]; **MMSE+C30-BN20** [89];			**NPB+C30-BN20-BCM20+MDASI** [128]; [124]; **KPS + C30-BN20**			**MMSE+C30-BN20** [132]; **NE+MMSE+C30-BN20** [138];		
Disease related endpoint	[8]; [23]						[61]; [71]			[82]; [86]; [91]; [98]; [100]; [103]			[107]; [112]; [114]; [118]; [121]; [122]; [123]; [125]			[133]; [134]; [138]; [144]; [146]; [149]; [150]; [151]; [152]; [154]		
Patient related endpoint	[16]			[29]; [31]; [32]; [36]; [39]			[51]; [57]; [64]; [70]; [74]; [75]			[79]; [80]; [81]; [83]; [85]; [89]; [90]; [92]; [93]; [94]; [96]; [102];			[109]; [116]; [121]; [124]; [127]; [128]			[132]; [138]; [141]; [147]; [148]		
Patient/Disease related endopoint	[7]; [12]; [17]			[43]			[49]; [50]; [65]; [66]; [68]			[99]			[108]; [120]; [121]			[131]; [136]; [138]; [139]; [142]; [143]; [149]		

* Abbreviations: PS: performance status; QoL: quality of life; MMSE: Mini Mental State Examination; 4 grade FNS: 4 grade functional neurological scale; NF: neurological functions; NPS: neurological performance status; CTB-Comp: Clinical Trial Battery-Composite; CTB-Comp LV: Clinical Trial Battery-Composite Long Version; NPI: Neuropsychological Inventory; SB: Severity Battery; NPB: Neuropsychological Battery; NR: no reference; Toronto: QoL instrument developed at the Princess Margaret Hospital, Toronto; Spitzer: Spitzer QoL Index; FACT: Functional Assessment Of Cancer Therapy

Tab. 1.3 Toxicity

	1990-1994 (22/25)			1995-1999 (15/18)			2000-2004 (27/32)			2005-2009 (29/30)			2010-2014 (24/24)			2015-2019 (28/28)		
Instruments / Domains	signs	ps	scale	signs	ps	scale	signs	ps	scale	signs	ps	scale	signs	ps	scale	signs	ps	scale
General (systemic)			**NR** [1]; [2]; [3]; [5]; [6]; [7]; [8]; [11]; [12]; [13]; [16]; [18]; [21]; [22]; [23]; [24] **WHO** [4]; [14]; [20]; [25] **RTOG** [9] **Southwest** [17]			**NR** [26]; [27]; [31]; [34]; [35]; [37]; [38]; [39] **WHO** [32]; [40]; [41]; [43] **RTOG** [29]; [39] **ECOG** [33]			**NR** [44]; [54]; [58]; [60]; [62]; [64]; [65]; [67]; [70]; [72]; **WHO** [51]; [66]; [69]; [73] **RTOG** [75] **ECOG** [59] **CTCAE** [45]; [47]; [48]; [49]; [50]; [52]; [53]; [57]; [63]; [68]; [71]			**NR** [77]; [84]; [85]; [89]; [94]; [95]; **WHO** [80]; [88]; [97]; [102] **CTCAE** [76]; [78]; [79]; [81]; [82]; [83]; [86]; [87]; [90]; [91]; [92]; [93]; [96]; [98]; [99]; [100]; [101]; [103]; [104]			**NR** [109]; [113]; [114]; [116]; [126] **WHO** [118] **CTCAE** [106]; [107]; [108]; [110]; [111]; [112]; [114]; [115]; [117]; [119]; [120]; [121]; [122]; [123]; [124]; [125]; [127]; [128]; [129]			**RTOG** [150] **CTCAE** [131]; [132]; [144]; [145]; [146]; [147]; [148]; [149]; [133]; [137]; [138]; [139]; [140]; [141]; [142]; [134]; [135]; [136]; [143]; [151]; [152]; [153]; [154]; [155]; [156]; [157
General (neurologic)				**NE** [27]; [37]; [39]; [41] **Q-TIME** [29]			**NE** [48]; [57]; [58]; [68]; [70]	**KPS** [58]		**NE** [78]; [86]; [87]; [88] **NIH Stroke** [86]	**KPS** [86] **ECOG** [89]		**NE** [114]			**NE** [137]; [150]	**KPS** [147]	
Focal (neurologic)	**Audiogram** [7]; [11]			**Audiogram** [27]			**Audiogram** [63]; [65]			**Audiogram** [87]								
Cognitive										**MMSE** [79]; [89]			**MMSE** [127]			**MMSE** [147]		**NPB** ([157]
Multiple instruments	**NR + Audiogram** [7]; [11]			**RTOG + NE** [37]; **WHO + NE** [39]; [41]			**CTCAE + NE** [57]; [68]; **NR + NE** [58]; [70]; **CTCAE + Audiogram** [63]; **NR + Audiogram** [65]			**CTCAE + NE** [78]; **CTCAE + MMSE** [79]; **CTCAE + NE + KPS** [86]; **NE + CTCAE** [87]; **WHO + NE** [88]; **NR + MMSE** [89]			**NR + NE** [114]; **CTCAE + MMSE** [127]			**CTCAE + NE** [137]; **CTCAE + KPS + MMSE** [147]; **RTOG+NE** [150]; **CTCAE + NPB** [157]		

* Abbreviations: RTOG: Radiation Therapy Oncology Group Scale; CTCAE: Common Terminology Criteria for Adverse Events; Q-TIME: Quality Survival Time; NIH Stroke: National Institutes of Health Stroke Scale

4. *Discussion*

During the Nineties, the methodological research has tried to properly define the construct of "quality of life" in order to select appropriate instruments (Aaronson et al., 1993; Testa, 1994) and Institutions supported this research. Then, the term “patient-reported outcome” was identified and the methodological problems associated with composite endpoints and complex construct were bypassed (Aaronson et al., 1993; Cella et al., 1993; Osoba et al., 1997; McLellan et al., 2007; Taphoorn et al., 2010).
Since 2009, the Food and Drug Administration (FDA) evolved toward the review and qualification of clinical outcome assessments (COAs) which were defined as any reported assessments used to document treatment benefit (Coyne et al., 2015; Walton et al., 2015; Gilbert et al., 2016; Molinari et al., 2019). The former focus on patient-reported outcome was overcome by the new concept of patient-oriented outcome, which regards any instrument (clinician, patient, observer and instrument driven) dedicated to describe the patient condition (Powers et al., 2017; US Food and Drug Administration, 2009; Bottomley et al., 2009).
In the present study, by separating tumor from patient-oriented outcome measures, we offered an historical overview on the outcome set in brain tumor trials with interventions followed by the analysis of what, how, and to what extent patient-oriented questions were pursued at instrument level.

4.1 Characteristic of the studies

The present study offers an appraisal of the evolution of the trials with a small or relevant contribution on patient assessment. The scenario is divided in 6 epochs of 5 years each documenting the evolution of brain tumor research. It reflects the large number of countries involved in this research activity, with approximately 20-30 studies every 5 years. Although the number of studies has remained constant since 2000, most of them have focused on chemotherapy treatments. Along the time, research has been evolved in phase III towards lesser duration and higher number of enrolled cases (Chang et al., 2008; Manchikanti et al., 2010; Reardon et al., 2011).

4.2 Outcome profile

To assess the context, before considering the criteria used to select the instruments, the time course of the development of outcome assessment at objective level was reported.
Overall, TOX remains the prevalent objective since the beginning while RTT and PFS grew and doubled to date. While primary outcome is time-dependent (OS and PFS), as expected, stable over time, the outcome set is untidy, due to the representation of all the four classical objectives in different combinations. From our descriptive analysis, it seems clear that the prevalent combination was OS±PFS+TOX before the 2000. Since then, RTT was the innovative issue, aimed at the tumor rather than at the patient and, in the majority of cases, it was joined to other objectives in order to combine multiple dimensions. This is also confirmed by attempts to use both multiple instruments for the same end-point and multiple patient-oriented end-point within the same study. In this period, the attempt to counteract a strictly tumor-based approach appairs.

However, what and how to combine instruments and/or endpoints and/or objective is still a great challenge to date, and comparative clinical effectiveness research is still hampered by the lack of a clear and common approach at objective level (we can define it as the conceptual framework at objective level (Chang et al., 2008; Reardon et al., 2011).

4.3 Objective, end point and instruments

Currently, symptoms, signs and performance are the pillars of assessment and outcome. As derived by the Classification of Functioning, the standard which assist in the selection of the appropriate instruments is based on the domains of the construct as expressed in the specific research question (end point) (WHO, 2001; Üstün et al., 2003; Geyh et al., 2004; Jerosch-Herold et al., 2006).
This means that any patient-oriented measure is expected to reflect disability and functioning into a domain-driven comprehensive conceptual framework, which indeed exists at instrument level, adjusted for additional criteria related to the context: modality of application, target population and treatment (Zarin et al., 2011).
Malignant brain tumors may have a common set of outcome measures based on the research question and treatment/s.
The PFS on the patient is investigated only in the 2,5% of the analyzed trials using the neurological examination.
Although the PFS is an emerging objective to assess disease progression and, together with disease-related measures, indicates a visible difference compared to previous assessment, RTT is a more sophisticated outcome since implies an unknown type and quality of changes. Actually, the former may be aggregated and expressed with a binary output; the latter, on the contrary, needs to be analytic (selective) and graduated.
Overall, the RTT is analyzed in 53% of the trials. As regards the outcome measures, construct is the overarching issue while appropriateness, accuracy and specificity are the crucial issues to judge instruments selection. The construct, the general concept, deserves attention. Although the construct is often heterogeneous between and within the studies, the broad concept of "neurologic domain" and the more specific "cognitive domain", part and parcel of the former, are both potentially measurable and objective and thus meet the basic requirement for brain functions assessment. However, as regards appropriateness and accuracy, our recent findings revealed relevant faults about the suitability of the most commonly used test of cognitive assessment concerning both the reliability and the architecture of existing neurocognitive assessment batteries (De Martino et al., 2020). At the same time, the neurological examination (clinician-reported) does not specify the impaired function/s and does not measure it/them, neither has a graduation but rather a binary output[1]. The described failures are added to the well-known limits of the Karnofsky Scale (Hutchinson et al., 1979; Buccheri et al., 1996; Frappaz et al, 2020). Indeed, functional domains have many facets which require multiple and simultaneous items to adequately characterize them.
As regards innovation, PRO has been widespread in the last decade; this gave to the patient both the opportunity to inform about their own condition and the

[1] These pitfalls have been overcome by the recent development of a standardized scale (Nayak et al., 2017).

possibility to be actively involved in the decision making process (Patrick, 2003; Food and Drug Administration, 2009). However, for its comprehensive nature, the QoL has critical issues to be used as an outcome measure. PRO are not recognized as measures of clinical benefit, nor they can replace the other instruments; rather, they should integrate them, combining with "hard" end points such as those measurable.

The "net clinical benefit" is an interesting, useful, composite measure of the impact of treatment in the analysis of efficacy. It combines PRO, QLQ-C, 30/QLQ, BN20 with mean symptom severity as measured by the MD Anderson Symptom Inventory–Brain Tumor module (MDASI-BT) and neurocognitive battery. However, after many years, it still lacks a mathematical model that aggregates the different measures (Amstrong et al., 2013; Amstrong et al., 2014).

In the neurologic field, traumatic brain injury can be exploited as an example of how functioning and disability are seen as multi-dimensional outcomes experienced at the level of both person and society in the context of a multidisciplinary high quality teamwork (Riemsma et al., 2001; Steyerberg et al., 2008; Koskinen et al., 2011).

Research is still needed in the field, since professionals and clinicians have difficulties when attempting to introduce innovative instruments. On the other hand, when they replicate previous approaches, they downgrade the trust for practical application, since many factors remain undetermined or hidden and make the outcome assessment in brain tumors underdeveloped and unreliable.

Some aspects need further analysis like the meaning of the response; it is supposed to measure the advantage of treatment in relieving patient complaints, in the context of the outcome set and its specificity by treatment. Thus, it can be used to verify whether the differences in terms of target area, time of delivering and effects can justify the adoption of different instruments.

An additional consideration is needed. Missing baseline assessment prevents to appreciate the impact of the tumor on the patient, since it is not possible to document the degree of impairment induced by the tumor, and reduces the sensitivity of following measurements. Indeed, a reliable estimation of treatment efficacy and monitoring presumes a different type of outcomes assessment.

II. Study 2 - THE ASSESSMENT OF COGNITIVE FUNCTIONS IN BRAIN TUMORS CLINICAL TRIALS OVER THE LAST 30 YEARS: A COSMIN CHECKLIST-BASED APPROACH

Clinical trials	Battery	Tests	Domains assessed

1. *Introduction*

Cognitive deficits occur in up to 90% of all brain tumor patients (van Loon et al., 2015). Attention, memory and executive functions are the typically compromised domains, albeit others elective damages related to tumor location are also feasible and may affect patient well-being (Meyers & Brown, 2006; Tucha et al., 2000). Cancer treatments may alleviate cognitive deficits, but they might produce neurotoxicity (i.e. neuro-cognitive side effects; Keime-Guibert et al., 1998; Saad & Wang, 2015; Douw et al., 2009). The availability of reliable measures of neurocognitive assessment is crucial. Neuropsychological assessment is a performance-based method grounded on standardized tests and aimed at providing objective measures about the cognitive consequences of brain damage over time.

In the last few years, a growing interest on cognitive response in clinical trials has been observed and the cognitive performance is now considered as an important patient-related outcome to assess response to treatment. It has been proposed that the gold standard neurocognitive assessment battery to be adopted in clinical trials should be brief (feasible), sensitive to specific patient- and/or disease-related signs and symptoms but it should be also pertinent to the clinical trial endpoints, for instance, evaluation of the cognitive impairment induced by brain tumor vs. evaluation of neurotoxicity of treatments (Helfer et al., 2016). In general, in order to disentangle if cognitive deficits depend on the tumor itself and/or on the treatment, a perioperative neuropsychological assessment should be provided (i.e. before and after treatment). Since neurotoxicity may occur after many years (Douw wt al., 2009), follow-up assessments are recommended. Nevertheless, nowadays there is no consensus on which is the "best" neurocognitive assessment battery to be used in clinical trials and no distinction is made between assessment devoted to the identification of cognitive deficits resulting from cancer as opposed to deficits resulting from direct or indirect effects of cancer therapy (Helfer et al., 2016). Furthermore, given the lack of neuropsychological tests specifically designed to assess cognitive functions in brain tumor population, some cognitive batteries or cognitive screening tests are often applied improperly.

A possible strategy to understand whether a given neuropsychological test could be adequate to detect cognitive deficits in brain tumor patients is to exploit methodologies and practical tools provided by the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN). It allows to assess the measurement properties of questionnaires and performance-based instruments in order to improve the quality of studies based on these tools (Mokkink et al., 2012).

In the present paper we give a brief description of the neuropsychological tests mainly used in the brain tumors clinical trials published over the last 30 years (1990-2017, see Table 1) and try to evaluate the methodological quality of studies on measurement properties by means of the COSMIN checklist (CC; Mokkink et al, 2010). We aim at verifying if such cognitive tests are adequate to assess the cognitive status of brain tumor patients and to detect their cognitive responses to treatment.

Tab. 1 Instrument used in brain tumor clinical trials

Dinapoli et al. (1993) Brem et al. (1995) Valtonen et al. (1997) Coughlin et a. (2000) Buckner et al. (2001) Shaw et al. (2002) Souhami et al. (2004) Stupp et al. (2005) Buckner et al. (2006) Cairncross et al. (2006) van den Bent et al. (2006) Grabenbauer et al. (2009) Stupp et al. (2009) Wick et al. (2010) Brandes et al. (2010) Wick et al. (2012) Chinot et al. (2014) Stupp et al. (2015) Baumert et al. (2016) Herrlinger et al. (2016) Stupp et al. (2017)	/	MMSE	Orientation, Registration, Attention and calculation, Registration recall, Language, and Visuo-constructional apraxia
Keime-Guibert et al. (2007)	**Severity Battery**	MMSE	See MMSE
		MDRS	Attention, Initiation-Perseveration, Construction, Conceptualization, and Memory
		NPI	Delusions, Hallucinations, Agitation/Aggression, Dysphoria, Anxiety, Euphoria, Apathy, Disinhibition, Irritability/lability, Aberrant motor activity, Night-time behavioral disturbances, and Appetite and eating abnormalities
Gilbert et al. (2013) Gilbert et al. (2014) Brandes et al. (2016)	**Clinical Trial Composite**	HVLT-R	Verbal Learning and Long Term Memory
		COWA	Inhibition, Flexibility and Processing speed
		TMT	Visual search research, Working memory and Shifting attention
Prados et al. (2003)	**Clinical Trial Composite-Long Version**	HVLT-R	See HVLT-R
		COWA	See COWA
		TMT	See TMT
		Digit span	Auditory attention, working memory, verbal short-term memory, information processing speed, and visual processing
		Digit symbol	Visual-scanning efficiency, graphomotor and perceptual-motor speed,and visual attention span
		Hand Dynamometer	Functionality and muscle strength
		Grooved Pagdoard	Motor speed, visual-motor coordination, and single-hand dexterity

2. Materials and Methods

This study analyzed brain tumors clinical trials over the last 30 years (1990-2017) and identified an overall set of 10 neuropsychological tests that were administered

to patients (Table 1). In order to simplify comprehension, when feasible, we grouped the tests into batteries.

2.1 Mini-Mental State Examination

The Mini–Mental State Examination (MMSE) was originally designed to quickly evaluate the cognitive status in dementia and psychiatric patients and to detect cognitive changes over time and response to treatment in these patients. It includes subscales for different domains (orientation, attention, memory, language and visual-spatial skills; Folstein et al., 1975).

2.2 Severity battery

A battery composed of the MMSE (described above), the Mattis Dementia Rating Scale (MDRS) (Mattis, 1976; Mattis, 1988) and the Neuropsychiatric Inventory (NPI; Cummings et al., 1994; Cummings, 1997) was employed in a brain tumor clinical trial (Keime-Guibert et al., 2013) where a severely impaired population was enrolled (≥ 70 years old patients with high-grade glioma): we refer to it as the "Severity battery", SB.
The MDRS was originally created to assesses the severity of Alzheimer's Disease (AD); it is composed of 36 tasks and provides 5 subscale scores about attention, initiation and perseveration, visuo-spatial construction, conceptualization and memory.
The NPI evaluates both neuropsychiatric symptoms commonly present in patients with dementia. It is administered to caregivers who are requested to indicate frequency, severity, and distress about 12 sub-domains of patients' behavioral functioning (delusions, hallucinations, agitation/aggression, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability/lability, aberrant motor activity, night-time behavioral disturbances, appetite and eating abnormalities).

2.3 Clinical Trial Battery Composite

The Clinical Trial Battery Composite (CTB-Comp; Johnson et al., 2012) consists of the Hopkins Verbal Learning Test – Revised (HVLT-R; Benedict et al., 1998), the Trail Making Test (TMT; Reitan & Wolfson, 1986) and the Controlled Oral Word Association Test (COWA; Benton & Hamsher, 1976; Benton & Hamsher, 1989). The battery is based on the International Cognition and Cancer Task Force recommendations (Wefel et al., 2011) and it is recommended by the Radiation Therapy Oncology Group; it was assembled in order to assess drug-related cognitive impairment in brain tumors clinical trials on neurotoxicity (Meyers & Brown, 2006). It was used in 3 different clinical trials (Gilbert et al., 2013; Gilbert et al., 2014; Brandes et al., 2016).
The HVLT-R is a verbal learning task and provides scores of learning and long term storage and retrieval.
The TMT is a pen-and-paper test that requires complex visual scanning, motor speed and agility, visual attention and task switching.
The COWA is a verbal fluency test where subjects are asked to generate 3 lists of words that begin with a specific letter within a time limit of 1 minute respectively.

2.4 Clinical Trial Battery Composite– Long Version

A further battery, only used in 1 clinical trial (Prados et al., 2003), is as an extension of the CTB-Comp battery: we refer to it as the CTB-Comp Long Version (CTB-Comp LV). It comprises the tests of the CBT-Comp battery and in addition the Digit span (DS; Wechsler, 1944), the Digit symbol (DSY; Wechsler, 1944), the Hand Dynamometer (HD; Bornstein, 1985) and the Grooved Pegboard test (GPT; Bornstein, 1985).
The DS is a test of verbal short memory based on repetition of sequences of digits in the presented (Digits Forward) or inverted (Digits Backward) order. Forward DS is associated with auditory attention and short term memory; backward DS is associated with the ability to hold in mind information while performing mental operations (Lezak et al., 2004).
The DSY is a visuo-motor test which is sensitive to sustained attention, speed of perceptual processing and visual search.
The HD provides a measure of hand-grip strength (Fess, 1981).
The GPT is a dexterity test that assesses eye–hand coordination and motor speed and requires sensory motor integration and a high level of motor processing (Roy & Square, 1994).

2.5 Selection Criteria

We searched the PubMed bibliographic database and selected the papers that meet the following criteria: full-text papers written in English concerning the reliability of the neuropsychological tests mainly used in the brain tumors clinical trials over the last 30 years (1990-2017).
Twenty-four papers were analyzed (see Table 4). Two independent reviewers (GC and AT) were involved in the selection phase of the study.

2.6 Measurement properties, Quality Assessment and Levels of Evidence

The measurement properties of cognitive tests are summarized in Table 2.

Tab. 2 Definitions of domains, measurement properties, and aspects of measurement properties

DOMAIN	MEASUREMENT PROPERTY	ASPECT OF A MEASUREMENT PROPERTY	DEFINITION

Reliability			The degree to which the measurement is free from measurement error
Reliability (extended definition)			The extent to which scores for patients who have not changed are the same for repeated measurement under several conditions: e.g. using different sets of items from the same instrument (internal consistency); over time (test-retest); by different persons on the same occasion (inter-rater); or by the same persons (i.e. raters or responders) on different occasions (intra-rater)
	Internal consistency		The degree of the interrelatedness among the items
	Reliability		The proportion of the total variance in the measurements which is due to 'true' differences between patients
	Mesaurement error		The systematic and random error of a patient's score that is not attributed to true changes in the construct to be measured
Validity			The degree to which an instrument measures the construct(s) it purports to measure
	Content validity		The degree to which the content of an instrument is an adequate reflection of the construct to be measured
		Face validity	The degree to which (the items of) an instrument indeed looks as though they are an adequate reflection of the construct to be measured
	Construct validity		The degree to which the scores of an instrument are consistent with hypotheses (for instance with regard to internal relationships, relationships to scores of other instruments, or differences between relevant groups) based on the assumption that the instrument validly measures the construct to be measured
		Structural validity	The degree to which the scores of an instrument are an adequate reflection of the dimensionality of the construct to be measured
		Hypothesis testing	Idem construct validity
		Cross-cultural validity	The degree to which the performance of the items on a translated or culturally adapted instrument are an adequate reflection of the performance of the items of the original version of the instrument
	Criterion validity		The degree to which the scores of an instrument are an adequate reflection of a 'gold standard'
Responsiveness			The ability of an instrument to detect change over time in the construct to be measured
	Responsiveness		Idem responsiveness

The CC was used to assess the quality of the selected studies.
The CC consists of 102 items, each scored on a 4-point rating scale ('poor', 'fair', 'good', 'excellent') and grouped into 9 boxes.
An overall score for the methodological quality of the study can be obtained separately for each measurement property (Terwee et al., 2011).

Finally, a level of evidence was established ('strong', 'moderate', 'limited', 'conflicting', or 'unknown'; Table 3). It was obtained by combining results from different studies and consists of a final qualitative rating ("positive", "indeterminate" or "negative") for each psychometric property of each single instrument (Schellingerhout et al., 2011).

Tab. 3 Levels of evidence for the quality of measurement property

LEVEL	RATING	CRITERIA
Strong	+++ or ---	Consistent findings in multiple studies of good methodological quality OR in one study of excellent methodological quality
Moderate	++ or --	Consistent findings in multiple studies of fair methodological quality OR in one study of good methodological quality
Limited	+ or -	One study of fair methodological quality
Conflicting	+/-	Conflicting findings
Unknow	?	Only studies of poor methodological quality

Note: + = positive rating, ? = indeterminate rating, - = negative rating.

3. Results

The CC scores are reported below and summarized in Table 4.

3.1 Mini Mental State Examination

The CC revealed a 'poor' score in the Internal Consistency (IC) box for the Kabátová and coll. (2016) and the Jorm & Korten (1988) studies. These 2 studies differed in their rating values: the former received a positive rating whereas the latter received a negative rating. The level of evidence was marked as conflicting.
The CC showed a 'fair' score in the Reliability box when applied to neurological patients (Folstein et al., 1975; Dick et al., 1984). The level of evidence was marked 'moderate' with a positive rating. The CC showed a 'fair' score in the Reliability box when applied to healthy subjects (Olin & Zelinski, 1991). The level of evidence was marked 'limited' with negative rating.

3.2 Severity Battery

Mini Mental State Examination
See previous paragraph.

Mattis Dementia Rating Scale
No data are available because the access to full-text papers was not possible.

Neuropsychiatric Inventory
The CC revealed a 'poor' score in the IC box for the Cummings and coll. (1994) study. The score in the IC box for the Binetti and coll. (1998) and the Kilmer and coll. (2006) was 'fair'. The level of evidence was marked as limited with a

positive rating when applied to studies on neurological patients (Cummings et al., 1994; Binetti et al., 1998; Kilmer et al., 2006).
The CC showed a ‘poor’ score (Cummings et al., 1994) and a ‘fair’ score (Binetti et al., 1998) in the Reliability box. The level of evidence was marked as limited with a positive rating.

3.3 Clinical Trial Battery – Composite

Controlled Oral Word Association Test
The CC revealed ‘fair’ scores in the IC box when applied to both Tombaugh and coll. (1999) and Ruff and coll. (1996). The level of evidence was marked ‘moderate’ with a positive rating.
The CC revealed ‘fair’ score in the Reliability box when applied to Tombaugh and coll. (1999), Ruff and coll. (1996), Ross (2003), Basso and coll. (1999) and Levine and coll. (2004). The level of evidence was marked ‘moderate’ with a positive rating.

Hopkins Verbal Learning Test
The CC revealed ‘fair’ score in the Reliability box when applied to Rasmusson and coll. (1995; negative rating) and Benedict and coll. (1998; positive rating). The level of evidence was marked as ‘conflicting’.
The CC revealed ‘fair’ score in the Reliability box when applied to a study on TBI patients (2012). The level of evidence was marked ‘limited’ with a negative rating.

Trail Making Test
The CC revealed ‘fair’ scores in the Reliability box when applied to Dikmen and coll. (1999), Levine and coll. (2004) and Giovagnoli and coll. (1996). The level of evidence was marked ‘moderate’ with a positive rating.

3.4 Clinical Trial Battery Composite—Long Version

Controlled Oral Word Association Test, Hopkins Verbal Learning Test and Trail Making Test
See previous paragraph.

Digit Span
The CC revealed ‘fair’ score in the Reliability box when applied to Dikmen and coll. (1999). The level of evidence was marked ‘limited’ with a positive rating.

Digit Symbol
The CC revealed ‘fair’ scores in the Reliability box when applied to Dikmen and coll. (1999), Morrison and coll. (2015) and Woods and coll. (2006). The level of evidence was marked ‘moderate’ with a positive rating.

Grooved Pegboard
The CC revealed ‘fair’ scores in the Reliability box with a positive rating when applied to Dikmen and coll. (1999), Ruff & Parker (1993) and Wang and coll. (2011). The CC revealed ‘fair’ scores in the Reliability box with a negative rating

when applied to Levine and coll. (2004) and Woods and coll. (2006). The level of evidence was marked 'conflicting'.

Hand Dynamometer
The CC revealed 'fair' score in the Reliability box with a positive rating when applied to Bohannon (1986) and 'poor' with a positive rating in Morris and coll. (2008). The level of evidence was marked 'limited'.

Tab. 4 Methodological quality of each study per reliability and cognitive instruments

INSTRUMENT	STUDY	INTERNAL CONSISTENCY	RELIABILITY
MMSE	Kabatova et al. (2016)	Poor	//
	Jorm & Korten (1988)	Poor	//
	Folstein et al. (1975)	//	Fair
	Dick et al. (1984)	//	Fair
	Olin & Zelinski (1991)	//	Fair
SEVERITY BATTERY *MMSE*	See above	See above	See above
MDRS	NA[a]	NA[a]	NA[a]
NPI	Cummings et al. (1994)	Poor	Poor
	Binetti et al. (1998)	Fair	Fair
	Kilmer et al. (2006)	Fair	//
CLINICAL TRIAL BATTERY COMPOSITE *COWA*	Tombaugh et al. (1999)	Fair	Fair
	Ruff et al. (1996)	Fair	Fair
	Ross (2003)	//	Fair
	Basso et al. (1999)	//	Fair
	Levine et al. (2004)	//	Fair
HVLTR-R	Rasmusson et al. (1995)	//	Fair
	Benedict et al. (1998)	//	Fair
	O'Neil-Pirozzi et al. (2012)	//	Fair
TMT	Dikmen et al. (1999)	//	Fair
	Levine et al. (2004)	//	Fair
	Giovagnoli et al. (1996)	//	Fair
CLINICAL TRIAL BATTERY COMPOSITE-LONG VERSION			
DIGIT SPAN	Dikmen et al. (1999)	//	Fair
DIGIT SYMBOL	Dikmen et al. (1999)	//	Fair
	Morrison et al. (2015)	//	Fair
	Woods et al. (2006)	//	Fair
	Dikmen et al. (1999)	//	Fair
GROOVED PEGBOARD	Ruff & Parker (1993)	//	Fair
	Wang et al. (2011)	//	Fair
	Levine et al. (2004)	//	Fair
	Woods et al. (2006)	//	Fair
HAND DYNAMOMETER	Bohannon (1986)	//	Fair
	Morrison et al. (2008)	//	Poor

4. *Discussion*

An overall set of 10 performance-based cognitive tests (MMSE, MDRS, NPI, HVLT-R, COWA, TMT, DS, DSY, HD and GPT) commonly used in brain tumors clinical trials from 1990 to 2017 and arranged into 4 main cognitive assessment batteries were evaluated.

We start our analysis from the MMSE. It is extensively used across brain tumors clinical trials from 1990 to 2017 and, interestingly, some authors found that MMSE performance is a prognostic factor for overall survival in glioma patients (Stupp et al., 2005; van den Bent et al., 2006).

Some critical issues emerged from the application of the CC on the MMSE: we obtained reliability and level of evidence scores that are insufficient to rely on its data as the only assessment tool in brain tumor clinical trials. In addition, the MMSE provides a quick, brief but not exhaustive screening of the explored cognitive domains: it does not assess motor, visuo-spatial and executive functions which can be supposedly impaired in brain tumor patients. Therefore, it can only recommend as part of a more comprehensive cognitive assessment or as a stratification factor at the baseline in clinical trials (Stupp et al., 2005; van den Bent et al., 2006).

Similar conclusion can be drawn about the SB. The reliability scores obtained through the CC as well as its architecture reveal that the SB provides vague and incomplete cognitive assessment. Nevertheless, it is worth noting that information provided from 1 of its test, the NPI, could be crucial in behavioral assessment in brain tumor patients. The NPI expressly investigates behavioral profiles in neurological patients; thus, it seems to more appropriate for brain tumor patients than behavioral inventories for psychiatric populations (e.g. MINI Plus; Sheehan et al., 1998). Furthermore, administering the test to the caregiver allows to detect behavioral disturbances in patients with language impairment or anosognosia and the caregiver distress can be exploited to offer and a targeted psychological support (Castellanos-Pinedo et al., 2011).

The CC evaluation revealed precarious rating also for the CTB-Comp: its levels of evidence received from limited to moderate scores. Albeit it allows assessment of cognitive functions which have been found to be correlated with the functional autonomy and quality of life of brain tumor patients (Giovagnoli & Boiardi, 1994), to be affected by neurotoxicity of treatments (Meyers & Brown, 2006) and to predict survival in patients with recurrent malignant glioma and with newly diagnosis of glioblastoma (Meyers et al., 2000; Meyers et al., 2004; Johnson et al., 2012), limitations concern its administration. Two of its tests, the COWA and the HVLT-R, are both verbal tasks and their consecutive administration might induce interference. In addition, the HVLT-R requires an interval of 20-25 minutes between the learning and the recognition phase. During this interval, only tasks involving visuo-spatial abilities should be given. But the third test in the battery, the TMT, takes approximately no more than 10 minutes to be completed. It would be more appropriate to provide additional non-linguistic tests during the assessment session.

Even for the last battery considered in this study, the CBT-Comp LV, the reliability of its tests scored via the CC were found to reach from limited to moderate levels of evidence. Therefore, although it provides a more articulated evaluation of patients' cognitive status, the CBT-Comp LV does not improve neurocognitive assessment when compared to the previously described batteries.

Actually, the battery provides only rough information about language and does not assess visual-spatial memory, executive functions and visuo-constructional abilities. Therefore, these last two batteries cannot be recommended as reliable cognitive instruments to be employed in brain tumor clinical trials. The assessment based on these two batteries could not be fully accepted even if the endpoint is focused on the direct effects of neurotoxicity of treatments on cognition. In fact, they only provide measures for the main (albeit not all) cognitive domains considered to be most frequently affected by chemotherapy and radiation (Correa, 2010). Moreover, a further difference should be made between patients who receive whole-brain radiations (WBRT) and patients who receive focused irradiation (FI). These two options give raise to qualitative and quantitative different patterns of cognitive dysfunctions (Gregor et al., 1996) not easily detectable by using these two batteries. On the other hand, if the endpoint is related to the neurocognitive effects of the brain tumor itself before and after treatments, the batteries turn out to be not indicated. Tumor induces cognitive deficits that depend on its location, size and grade (Scheibel et al., 1996; Duffau et al., 2005; Talacchi et al., 2011). For instance, Tucha and coll. (2000) and Talacchi and coll. (2011) found that visuo-constructive and visuo-spatial deficits are very frequent before and after treatments. These domains cannot be adequately assessed through the CTB-Comp and its Long Version.

III. Study 3 - LANGUAGE ASSESSMENT IN MULTILINGUALISM AND AWAKE NEUROSURGERY

1. *Introduction*

In a broad and inclusive sense multilingualism can be defined as the acquisition and use in everyday life of two or more languages (Butler, 2013; Grosjean, 2013). In order to cope with challenges resulting from migration and globalization, current human societies support multilingualism since it promotes education, cognitive health (Antoniou and Wright, 2017; Baumgart and Billick 2018; Calabria et al., 2020), cultural, social and economic inclusion (Aronin and Singletone, 2008).Worldwide, multilingual people are actually the rule rather than the exception, mostly if one considers that, beyond the official and standardized languages, many people use dialect for communication in everyday life (Eurostat, 2015; Grosjean, 1992; Hartsuiker et al., 2016). However, the monolingual brain and the monolingual language processing system are still considered as the norm both in neurocognitive models of language and in clinical practice. This is probably due to mixed and inconsistent findings and to several extant controversies on the functioning, the architecture and the neural underpinnings of language processing in multilinguals.

Starting from late '70, aphasiology, neurosurgery and neuroimaging studies have provided evidence about the multilingual brain (Albert and Obler, 1978; Bhatia and Ritchie 2006; Ojemann and Whitaker, 1978; Paradis 2004). Two major issues have been addressed:

1) whether multilingual speakers recruit the same regions as monolinguals during linguistic tasks or multilingualism requires recruiting additional brain regions;
2) whether or not different languages require the support of specific cortical regions.

In general, clinical observations on multilingual aphasic individuals documented different patterns of impairment and of post-insult recovery in each of the languages spoken by the patients and described complex correlations between language and brain sites (Albert and Obler, 1978; Aglioti and Fabbro, 1993; Giussani et al., 2007; Paradis, 2000). Consistent findings were reported in neurosurgical settings where multilingual patients showed language-specific responses to brain stimulation (see Połczyńska and Bookheimer, 2020 for a recent review). These data have often been used as evidence that different languages are represented in different brain regions. However, neuroimaging studies in healthy multilinguals provided evidence that the neural representation of L1 converges with that of additional spoken languages (Abutalebi and Green, 2007; Green, 2003; García-Pentón et al., 2016). The contrasting results that emerge from studies on brain-damaged patients and from neuroimaging investigations on neurotypical individuals do not yet have a straightforward explanation. Reliable accounts will require substantial progress in at least two areas of investigation. In the first place, a finer-grained knowledge of the neural representation of linguistic knowledge and domain-general resources is mandatory. So far studies focused on single-word processing (mostly nouns) but largely steered clear of language-specific aspects of syntax and morphosyntax, and of their interactions with

processing resources. Obviously, studies should be carried out in more languages than currently available Secondly, results should be interpreted based on an in-depth knowledge of experimental methods. To mention but one issue, neuroimaging investigations analyze BOLD signal changes in macroareas (Regions Of Interest, ROIs) during exposure to a relatively large number of stimuli, whereas DES (Direct Electrical Stimulation) is delivered over very small areas of the brain, each of which may occupy a minimal fraction of said ROIs, and results are inferred based on a necessarily limited number of stimuli.

At present, despite the growing amount of evidence, it is hard to draw clear and firm conclusions about the neural and cognitive organization of multilingualism. As a matter of fact, multilingualism poses a number of critical questions on both theoretical and methodological grounds. The linguistic profiles of multilingual speakers are very heterogeneous, since a multitude of experience-related factors determine the multilingual competence: age (early vs. late) and type of acquisition (formal vs. informal education; simultaneous vs. sequential acquisition), amount of exposure to the different languages, modality (oral vs. written or both) and context (familiar vs. professional or both) of use, proficiency level and degree of similarity/distance between languages. Recent reviews and meta-analyses (Cargnelutti et al., 2019; Połczyńska and Bookheimer, 2020) have shown that those factors affect the performance of multilinguals in linguistic tasks and have an impact on the neural organization of languages. In addition, the interaction among the spoken languages has been shown to modulate their neural underpinnings (De Bot, 2004; Del Maschio and Abutalebi, 2019; Kroll and Bialystok, 2013; Kroll and Ma, 2018). However, there are no standardized objective measures or procedures to operationalize these variables. From a research/academic perspective, this is conducive to results that are not comparable across studies and thus hampers an adequate comprehension of the multilingual system and of its cerebral organization. From a clinical standpoint, a potential underestimation of the role of those factors during language assessment may produce skewed profiles of the pattern of compromised/preserved linguistic abilities in multilingual patients. For instance, an incorrect estimation of the proficiency or of the frequency of usage of the languages spoken by a multilingual speaker may produce confounds when assessing the presence of linguistic deficits. In other words, it is crucial to distinguish a true anomia, or a true semantic/phonological paraphasia, from errors due to inaccurate knowledge or infrequent use of a given language. Similarly, increased latencies in reading or naming tasks could indicate either difficulties in lexical access, or cross-language interference, or even a language-switching cost in speakers with strong dominance of one language over the others. Such a problem has relevant consequences especially for the procedures adopted during awake glioma surgery in language-sensitive brain regions. The surgical procedure with the patient in awake state has been introduced in brain tumor treatment in the ‘90s and requires the patient to perform cognitive tasks while specific parts of the brain are stimulated. If stimulation interferes with the task, the stimulated area should not be resected to prevent post-surgery deficits. This technique offers two primary advantages: it allows enrolling in surgical treatment patients who were previously excluded because their tumors were located in brain areas critical for specific cognitive functions, such as language; furthermore, it preserves full functionality while allowing maximal resection of pathological tissue. The potential variation of both

linguistic competence and anatomical differences in the cortical representation of the different languages in multilingual patients may induce additional post-surgical deficits if all the languages are not comprehensively and adequately assessed preoperatively and if an appropriate intraoperative testing has not been prepared.

This paper analyses the perioperative language assessments adopted in awake surgery studies on brain tumors in multilingual patients published from 1991 to 2021. Albeit awake surgery procedures are usually adopted to treat severe epilepsy while preserving language functions, we focused only on brain tumor surgery. The reason is that epilepsy frequently has a childhood onset and may affect language acquisition, thus adding a possible confound in the analysis of language assessment procedures in multilingual speakers. The aim of the present paper is to verify to what extent the variables that affect linguistic processing in multilingual speakers have been considered during planning and decision making in awake surgery for brain tumors. The following main issues will be addressed: whether and how AoA and proficiency in each language are evaluated; how language skills are assessed in all the languages; whether the distance/similarity across languages is kept under control in the direct comparison of language-specific performance accuracy; how the language for the global neuropsychological assessment of the multilingual patient is selected and which tasks are used in the intraoperative setting. In the following paragraphs, each of the variables analyzed in the paper is described. Results are summarized in separate sections. Finally, strengths and weaknesses of the most frequently used clinical approaches to multilingualism in awake surgery for brain tumors are discussed.

2. Materials and Methods

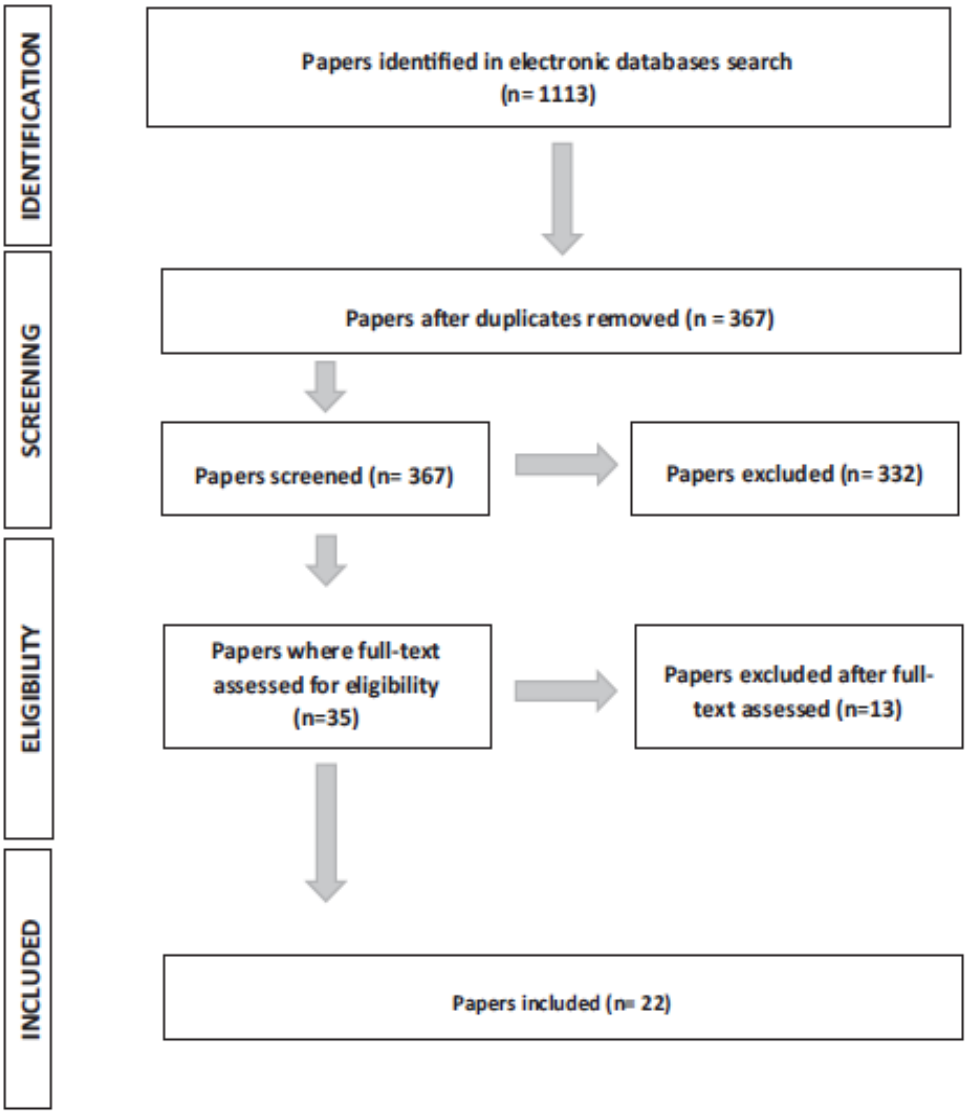
A literature search using PubMed and Web of Science databases was performed between March and May 2021. The following terms were used: plurilingual*, multilingual*, bilingual*, trilingual*, quadrilingual*, polyglot, brain tumor, brain tumor, brain cancer, cerebral cancer, glioma, glioblastoma, meningioma, awake surgery, craniotomy, neurosurgery, direct electrical stimulation, electrocorticography. Papers published between 1991 and 2021 were considered.

We found 1113 peer-reviewed papers, removed duplications (746 papers) and among the remaining 367 papers we only focused on those that included multilingual individuals who underwent awake surgery. A flowchart of the research strategy is reported in Figure 1.

The following exclusion criteria were applied: review article, sign languages, not in English, not an article, not brain tumor, not multilingual, not adult, not intraoperative language mapping in awake surgery, not multilingual intraoperative testing, insufficient details about the preoperative and/or the intraoperative multilingual language testing.

Ultimately, 22 papers were selected and reviewed. The list of the selected papers is reported in the first column on the left of tables 1 to 6.

Fig. 1 Flowchart of the search process



The following data were extracted from the reviewed papers: demographic and clinical information about patients (Table 1), languages (number and types of studied languages, multilingual profiles and language distance/similarity, Table 2), AoA (Table 3), proficiency (Table 4), language assessment and intraoperative tasks (Table 5), general neuropsychological assessment (Table 6).

2.1. Analyzed variables

2.1.1 Language distance

The concept of distance between languages has to do with qualitative and quantitative differences that may involve many domains: phonetics (tonal vs. non-tonal languages, e.g., Mandarin Chinese vs. English), orthographic systems (alphabetic vs. logographic, e.g., English vs. Japanese Kanji; direction of writing,

e.g., right to left vs. left to right vs. top to bottom, as in Arabic vs. French vs. traditional Japanese; deep vs. transparent orthography, e.g., English vs. Italian), vocabulary (e.g., presence/absence of cognates), grammar (e.g., presence/absence of determiners, grammatical gender), morphology (e.g., inflectional systems, agreement patterns; auxiliaries) and syntax (e.g., word order, phrase structure). There is no well-established method to quantify the similarity between languages and it is hard to reduce all these parameters to a single distance score (Gamallo et al., 2017). Usually, linguistic distance is determined by measuring the number of branches between two languages on the language family tree model (Dimmendaal, 1995; Połczyńska and Bookheimer, 2020). This system is based on the possibility to identify common ancestors of languages and to define broad categories of language families (e.g.,, Romance, Germanic, Scandinavian, African, Slavic, Semitic, Asiatic, isolated). However, and even beyond its theoretical limitations, such an approach is scarcely useful when attempting to understand how language distance affects cognitive aspects of language processing in multilinguals. Conversely, the problem has been dealt with repeatedly in neuroscience and psycholinguistics (Bassetti, 2008; Cenoz et al., 2001; Gleitman, 1985; Koda, 2005; Kim et al., 2016; Odlin, 1989; Schepens et al., 2016; Shinozuka et al., 2021; Vaid, 1983; Zawiszewski, and Laka, 2020). Models of multilingual processing have tried to define how the cognitive system manages shared and distinctive features between languages. In general, it is assumed that conceptual information on words is represented in a language-independent fashion, as it is related to the semantic properties of the word's referents (Francis, 2005). Other aspects are controversial. On the "shared syntax" approach, syntactic-grammatical properties common to different languages are represented only once in the multilingual language system, thus reducing redundancy and increasing efficiency of language processes (Hartsuiker et al., 2004). On the other hand, the structural similarity across languages modulates the functioning of the hypothesized unified syntax (Runnqvist et al., 2013). Similarly, Peeters et al. (2013) demonstrated that identical interlingual cognates are stored as a single orthographic representation but as two distinct phonological and morphological representations, and that the activation of each representation can vary with the linguistic operation to be performed. In a study on the behavioural and neural correlates of naming in L2 in healthy speakers, Ghazi-Saidi and Ansaldo (2017) found that naming in L2 is more effortful and demanding in distant language pairs than in close language pairs.

To sum up, despite the difficulty operationalizing the distance/similarity across languages and even though the mechanisms of cerebral-cognitive assimilation and accommodation during the processing of multiple languages are still largely unknown (Kim et al., 2016), it is reasonable to conclude that specific properties of each language impose different cognitive demands on multilingual speakers. The obvious implication for researchers and clinicians is to adapt the perioperative procedures used when selecting tasks and stimuli for language assessment so as to properly address the language distance issue.

2.1.2 Age of Acquisition

The AoA generally indicates the age of exposure to a language and is taken as an indication of the moment in life when that language is acquired. The AoA

parameter provides indirect information on the way a language is acquired: for instance, it can be used to make inferences about whether or not the speaker received any kind of formal education in his/her additional languages. Qualitatively different multilingual conditions have been described by using the AoA parameter (Kim et al., 1997). Simultaneous multilingualism applies to children who are exposed to two or more languages from birth or shortly after birth. In this case, there is no chronological gap between the first language (L1) and other languages (L2, L3, etc.); thus, it is assumed that simultaneous multilingual speakers acquire all their languages through similar developmental trajectories and learning mechanisms. Early-sequential multilinguals begin to acquire additional languages after acquiring the basic grammatical structures of L1; this happens from ages 3 to 5-7 years. Late-sequential multilinguals acquire additional languages by the age of 5-7 years and often, albeit not always, receive formal education in these other languages (Leonard et al., 2011; Perani et al., 2003; Połczyńska et al., 2016). In the literature, different age ranges have been proposed to distinguish simultaneous, early and late bilingualism and it is plausible that AoA should be thought of as a continuous rather than a categorical parameter. Several studies demonstrated that people who learn a language in infancy generally achieve greater proficiency than late learners (Birdsong, 1999; Johnson and Newport, 1989; Perani et al., 2003), that AoA affects several language-specific skills like lexical access, phonology, grammar and syntax (Frenck-Mestre et al., 2005; Hernandez et al., 2007; Isel et al., 2010; Mahendra et al., 2003; Perani et al., 2003; Waldron and Hernandez, 2013; Wartenburger et al., 2003; Weber-Fox and Neville, 1996; Wei et al., 2015) as well as domain-general cognitive control mechanisms (Luk et al., 2011; Tao et al., 2011). Moreover, AoA has an actual role in shaping multilingual brain networks (Abutalebi et al., 2013; Del Maschio and Abutalebi, 2019; Fabbro, 2001; Klein et al., 2014; Liu and Cao, 2016; Mechelli et al., 2004; Perani et al., 1996; 1998, 2003; Wartenburger et al., 2003; Wei et al., 2015).

2.1.3 Proficiency

Proficiency indicates how well a language is known either in production or in comprehension and denotes the level of competence attained in each language (Del Maschio and Aboutalebi, 2019). It is strictly related both to fluency, which refers to the speed and automaticity of linguistic behaviour (Segalowitz, 2010), and to the context and amount of use and exposure to a given language. Proficiency is a multidimensional construct (Treffers-Daller, 2019), which can be differently related to specific aspects of linguistic competence such as modality (oral vs. written), task (e.g., single word/sentence or discourse production, word recognition, language comprehension), domain (syntax, semantics, morphology, phonology, vocabulary). Proficiency in a language can change over time: for instance, multilingual speakers can become more proficient in later-acquired languages than in their mother tongue if they stop using the latter in everyday life or only use it occasionally. For similar reasons, they can be very proficient in a specific modality, or achieve better vocabulary than grammatical skills, or vice versa.

Even if the relative relevance of the many features that define language proficiency remains unclear, the measures of proficiency used to assess the linguistic competence of multilingual speakers should be spelled out in published

reports. Recent findings indicate that proficiency and frequency of use of additional languages are key factors in the organization of language networks in the multilingual brain (Consonni et al., 2013; Kotz, 2009; Stowe and Sabourin, 2005; Sugiura et al., 2015).

2.2 Cognitive Assessment

2.2.1 Preoperative language assessment

Preoperative language testing for patients undergoing awake surgery should provide detailed information on all aspects of their linguistic competence to detect aphasic deficits, identify the functional locus of damage to the language system and select the most suitable tasks/stimuli for intraoperative testing (Miceli et al., 2012). Usually, this goal is accomplished by employing standardized language batteries that provide tasks for the evaluation of different modalities (written, oral), functions (production, comprehension, transcoding, verbal memory), and levels of language organization (materials controlled for distributional, phonological, lexical, grammatical/morphological, syntactic and semantic features). The language assessment of multilingual patients eligible for awake surgery has specific requirements but suffers from the lack of standard procedures. Few standardized tests include multilingual materials and provide normative data from multilingual individuals (Fernández-Coello et al., 2021; Goral and Conner, 2013; Gisbert-Muñoz et al., 2021). Even when such data exist, it is practically impossible to find tests that are adequately matched in all the possible language combinations of the multilingual population. In clinical settings, the standard practice consists of adapting the tests available in one of the languages spoken by a multilingual person to the other languages.

2.2.2 General neuropsychological assessment

Extensive neuropsychological investigations are indispensable in the clinical work-up of brain tumors. More in detail, executive functions, working memory, attention, and emotional status, at the minimum, must be assessed since they impact on linguistic performance and on the ability to tolerate the brain stimulation procedure (Talacchi et al., 2013). The preoperative assessment provides critical information about the cognitive deficits induced by the tumor so that results can be used to plan the surgical approach and define a baseline for subsequent evaluations. The postoperative assessment allows identifying the short-term and long-term outcomes of treatment and provides indications for rehabilitation (Miceli et al., 2012).

Neuropsychological assessments in multilinguals suffers from several biases. The main bias is related to the socio-cultural background of multilingual speakers, especially in immigration contexts (Ardila et al.,1994; Fortuny and Mullaney, 1997; Gasquoine, 1999). Additional biases stem from the properties of testing tools: low scores in a test obtained by a person belonging to an ethnical/linguistic group different from that in which normative data were collected, may be due to reasons other than neurological or cognitive factors (Anastasi, 1988). Potentially unpredictable biases may depend on the unique characteristics of the individual, such as the number, type, and combination of the spoken languages.

Informal testing and translated test materials are frequently used in clinical settings and may be the best possible compromise when a balance between acceptability and adequacy is warranted. However, a crucial issue concerns the selection of the language for the neuropsychological assessment. This decision is strictly related to the linguistic profile of the patient, as s/he must be able to complete the clinical interview and to understand test instructions with as little difficulty as possible. Multilinguals who are equally proficient in all their languages collaborate without difficulty during interviews and testing, as their competence is not dissimilar from that of monolingual speakers. Under the same circumstances, however, so-called functional multilinguals, who use different languages depending on the context (e.g., at work vs. in the family) may face serious difficulties. This is frequently the case of newly arrived immigrants.

2.2.3 Intraoperative testing

Language is by far the cognitive function tested most frequently in awake surgery for brain tumors. However intraoperative tasks and/or batteries show an extreme variability across studies. Automatic speech (e.g., counting, reciting word series) and object naming, especially adaptations of the Test de Dénomination Orale D'Images (DO80, Deloche and Hannequin, 1997) and of the Boston Naming Test (BNT, Kaplan et al., 1983), are the most commonly used tasks. Standardized tests and many other tasks are also employed (see Rofes and Miceli, 2014; Ruis, 2018; and Papatzalas et al., 2021, for recent reviews). In general, intraoperative paradigms must meet specific criteria that allow both to perform an accurate and sensitive language assessment and to minimize risks in the surgical procedure. Rofes and Miceli (2014) suggested that intraoperative tasks specific for language mapping should be adapted to different kind of constraints. Some constraints are imposed by the requirements of language mapping techniques: thus, tasks should be short, allow fast stimulus-response cycles and require simple responses that can be easily scored. Other constraints depend on the language under scrutiny: relevant language-specific properties should be tapped. Furthermore, clinical constraints require that tasks and stimuli should be sufficiently sensitive as to identify fine-grained deficits, should tap specific components of the language system and should be appropriately related to the brain areas associated with the assessed language processes.

These criteria are even more stringent when multilingual people must be assessed intraoperatively.

Recently, a multilingual naming task has been standardized in seven different languages (Spanish, Basque, Catalan, Italian, French, English, German, Mandarin Chinese, and Arabic) with the specific aim to minimize linguistic distance between different groups of items. It includes colored drawings of objects and actions; stimulus words are controlled for name agreement, frequency, length and substitution neighbors. Depending on the language combination, the test includes between 25 and 30 items and can be administered in a maximum of 5 minutes per language (Gisbert-Muñoz et al., 2021).

3. *Results*

3.1 Patient characteristics

Overall, the studies reviewed here included 127 multilingual patients with brain tumors who underwent awake surgery. The histology of the tumor was reported in 93 cases (56 gliomas, 6 metastases, 31 other tumors). Lesions were predominantly located in the left hemisphere (LH) but 9 cases with right hemisphere (RH) lesions were reported (see Table 1 and Figure 2).

Tab. 1 Patients information*

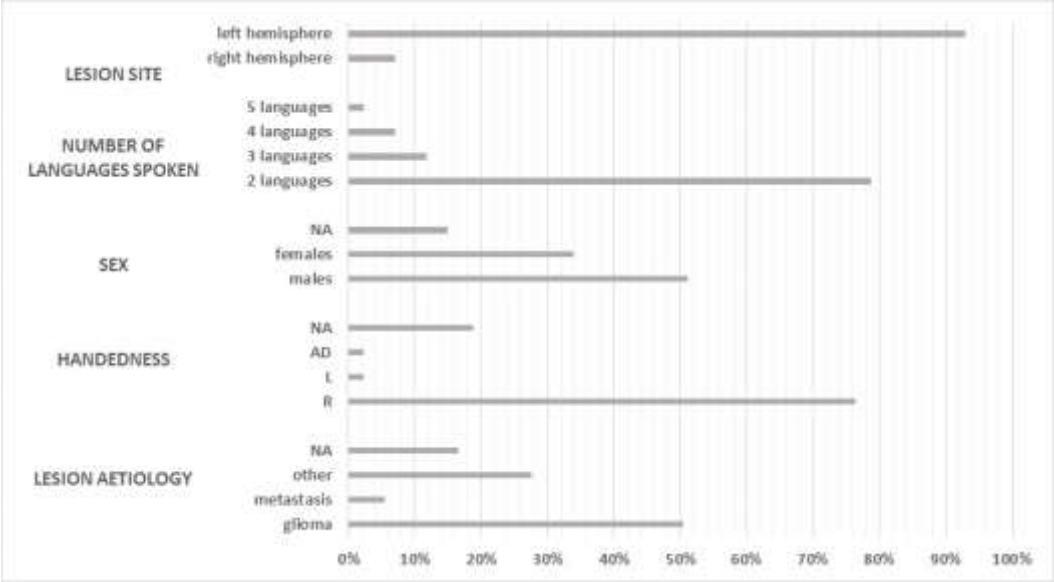
Study	Number of patients	Aetiology			Lesion location			Age	Handedness			Sex	
		glioma	metastasis	other	RH	LH	other		R	L	AD	M	F
Pouratian et al., 2000	1	1	-	-	-	1: Perysilvian cortices	-	43	1	-	-	-	1
Roux and Trémoulet., 2002	12	5	5	2	-	12	-	30-74	12	-	-	8	4
Lubrano et al., 2004	2	NA	NA	NA	1: Frontal	1: Frontal	-	1: 47 1: 67	2	-	-	1	1
Roux et al., 2004	19	NA	NA	NA	5	14	-	13-76	18	1	-	NA	NA
Walker et al., 2004	17	17	-	-	-	Precentral gyrus Central sulcus Postcentral gyrus Frontal operculum Angular gyrus	-	15-57	14	-	3	11	6
Bello et al., 2006	7	7	-	-	-	Frontal	-	32-58	7	-	-	4	3
Bilotta et al., 2011	1	1	-	-	-	Wernicke area	-	54	NA	NA	NA	-	1
Cervenka et al., 2011	1	-	-	1	-	Hippocampus	-	28	3	-	1	1	-

Borius et al., 2012	7	5	1	1	2: Superior and middle frontal gyri	1: Inferior frontal and superior temporal gyri 1: Superior, middle and inferior frontal gyri 1: Supramarginal and superior temporal gyri 1: Supramarginal gyrus 1: Supramarginal, superior temporal and inferior frontal gyri	-	26-45	5	2	-	3	4
Lubrano et al., 2012	1	1	-	-	-	Prefrontal	-	31	1	-	-	-	1
Kin et al., 2013	1	-	-	1	-	Temporal	-	40	1	-	-	1	-
Sierpowska et al., 2013	2	-	-	2	-	1: Fronto-opercular 1: Temporal	-	1: 60 1: 36	2	-	-	2	-
Wang et al., 2013	1	1	-	-	-	Frontal	-	25	1	-	-	-	1
Gao et al., 2015	11	11	-	-	-	11	-	24-46	11	-	-	8[i]	3[i]
Gao et al., 2016	6	1	-	5	-	1: Parietal 2: Temporal 1: Fronto-temporal 1: Temporal-occipital 1: Temporal	-	21-34	6	-	-	4	2
Połczyńska et al., 2016	1	-	-	1	-	Frontal	-	60	1	-	-	-	1
Fernández-Coello et al., 2017	13	8	1	4	-	13: Perisylvian language region	-	25-62	13	-	-	5	8

Sierpowska et al., 2018	7	3	-	4	-	2: Frontal 3: Fronto- temporal 2 Fronto-temporo-parietal	-	33-54	NA	-	-	5	2
Chan et al., 2019	1	1	-	-	-	Inferior frontal gyrus	-	28	1	-	-	1	-
Jain et al., 2019	1	-	-	1	frontal	-	-	60	NA	-	-	-	1
de Macêdo Filho et al., 2020	1	-	-	1	-	Frontal	-	45	NA	-	-	1	-
ReFaey et al., 2020	14	2	-	12	-	9: Frontal [ii] 8: Parietal 5: Temporal	-	45.2	NA	NA	NA	10	4

* Abbreviations: RH = Right hemisphere; LH = Left hemisphere; R = right; L = left; AD = Ambidextrous; M = Male; F= Female; NA= Not Available.
i: We report here a verbatim quote: “All 11 patients were native to Guangdong, and included eight males and four females aged from 24 to 46 (mean 28.6) years”. Since 8+4=12, here we assumed that there were 8 males and 3 females.
ii: Tumor may be located in overlapping eloquent regions.

Fig. 2 Patient information: lesion site, number of languages spoken, sex, handedness, and aetiology



3.2 Language assessment

3.2.1 Number and types of studied languages, multilingual profiles and language distance/similarity

The selected papers investigated 31 languages and reported on different multilingual profiles. The majority of patients were bilingual (100), 15 were trilingual, 9 were quadrilingual and 3 patients spoke 5 languages. A great heterogeneity in the number and type of language combinations was observed, ranging from very close (e.g., Spanish/Catalan; Mandarin Chinese/Cantonese Chinese) to very distant pairs (e.g., Arabic/French; Japanese/English).

Tab. 2 Number and types of studied languages and language distance/similarity

Study	**Languages**					**Language distance**
	L1	**L2**	**L3**	**L4**	**L5**	
Pouratian et al., 2000	1: Spanish	1: English	-	-	-	Not considered
Roux and Trémoulet, 2002	12: French	6: English 2: Spanish 4: Occitan	1: German	1: Mandarin Chinese	-	Post hoc considerations on the role of different writing systems and on the opposition between Romance vs. Slavic vs. Asiatic languages
Lubrano et al., 2004	1: Arabic 1: English	2: French	-	-	-	Post hoc considerations on the role of alphabetic vs. ideographic writing systems
Roux et al., 2004	19: French	8: English 3: Spanish 5: Occitan 2: German 1: Arabic	1: German 1: Russian	1: Mandarin Chinese	-	Not considered
Walker et al., 2004	1: Chinese 3: Spanish 1: Punjabi 1: Turkish 5: English 1: Norwegian 1: Portuguese 1: Korean 1: Russian 1: Tagalog 1: Slovenian	4: Spanish 11: English 1: Tagalog 1: French	1: English	-	-	Not considered

Bello et al., 2006	1: Dutch 1: English 1: French 1: Czech 1: Korean 1: Italian 1: Arabic	2: English 1: French 3: Italian 1: Spanish	2: French 2: Italian 3: English	1: Italian 1: German 1: Spanish 1: Hungarian 1: French	2: German	Not considered
Bilotta et al., 2011	English	Italian	-	-	-	Not considered
Cervenka et al., 2011	Igbo	English	-	-	-	Post hoc considerations about differences between language families and about differences in prosody, syntax and phonology across languages
Borius et al., 2012	4: French 1: Italian 1: Arabic 1: Kinyarwanda	4: English 2: French 1: German	-	-	-	Not considered
Lubrano et al., 2012	German	English	French	-	-	Not considered
Kin et al., 2013	Japanese	English	-	-	-	Not considered
Sierpowska et al., 2013	1: Catalan 1: Spanish	1: Spanish 1: Catalan	-	-	-	Cognate words not included in the intraoperative task
Wang et al., 2013	Chinese	English	-	-	-	Not considered
Gao et al., 2015	11: Mandarin Chinese	11: Cantonese Chinese	-	-	-	Not considered
Gao et al., 2016	6: Chinese	6: English	-	-	-	Not considered
Połczyńska et al., 2016	Swiss German	French	English	German	-	Language similarity (Swiss-German vs. German) was not associated to

						similarity in neural representation
Fernández-Coello et al., 2017	4: Catalan 6: Spanish 3: German	6: Spanish 4: Catalan 2: Basque 1: French	9: English 1: Catalan 2: French 1: Spanish	2: French 1: Galician 1: Russian	1: English	Description of the languages based on the distinction between Romance, Germanic, Slavic and isolate languages
Sierpowska et al., 2018	3: Spanish 4: Catalan	3: Catalan 4: Spanish	-	-	-	Cognate words not included in the intraoperative task
Chan et al., 2019	Tamil	English	Malay	-	-	Post hoc considerations about the diglossic nature of Tamil language
Jain et al., 2019	Hindi	English	-	-	-	Post hoc discussion about possible influence of writing systems (English vs. Hindi) on the RH involvement during intraoperative testing
de Macêdo Filho et al., 2020	Portuguese	English	-	-	-	Not considered
ReFaey et al., 2020	Not specified	Not specified	-	-		Not considered

In the reviewed papers, the issue of language distance was either not considered (13 studies out of 22) or poorly addressed. A possible reason is that it is taken for granted that some language combinations have higher levels of mutual intelligibility than others and that the processing of a given language is influenced by the properties it shares with other languages (Gooskens et al., 2018; Jeong et al, 2007). In 2 studies (Sierpowska et al., 2013; 2018) special attention was paid to the selection of stimuli for the intraoperative task, where a possible confound due to high language similarity was avoided by excluding cognates. In 1 study (Fernández-Coello et al., 2017) languages were classified in different families but authors did not describe whether and how they exploited such information in surgical planning. Five studies (Roux and Trémoulet, 2002; Lubrano et al., 2004; Cervenka et al., 2011; Chan et al., 2019; Jain et al., 2019) reported only post hoc considerations on how across-language variations of different factors may have affected performance. One study (Połczyńska et al., 2016) explicitly investigated if language similarity (Swiss-German and German) was associated to similarity in neural representation and found this not to be the case.

3.2.2 Age of Acquisition

With one exception (Lubrano et al., 2004), all the selected studies reported data about the AoA of all the languages spoken by the patients (see Table 3). Most studies distinguished between early and late acquired languages but operationalized the variable differently; 4 studies only distinguished languages acquired during childhood vs. adulthood (Bilotta et al., 2011; Jain et al., 2019; de Macêdo-Filho et al., 2020; Chan et al., 2019). The remaining studies either reported AoA or distinguished between early-acquired and late acquired multilingualism. In these cases, 7 years and 5 years were the most used cut-offs between early and late AoA.

Tab. 3 Age of Acquisition*

Study	AoA modality of assessment	AoA			
		L2	**L3**	**L4**	**L5**
Pouratian et al., 2000	Patient report	6 years	-	-	-
Roux and Trémoulet, 2002	Qualitative system of classification that collapses AoA, proficiency and frequency of usage	4: before 7 years 8: after 7 years	1: after 7 years	1: after 7 years	-
Lubrano et al., 2004	NA	NA	NA	-	-
Roux et al., 2004	Qualitative system of classification that collapses AoA, proficiency and frequency of usage	NA	NA	NA	-
Walker et al., 2004	Patient report	3: before 5 years 6: 5 years 1: 6 years 1: 8 years 1:10 years 2: 13 years 1: 14 years 1: 26 years 1: 29 years	1: 6 years	-	-
Bello et al., 2006	Patient and family report	NA	NA	NA	NA
Bilotta et al., 2011	Patient report	after 18 years	-	-	-
Cervenka et al., 2011	Patient report	14 years	-	-	-

Borius et al., 2012	Beginning of L2 formal education	3: 11 years 1: 6 years 1: 3 years 1: 4 years 1: 5 years	-	-	-
Lubrano et al., 2012	Beginning of L2 and L3 formal education	10 years	12 years	-	-
Kin et al., 2013	Patient report	25 years	-	-	-
Sierpowska et al., 2013	Patient report	1: 7 years 2: 14 years	-	-	-
Wang et al., 2013	Bilingual history questionnaire	13	-	-	-
Gao et al., 2015	Patient report	< 5 years	-	-	-
Gao et al., 2016	Patient report	6: after 5 years	-	-	-
Połczyńska et al., 2016	Patient report	5 years	15 years	16 years	-
Fernández-Coello et al., 2017	Patient report	11: before 7 years 2: after 7 years	13: after 7 years	3: after 7 years	1: after 7 years
Sierpowska et al., 2018	Patient report	3: before years 4: after 7 years	-	-	-
Chan et al., 2019	Patient report	School age	Adulthood	-	-
Jain et al., 2019	Patient report	Childhood	-	-	-
de Macêdo Filho et al., 2020	Patient report	Adulthood	-	-	-
ReFaey et al., 2020	Patient report	14: after 6 years	-	-	-

*Abbreviations: NA: not available.

The variable was assessed differently across studies. Wang et al. (2013) used a Bilingual History Questionnaire (BHQ, Li et al., 2006). Two studies indicated the age at which patients started receiving formal education in languages other than L1 (Borius et al., 2012; Lubrano et al., 2012). Two studies (Roux and Trémoulet, 2002; Roux et al., 2004) used a qualitative classification of multilingualism where measures of AoA, proficiency and frequency of usage were collapsed into a unique score. The remaining studies (16 out of 22) collected information on AoA through patients' or family reports.
The only study (Fernàndez-Coello et al., 2017) that focused specifically on how AoA influences the cortical organization of language in multilinguals undergoing awake surgery procedures for glioma resection reported more early-specific than late-specific cortical language sites, irrespective of the location of the stimulated area.

3.2.3 Proficiency

In our sample, 3 studies (Bilotta et al., 2011; de Macêdo Filho et al., 2020; Lubrano et al., 2004) did not report any information about how proficiency was assessed.
Two studies (Jain et al., 2019; Sierpowska et al., 2013) chose self-ratings on Likert-like scales to obtain information on language proficiency. In 1 case (Sierpowska et al., 2013) proficiency was evaluated also from a receptive point of view through the judgement provided by a certified translator.
Two studies (Roux and Trémoulet, 2002; Roux et al., 2004) used a qualitative measure of linguistic performance classification which collapsed AoA, proficiency and frequency of usage. In 2 studies (Gao et al., 2016; Wang et al., 2013) the proficiency in L2 was assessed by using the level achieved in the formal education of L2. Two studies (Fernández-Coello et al., 2017; Walker et al., 2004) used the scores obtained in naming tasks, while 2 (Bello et al., 2006; Lubrano et al., 2012) used the results of formal language assessment as indexes of proficiency in the different languages. The remaining 9 studies used patient self-reports as the only indicator of proficiency in all the languages.

Tab. 4 Language Proficiency*

Study	Proficiency modality of assessment	Proficiency/Amount of use/Context of use				
		L1	**L2**	**L3**	**L4**	**L5**
Pouratian et al., 2000	Patient report	NA/ 15 times per month/ family and work	NA/ daily from 25 years/ family and work	-	-	-
Roux and Trémoulet, 2002	Qualitative system of classification that collapses AoA, proficiency and frequency of usage	12: high proficiency/ spoken daily/ NA	7: high proficiency/ spoken daily/ NA 5: low proficiency/ not spoken every day/ NA	1: low proficiency/ not spoken every day/ NA	1: low proficiency/ not spoken every day/ NA	-
Lubrano et al., 2004	NA	high proficiency/ NA/ NA	high proficiency/ NA/ NA	-	-	-
Roux et al., 2004	Qualitative system of classification that collapses AoA, proficiency and frequency of usage	NA	NA	NA	NA	-
Walker et al., 2004	% of correct responses in a 64 item object naming task	> 85% / NA/ NA	> 85% / NA/ NA	> 85% / NA/ NA	-	-
Bello et al., 2006	Formal testing	score > 80% in all the tests/ NA / NA	score > 80% in all the tests/ NA / NA	score > 80% in all the tests/ NA / NA	score > 80% in all the tests/ NA / NA	score > 80% in all the tests/ NA / NA
Bilotta et al., 2011	NA	NA	NA	-	-	-

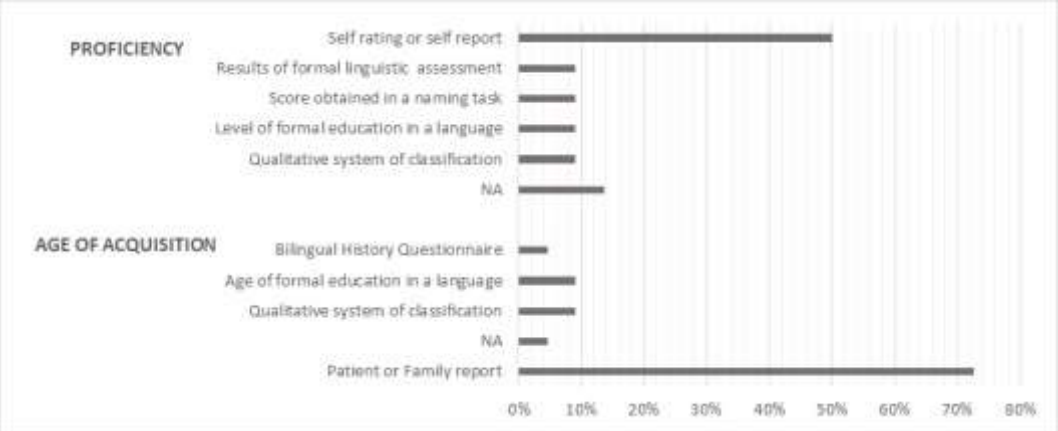
Cervenka et al., 2011	Patient report	NA/ NA/ family life	NA/ NA/ family life	-	-	-
Borius et al., 2012	Patient report	highly proficiency/ NA/ translation activity on a daily base/ work activity	highly proficiency: fluent in their L2 for at least 14 years/ translation activity on a daily base/ work activity	-	-	-
Lubrano et al., 2012	Formal linguistic testing and patient report	highly proficiency/ only with a few friends/ family life	NA / not used in the past 13 years / NA	highly proficient / daily / work and family life	-	-
Kin et al., 2013	Patient report	NA / daily spoken / NA	NA / daily spoken / NA	-	-	-
Sierpowska et al., 2013	Self-rated skills in comprehension, reading, speaking, and writing on a 4-point scale Language use assessed on a 7-point scale	1:4/ predominant use/ NA 2: 4/ predominant use/ NA	1: 3.5/ less frequently used/ NA 2:4/ less frequently used/ NA	-	-	-
Wang et al., 2013	National College English Test for L2; Self-rating of L2 reading, writing, speaking and listening skills	highly proficiency/ NA / NA	highly proficiency/ NA / NA	highly proficient/ NA / NA	-	-
Gao et al., 2015	Patient report	highly proficiency/ NA / NA	highly proficiency/ NA / NA	-	-	-

Gao et al., 2016	National College English Test for English as L2,	high proficiency/ daily use/ work and family life	Level 6 in the NCET but not proficiency as L1/ frequently/ work and study	-	-	-
Połczyńska et al., 2016	Patient report	high proficiency/ frequently used/ family life	high proficiency/ frequently used/ family life	high proficient/ frequently used/ work and family life	high proficiency	-
Fernández-Coello et al., 2017	Score at a modified version of the Boston Naming Test Patient report	high proficiency/ routinely used / NA	high proficiency/ routinely used/ NA	high proficient/ routinely used/ NA	high proficient/ routinely used/ NA	high proficient/ routinely used/ NA
Sierpowska et al., 2018	Self-reported measures	high proficiency/ NA/ NA	high proficiency/ NA/ NA	-	-	-
Chan et al., 2019	Patient report	NA/ NA/ family life	High proficiency/ daily basis/ spoken with other none Tamil-speaking individuals	NA/ NA/ work life	-	-
Jain et al., 2019	Self-rating on a 10 points scale	8-9/10	4/10	-	-	-
de Macêdo Filho et al., 2020	NA	NA	NA	-	-	-
ReFaey et al., 2020	Patient self-report (speaker's point of view) Certified translator evaluation (listener's point of view)	NA	NA	-	-	-

*Abbreviations: NA: not available.

Across the selected studies, additional information was occasionally provided about the amount of use/exposure and the context of use of the languages spoken by the patients. However, only qualitative information was provided, in the absence of objective measures. All these results are reported in Table 4. It is worth noting that only in 1 case (Lubrano et al., 2012) information on proficiency, context and amount of language use was considered in surgical planning, in order to decide which languages should be tested intraoperatively.

Fig. 3 Methods used to assess proficiency and age of acquisition.

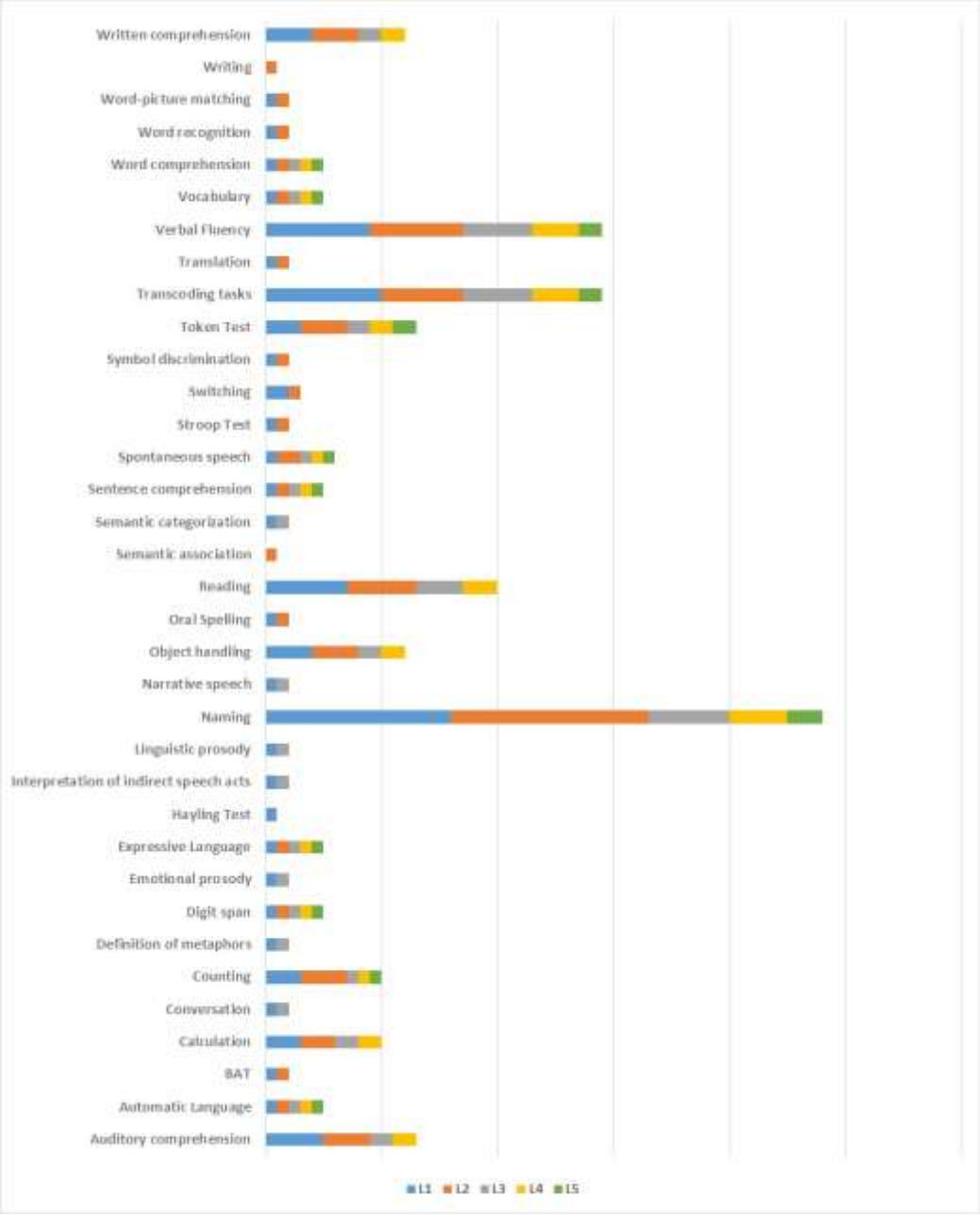


3.2.4 Preoperative language assessment

Of the studies considered in this paper, 4 did not describe the procedures used for language assessment (Bilotta et al., 2011; de Macêdo Filho et al., 2020; Wang et al., 2013; ReFaey et al., 2020). In 1 case (Pouratian et al., 2000) the authors reported that extensive testing was performed in all the languages of the patient but did not describe it. Six studies out of 22 directly compared performance accuracy in the languages spoken by the patient (Bello et al., 2006; Borius et al., 2012; Fernández-Coello et al., 2017; Lubrano et al., 2004; Roux and Trémoulet, 2002; Roux et al., 2004). In these studies, a variety of standardized tests was administered in all the relevant languages. When this was not feasible, ad hoc translations of the materials were used. Walker et al. (2004) used only a naming task. Połczyńska et al. (2016) assessed only one of the languages used most frequently by the patient (L3) via a composite test battery; for L1, L2 and L4 only a naming test was used. In 2 studies (Kin et al., 2013; Sierpowska et al., 2018) L1 was tested in a variety of tasks, while other languages were either not assessed at all (Kin et al., 2013), or were assessed only through the tasks that were going to be used intraoperatively (Sierpowska et al., 2018). In 2 studies (Cervenka et al., 2011; Sierpowska et al., 2013) authors only assessed the language for which standardized tests were available. In 1 of these studies (Cervenka et al., 2011) L1 was not assessed at all, while in the other (Sierpowska et al., 2013) it was assessed only through a picture naming task. Gao et al. (2015) tested word counting (from 1 to 100), reading aloud and naming in all the languages, while Gao et al. (2016) only tested word counting (from 1 to 100) and naming. Jain and colleagues (2019) administered the BAT and a naming task in the languages they studied. Chan et al. (2019) tested L2 by means of counting, naming and a semantic association task,

and L1 and L2 only through a naming task that was planned to be used intraoperatively. Language assessment procedures are summarized in Figure 4 and Table 5.

Fig. 4 Tests used in preoperative language assessment in each language



Tab. 5 Language assessment and Intraoperative tasks*

Study	Language assessment					Intraoperative Task
	L1	**L2**	**L3**	**L4**	**L5**	
Pouratian et al., 2000	Extensive language testing reported but NA	Extensive language testing reported but NA	-	-	-	Naming objects only in L2 during DES + 8 trials in L1 all languages during optical imaging
Roux and Trémoulet, 2002	Written and oral comprehension Naming Verbal fluency Reading Calculation Dictation Repetition Written transcription Object handling	Written and oral comprehension Naming Verbal fluency Reading Calculation Dictation Repetition Written transcription Object handling	Written and oral comprehension Naming Verbal fluency Reading Calculation Dictation Repetition Written transcription Object handling	Written and oral comprehension Naming Verbal fluency Reading Calculation Dictation Repetition Written transcription Object handling	-	Counting, all languages Naming objects (This is a...), all languages Reading (sentences), all languages
Lubrano et al., 2004	Written and oral comprehension Naming Verbal fluency Reading Dictation Repetition Written transcription Calculation Object handling	Written and oral comprehension Naming Verbal fluency Reading Dictation Repetition Written transcription Calculation Object handling	-	-	-	Naming (This is a...). all languages Reading (sentences) all languages Writing (dictated text), all languages
Roux et al., 2004	Written and oral comprehension Naming	Written and oral comprehension Naming	Written and oral comprehension Naming	Written and oral comprehension Naming	-	Naming 30 objects (This is a...), all languages

	Verbal fluency Reading Dictation Repetition Written transcription Calculation Object handling	Verbal fluency Reading Dictation Repetition Written transcription Calculation Object handling	Verbal fluency Reading Dictation Repetition Written transcription Calculation Object handling	Verbal fluency Reading Dictation Repetition Written transcription Calculation Object handling		Reading (sentences, 30 items), all languages
Walker et al., 2004	Naming	Naming	Naming	-	-	Naming objects (single words), all languages
Bello et al., 2006	Spontaneous speech Verbal fluency Naming (famous faces, objects, actions) Word comprehension Sentence comprehension Transcoding tasks Token test Digit span Counting	Spontaneous speech Verbal fluency Naming (famous faces, objects, actions) Word comprehension Sentence comprehension Transcoding tasks Token test Digit span Counting	Spontaneous speech Verbal fluency Naming (famous faces, objects, actions) Word comprehension Sentence comprehension Transcoding tasks Token test Digit span Counting	Spontaneous speech Verbal fluency Naming (famous faces, objects, actions) Word comprehension Sentence comprehension Transcoding tasks Token test Digit span Counting	Spontaneous speech Verbal fluency Naming (famous faces, objects, actions) Word comprehension Sentence comprehension Transcoding tasks Token test Digit span Counting	Naming objects, actions and famous people (30 items), all languages
Bilotta et al., 2011	NA	NA	-	-	-	Counting, all languages Naming objects, actions and famous people (30 items), all languages
Cervenka et al., 2011	NA	Verbal fluency Spontaneous Speech Writing Token Test	-	-	-	Naming objects (40 item with EMS; 85 items ECoG), all languages

Borius et al., 2012	Written and oral comprehension Naming Verbal fluency Reading (words, non-words, sentences) Calculation Dictation Repetition Written transcription Object handling Translation (from L2 to L1) Comprehension of oral spelling Word recognition Word-picture matching Symbol discrimination	Written and oral comprehension Naming Verbal fluency Reading (words, non-words, sentences) Calculation Dictation Repetition Written transcription Object handling Translation (from L2 to L1) Comprehension of oral spelling Word recognition Word-picture matching Symbol discrimination	-	-	-	Naming objects, all languages Reading (sentences), all languages Translating form L2 to L1
Lubrano et al., 2012	Naming (nouns, verbs) Repetition (words, sentences) Narrative speech Definition of metaphors Semantic categories (judgement, justification) Linguistic prosody (comprehension, repetition) Emotional prosody (comprehension, repetition) Indirect speech acts (interpretation)	NA	Naming (nouns, verbs) Repetition (words, sentences) Narrative speech Definition of metaphors Semantic categories (judgement, justification) Linguistic prosody (comprehension, repetition) Emotional prosody (comprehension, repetition) Indirect speech acts (interpretation)	-	-	Naming, L1 and L3

	Verbal fluency Conversation		Verbal fluency Conversation			
Kin et al., 2013	Auditory comprehension Naming Sentence repetition Reading aloud short sentences Reading for comprehension Dictation of Kana letters Dictation of short sentences	NA	-	-	-	Naming, all languages Auditory responsive-naming task, all languages
Sierpowska et al., 2013	*Only Spanish language was tested:* Naming Verbal fluency Token Test Non-words repetition Bilingual Switching Questionnaire	*Only Spanish language was tested:* Naming Verbal fluency Token Test Non-words repetition Bilingual Switching Questionnaire	-	-	-	Naming, all languages Language switching naming (40 items)
Wang et al., 2013	NA	NA	-	-	-	Naming, all languages Language switching task a: Naming objects, a cue indicated the language to be used Language switching task b: a cue indicated if the colour or the shape of objects had to be named
Gao et al., 2015	Counting from 1 to 100 Naming Word reading	Counting from 1 to 100 Naming Word reading	-	-	-	Counting (from 1 to 10), all the languages Naming (This is a ...), all languages Reading (words), all languages

Gao et al., 2016	Counting from 1 to 100 Naming	Counting from 1 to 100 Naming	-	-	-	Counting, all languages; Naming, all languages; Word reading, all languages
Połczyńska et al., 2016	Naming	Naming	Visual naming Auditory naming Verbal fluency Repetition Reading (word and non-word)	Naming	-	Naming objects, all languages
Fernández-Coello et al., 2017	Expressive language Naming Token Test (brief version) Automatic language Verbal fluency Reading task Non-word repetition Vocabulary	Expressive language Naming Token Test (brief version) Automatic language Verbal fluency Reading task Non-word repetition Vocabulary	Expressive language Naming Token Test (brief version) Automatic language Verbal fluency Reading task Non-word repetition Vocabulary	Expressive language Naming Token Test (brief version) Automatic language Verbal fluency Reading task Non-word repetition Vocabulary	Expressive language Naming Token Test (brief version) Automatic language Verbal Fluency Reading task Non-word repetition Vocabulary	Naming, all languages
Sierpowska et al., 2018	Naming Comprehension Non-words repetition Stroop test Verbal fluency The Hayling test Bilingual Switching Questionnaire	Naming Stroop test	-	-	-	Naming, all languages Language switching naming
Chan et al., 2019	Naming	Counting Naming	Naming	-	-	Counting, all languages Naming, all languages

		Semantic Association				Pyramids and Palm Trees test, all languages
Jain et al., 2019	Bilingual Aphasia Test Naming	Bilingual Aphasia Test Naming	-	-	-	Counting, all languages Naming, all languages Reading the mind in the Eyes Test (attempted but not completed)
de Macêdo Filho et al., 2020	NA	NA	-	-	-	Naming, all languages Pyramids and palm trees test, in L1
ReFaey et al., 2020	NA	NA	-	-	-	Object naming, all languages Non-word repetition, all languages Word comprehension, all languages

*Abbreviations: NA: not available.

In 8 studies out of 22, pre-surgical language mapping methodologies were employed: Walker et al. (2004) used the WADA test to determine language laterality, while 7 studies employed fMRI procedures (Bello et al., 2006; Fernández-Coello et al., 2017; Gao et al., 2016; Połczyńska et al., 2016; Pouratian et al., 2000; ReFaey et al., 2020; Sierpowska et al., 2018).

3.3 General neuropsychological assessment

In our sample, 3 studies (Bilotta et al., 2011; Pouratian et al., 2000; Walker et al., 2004) did not report details about the general neuropsychological assessment. The remaining studies provided very heterogeneous selections of tests in both pre and postoperative assessments (see Table 6).

Tab. 6 Preoperative and postoperative neuropsychological assessment and preoperative language mapping*

Study	Language used for neuropsychological assessment	Preoperative neuropsychological assessment	Postoperative neuropsychological assessment	Preoperative language mapping
Pouratian et al., 2000	NA	NA	NA	fMRI in L2
Roux and Trémoulet, 2002	NA	EHI	Language assessment	NA
Lubrano et al., 2004	NA	EHI	Language assessment	NA
Roux et al., 2004	NA	EHI	Language assessment	NA
Walker et al., 2004	NA	NA	NA	WADA test for lateralization in 2 patients
Bello et al., 2006	NA	EHI Ideomotor apraxia Face apraxia Digit span	NA	fMRI in some cases
Bilotta et al., 2011	NA	NA	NA	NA
Cervenka et al., 2011	English (L2), language most frequently used and where normative data were available	WAIS-R RAVL test	NA	NA
Borius et al., 2012	NA	NA	Language assessment	NA
Lubrano et al., 2012	NA	EHI Figure Copying (2 intersecting pentagons) Clock drawing	Language assessment	NA
Kin et al., 2013	NA	MMSE FAB	Language assessment (L1)	NA
Sierpowska et al., 2013	Spanish, language where normative measures were available	EHI Digit span	Language assessment Digit span	NA
Wang et al., 2013	NA	KPS	NA	NA

Gao et al., 2015	Mandarin Chinese (L1) and Cantonese Chinese, (L2)	EHI MOCA	MOCA Language assessment	NA
Gao et al., 2016	NA	EHI MMSE	Language assessment	fMRI
Połczyńska et al., 2016	English (L3), language most frequently used and where normative data were available	Attention task Working memory task Verbal executive ability	NA	fMRI
Fernández-Coello et al., 2017	NA	EHI Digit Span	Digit span Language assessment	fMRI
Sierpowska et al., 2018	Catalan, Spanish (L1)	EHI Stroop test Digit span	Stroop test Digit span Language assessment	fMRI
Chan et al., 2019	English (L2), language most frequently used and where normative data were available	MOCA List learning Story memory Figure copy Line orientation Digit span Coding Figure recall Spatial span Block design Stroop test Colour trails test Praxis test Interlocking fingers	MOCA List learning Story memory Figure copy Line orientation Digit span Coding Figure recall Spatial span Block design Stroop test Colour trails test Praxis test Interlocking fingers	NA
Jain et al., 2019	Hindi (L1); English (L2)	MOCA Verbal new learning immediate and delayed recall RME test	MOCA more comprehensive neuropsychological testing (NA)	NA
de Macêdo Filho et al., 2020	NA	NA	Complete neurologic examination and linguistic neurocognitive assessment (tests NA)	NA
ReFaey et al., 2020	NA	KPS	KPS	fMRI

* Abbreviations: NA = Not Available; EHI = Edinburgh Handedness Inventory; WAIS-R = Wechsler Adults Intelligence Scale – Revised; RAVL = Rey Auditory Verbal Learning; MMSE = Mini Mental State Examination; FAB = Frontal Assessment Battery; KPS = Karnofsky Performance Scale; MOCA = Montreal Cognitive Assessment; RME = Reading the Mind in the Eyes; fMRI = Functional Magnetic Resonance Imaging.

Seven studies provided details on pre and postoperative neuropsychological assessments (Chan et al., 2019; Gao et al., 2015; Fernández-Coello et al., 2017; Jain et al., 2019; ReFaey et al., 2020; Sierpowska et al., 2013; 2018). Four studies did not report any information on postoperative assessments (Bello et al., 2006; Cervenka et al., 2011; Połczyńska et al., 2016; Wang et al., 2013). In 7 studies the postoperative assessment was restricted to language (Borius et al., 2012; Gao et al., 2016; Roux and Trémoulet, 2002; Lubrano et al., 2004; 2012; Kin et al., 2013; Roux et al., 2004). In 1 study (de Macêdo Filho et al., 2020) a complete neurologic examination and the language assessment were performed only after surgery but no information was provided.

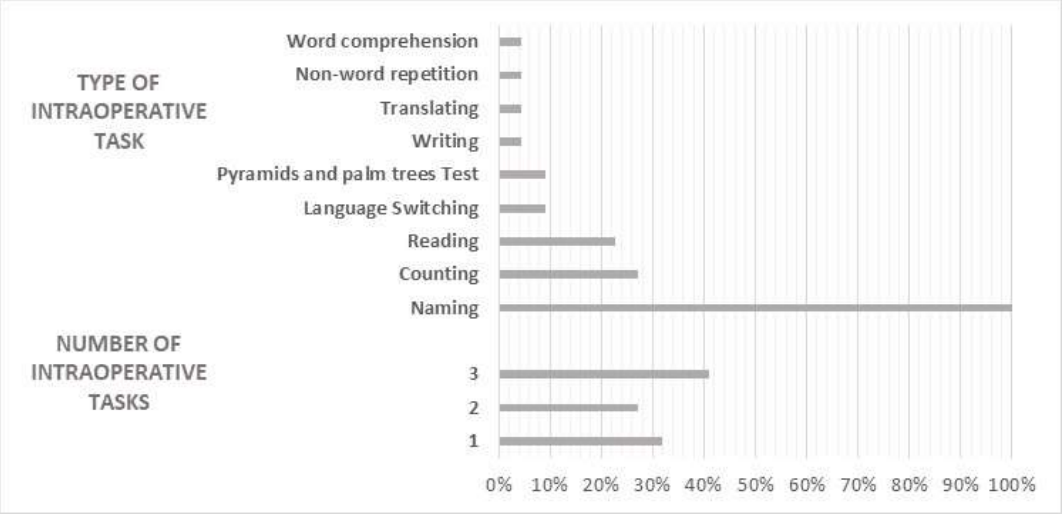
The procedures adopted for preoperative assessment in the reviewed papers can be thus summarized. Two studies (Wang et al., 2013; ReFaey et al., 2020) reported only the Karnofsky Performance Scale (KPS, Karnofsky and Burchenal, 1949). Three studies (Lubrano et al., 2004; Roux and Trémoulet, 2002; Roux et al., 2004) reported the Edinburgh Handedness Inventory (EHI, Oldfield, 1971). Seven studies used the EHI and additional tests for apraxia, working memory and global screening scales (Bello et al., 2006; Fernández-Coello et al., 2017; Gao et al., 2015; 2016; Lubrano et al., 2012; Sierpowska et al., 2013; 2018). Three studies provided global screening scales and a few additional tests (Cervenka et al., 2011; Jain et al., 2019; Kin et al., 2013). Połczyńska et al. (2016) assessed attention, working memory, and verbal executive abilities but did not report the employed tests. Chan and coll. (2019) administered a composite battery for neuropsychological assessment.

Seven studies out of 17 provided additional information about the language selected for neuropsychological assessment: Sierpowska et al., (2018) performed neuropsychological assessment in L1; Gao et al. (2015) and Jain et al. (2019) in both L1 and L2; Chan et al. (2019), Cervenka et al. (2011) and Połczyńska et al. (2016) used the language spoken most frequently by their patients and for which standardized tests were available.

3.4 Intraoperative tasks

A variety of tasks and of task combinations were employed for intraoperative testing in the studies reviewed here: 7 studies used 1 task, 6 used 2 tasks, 9 used 3 tasks (see Table 5 and Figure 5).

Fig. 5 Number and type of intraoperative tasks



A picture naming task was used in all studies. Number and type of stimuli varied (objects, actions, famous faces) as well as the naming context (single word vs. short sentence ("This is a…"). Six studies used a counting task (Bilotta et al., 2011; Chan et al., 2019; Gao et al., 2015; 2016; Jain et al., 2019; Roux and Trémoulet, 2002), 3 used a sentence reading task (Borius et al., 2012; Lubrano et al., 2004; Roux and Trémoulet, 2002); 2 a word reading task (Gao et al., 2015; 2016), 3 a specific language switching task (Sierpowska et al., 2016; 2018; Wang et al., 2013), 2 studies (Chan et al., 2019; de Macêdo Filho et al., 2020) used the Pyramids and Palm Trees Test (PPT, Howard and Patterson, 1992) in order to test the patient's ability to access meaning from words. The following tasks were also employed: writing to dictation, translation form L2 to L1, naming orally described objects, word comprehension, repetition (see Table 5 for details). In addition to linguistic tasks, 1 study (Jain et al., 2019) included a mentalizing test in the intraoperative protocol (The reading the mind in the eyes test (RME, Baron-Cohen et al, 1997); however, the test was only attempted but not concluded by the patient during the surgical session.
None of the selected studies reported on how stimuli were matched across languages, nor provided information on the specialty and linguistic competence of the clinician who conducted the linguistic evaluations. The tasks described in these studies tapped different aspects of the functional architecture of language, but authors did not specify the criterion followed in task selection, except for the studies focusing on voluntary language-switching (Sierpowska et al., 2013; 2018; Wang et al., 2013).

4. Discussion

This paper aimed at describing the state of the art in the perioperative language assessment of multilingual patients undergoing awake surgery for brain tumor. Twenty-two studies, published over the last 30 years, were reviewed. Special attention was devoted to the procedures employed to describe the patients' multilingual profiles for their crucial role in determining the neuroanatomical organization of multiple languages and effects on cognitive functioning (Cargnelutti et al., 2019; Połczyńska and Bookheimer, 2020). Among the linguistic experience-related factors, AoA and proficiency were analyzed. Almost all the reviewed studies provided scores for those variables but assessed them differently. Noteworthy, no strong statement was reported about whether and to what extent AoA and proficiency scores helped planning intraoperative procedures (e.g., selecting languages, tasks, stimuli, stimulation sites) nor if they had an impact on the outcome of surgery. This finding alone shows that information on AoA and proficiency has not been properly used to shed light on the cerebral organization of multiple languages. Such a bias could be neutralized if multilingual patients eligible for awake surgery were systematically questioned to obtain objective measures of their multilingualism. As for multilingualism history, the following data should be collected: AoA of L1 and of other languages; setting in which languages were acquired/learned; primary language used in school education; formal education received in each language; global amount of exposure to each language. Where and how languages are used should be ascertained through questions about context (familiar, social, professional), linguistic profiles of interlocutors (native vs. non-native speakers), modality (spoken, written, formal, informal), language-related media preferences (e.g., television, radio, newspaper, internet), frequency of use of each language in each modality in recent months.

Proficiency should be assessed preferably through subjective and objective ratings along several dimensions: proficiency in different contexts, modalities and linguistic domain, perceived accent in different languages, probability of spontaneous language switching, cross-linguistic flexibility, amount of engagement in translation activity, skills associated with effective communication, family/friends and patient's sense of impairment in the different languages. It is worth to underline here that all these variables related to multilingualism should be operationalized and treated comparably in awake surgery settings, in order to obtain reliable findings that could be additionally supported by formal statistical analyses in cross-linguistic studies. This might significantly improve the understanding of cerebral organization of multiple languages.

A precise and objective description of the patient's multilingual profile should be efficiently used also for the general neuropsychological assessment. So far, 7 studies reviewed in this paper specifically addressed this issue and reported that language used for testing was carefully chosen. Language selection depended on the availability of standardized neuropsychological tools in the language most frequently used by the patient at the moment of surgery. Such an approach should be encouraged as it prevents misinterpretation deriving from patients' unbalanced proficiency or mastery of one language over the others, which may in turn reduce compliance with the evaluation setting, produce inaccurate comprehension of task requirements and, consequently, induce unreliable performances in neuropsychological tests (Bender, 2015; Gasquoine et al., 2007; Rosselli et al., 2002). Obviously, when the linguistic competence of the neuropsychologist is not sufficient to conduct the evaluation in the selected language, the support of (psycho)linguists and interpreters is needed. This is often difficult to afford, but it holds the obvious advantage that it allows collecting reliable information on the cognitive status of the patient.

A final aspect of the general neuropsychological assessment is worth considering. Given that the requirement of well-matched normative data is unlikely to be ever met due to the heterogeneity and variability of multilingual populations, an effective approach would consist in relying less on quantitative information (comparison of the patient's score with that of a normative sample) and more on qualitative information about the patient's performance in various tests.

A further crucial feature addressed in this review is the type of preoperative language assessment to be used for all the languages spoken by multilingual patients. The reviewed papers showed great variability with respect to this dimension but, due to the lack of standardized multilingual tests, they did not prevent the possibility that languages may be accidentally assessed by non-equivalent modalities and at different levels of difficulty. The risk here is to underestimate or overestimate language difficulties in one language over the others, and consequently to miss the specific goal of intraoperative testing. Most studies reviewed in this paper suggest that, in principle, all languages should be assessed across functions (reading, writing, repetition of words and non-words, comprehension and production of words and sentences) and domains (lexicon, semantics, phonology, grammar, morphology, syntax). In those papers, the use of translated materials is common but only few details are provided about the implementation of the tasks and of the lists of stimuli.

Noteworthy, caveats should be considered. Items and tasks selected for language assessment must respect the culture standards of the languages under scrutiny; thus, culturally biased items should be avoided (Luke et al., 2002; Cheung et al., 2006).

When translated from one language into another, test items should also undergo an independent back-translation in order to avoid phenomena of lexical ambiguity or synonymy. Conversely, when translation does not achieve the purpose of obtaining well-matched testing materials across different languages, additional criteria should be respected. Some examples may help clarify this point. The English verb "to knit" can be translated to Italian by using the multi-word expression "lavorare a maglia". Since the two items are not equivalent on a lexical ground, they should be replaced by alternative pairs. In other words, it is not necessary to include the same items in all the languages under scrutiny but, rather, it is recommended that the words used in each language be matched for the main variables that affect linguistic processing (length, phonological complexity, frequency, AoA, imageability, grammatical class, semantic category, syntactic features, morphological structure). This allows a good control on the cross-linguistic difficulty of tasks. Similarly, in comprehension tasks (e.g., word/picture matching or verification), the selected stimuli should be associated with appropriate semantic and phonological foils. Semantic foils usually do not suffer from translation biases, but phonological foils do. For instance, in Italian, "sarta" (seamstress) is a good phonological distractor for "carta" (paper); the same pair does not work when translated to English and should be changed by an equivalent pair (e.g., "boy/toy"). Again, language-specific critical features (e.g.,, presence/absence of case-marking, specific morphological rules, word-order constraints, pro-drop patterns, etc.) might preclude the possibility to build perfectly matched lists of materials. For instance, the sentence "mangio la mela" is not fully equivalent to its English version "I eat the apple". Italian is a pro-drop language where independent clauses may lack an explicit subject/pronoun since it is grammatically inferable by verbal inflection that, in turns, provides information on person and number. In English, an explicit subject is normally needed in sentence structure. Moreover, in Italian, in order to select the appropriate determiner for "mela", speakers must retrieve information about grammatical gender and perform an operation of determiner + noun agreement while English speakers do not. This also holds for naming tasks when a minimal sentential context is required: "This is the boy", noun + determiner (gender) agreement not required, vs. "Questo è il ragazzo", noun + determiner (gender) agreement required. These few examples are a strong reminder that the specific properties of each language under evaluation should be carefully considered so that their distance and similarities are clearly and 'objectively' defined. This is indispensable for a reliable language assessment in multilinguals as shared properties impact their language-specific cerebral organization (Połczyńska and Bookheimer, 2020). Nevertheless, the present review shows that this problem has been almost totally neglected in multilingual awake surgery settings.

Similar considerations hold for materials to be included in the tasks for intraoperative testing. In addition, in this latter case, the issue of how to overcome the problem of language-specific properties intersects other critical concerns. The goal of language testing during awake surgery in multilinguals is to find shared/distinct areas and networks related to language-specific, so as to minimize the likelihood of postoperative (multi)linguistic disorders. On the other hand, it is necessary to find an optimal trade-off between the duration of the intraoperative testing and the neurosurgical procedure (Mandonnet et al., 2020). Thus, the number of languages to be tested and the range of intraoperative linguistic tasks must comply both with the time constraints and with the (multi)linguistic needs of the patient. The patient

should be asked which language is most important to him/her and in which language(s) s/he would like to be tested during surgery. On the other hand, s/he should feel comfortable and not overwhelmed throughout the operation and should be aware of the benefits and risks of testing or not all his/her languages. In the reviewed studies, 20 surgical teams out of 22 tested all languages and agree that the ideal testing should include all the languages or at least all the most relevant spoken by the patient. However, they used different (combinations of) tasks and did not report on how they dealt with the problems linked to direct comparison between languages, language distance and lack of standardized tools.

An accurate analysis of the linguistic behavior of the patient is crucial to optimize intraoperative procedures and, consequently, to evaluate postoperative outcomes. When standardized multilingual instruments are not available, the preparation of sufficiently specific and sensitive patient-tailored intraoperative testing should include the following steps. A picture naming task should be included, since tasks of this type have been extensively employed in awake surgery and meet the main requirements of the stimulation setting: fast presentation, easy scoring, good patient compliance (De Witte and Marien, 2013; Miceli et al., 2012). Nouns (objects) and finite verbs (actions) inserted in a minimal phrasal context ("This is the…."; "He/she/it ….") should be selected as stimuli for each language. This paradigm affords the opportunity to tap semantic processing and lexical retrieval while manipulating and keeping under control the main language-specific features, e.g., morphology (nominal and verbal inflection) and syntax (determiner + noun agreement; subject + verb agreement). A third task should be dedicated either to specific properties of the languages spoken by the patients (e.g., relevant differences in the orthography) or to other language abilities (e.g., language switching or cross-linguistic translation) relevant for the linguistic needs and quality of life of patients (e.g., simultaneous translators, people living in multilingual countries like the Basque Country, Singapore, Switzerland, Italian autonomous provinces). When possible, the materials to be used in the intraoperative assessment of a multilingual patient should be tested on control groups composed of healthy speakers from the same environment (family members, friends, multilingual speakers with similar linguistic profiles) in which reaction times and response accuracy are in principle roughly comparable with those of the patient.

Tab. 7 Recommended perioperative assessment procedures in multilingual awake neurosurgery settings

Experience-related linguistic factors	Variables to be assessed	Perioperative assessment	Recommendations
Multilingual profile	AoA of each language Setting where each language was acquired/learned Primary language used in school education Formal education received in each language Global amount of exposure to each language	**General preoperative assessment**	To perform an exhaustive neuropsychological examination To use standardised tests in the language most frequently used by the patient at the moment of surgery To obtain qualitative information about the patient's performance
Use of each language	Context Modality Language-related media preferences Linguistic profile of interlocutors Frequency of use of each language in each modality in recent months	**Preoperative language assessment**	To match the stimuli used in each language for length, phonological complexity, frequency, AoA, imageability, grammatical class, semantic category, syntactic features, morphological structure Do not include culturally biased stimuli To use appropriate semantic and phonological foils in comprehension tasks To provide clear and objective data about the distance and similarities between the languages spoken by the patient To provide assessment tests for the language-specific properties
Proficiency	Context Modality Domain Perceived accent in each language Probability of spontaneous language switching Cross-linguistic flexibility Amount of engagement in translation activity Skills associated with effective communication in each language Family/friends and patient's sense of impairment in each language	**Intraoperative testing**	To test all languages To use a naming task with nouns (objects) and verbs (actions) inserted in a minimal phrasal context ("*This is the…; He/she/it …*") To use an additional task dedicated to specific properties of the languages spoken by the patient or to language abilities relevant for his/her linguistic needs and quality of life (switching, translation, writing, reading) To test the selected materials and tasks on control groups of healthy speakers from the same linguistic environment of the patient

CONCLUSION

We have conducted this research to organize concepts and resources dedicated to outcome measures since the advent of evidence-based medicine considering all the instrument types and categories in the attempt to make a clear appraisal of the past and current trends. This work indicates that outcome set is untidy and since 2000 the increase attention to the response to treatment is not parallel with fruitful information. There are domains of functioning that are important for the quality of life of persons but that are not traditionally sufficiently documented as cognition, mood, social activities, etc. A frame of reference in achieving such an understanding was neglected to date. As a consequence, the underdeveloped toolkit do not support a comprehensive assessment to recognize the effect of the tumor, of the treatment and the related factors. Taking into account that dedicated PRO is the only novel instrument to date, some questions about the policy adopted are reasonable. Centrality of the patient is not given by an instrument (i.e. PRO) but by the approach to the patient. Moving from a single multidimensional instrument towards the combinations of multiple accurate instruments covering different category and domains, could redirect the research on the basis of the current valid instruments, new criteria for outcome research and modeling.

Unfortunately, in the last 30 years a lot of brain tumor clinical trials used tests or cognitive batteries to assess both neurotoxicity and cognitive status after treatment. To date, these trials exploited instruments not specifically created to assess cognitive functions in brain tumor patients. We exploited information provided by the CC in order to discuss the suitability of these tools for neuropsychological assessment in brain tumors clinical trials and tried to establish to what extent they should be eligible when neurocognitive endpoints are included in clinical trials for brain cancer. This point is challenging since, reasonably, different endpoints could require different approaches for neurocognitive assessment (Platta et al., 2010; Meyers et al., 2012). In general, if the endpoint is on cognitive deficits induced by brain tumors and on the monitoring of cognitive status after treatment, comprehensive assessment procedures devoted to the identification of all the possible deficits should be implemented (Taphoorn & Klein, 2004; Klein et al., 2004). Conversely, when clinical trials endpoints are focused on neurotoxicity, neurocognitive assessment could be limited to the cognitive domains shown to be the most affected by chemotherapy and radiotherapy: global cognitive function, memory, executive functioning, attention and grapho-motor speed (Correa, 2010).

Our findings revealed relevant faults about the suitability of the most commonly used test of cognitive assessment in brain tumor clinical trials concerning both the reliability scores obtained by studies addressing the quality of measurements of single tests and the architecture of existing neurocognitive assessment batteries.

Finally, regarding the assessment of multilingual patients, there is a critical need for a structured, theory-driven and evidence-based principled approach in several clinical settings (neurological, neuropsychological, psychological, neurosurgical, rehabilitative) since the number of people who use more than one language in everyday life is steadily increasing. For multilingual patients with tumors in language areas, awake brain surgery is used ever more often, as it allows maximizing the extent of resection while minimizing the functional risk.

However, this work shows that there is no consensus on the rationale that should underlie the selection of the neuropsychological tests to be included in the preoperative clinical work-up, and of the language paradigms to be used during

language mapping procedures. The patient-tailored approach for perioperative assessment is still, necessarily, the preferred method due to the impossibility to predict all the combinations of languages spoken by multilinguals and to the difficulty in matching language-specific properties. The lack of such criteria may have serious implications and weaken the potential clinical benefit of awake surgery. For example, it could induce biases in deciding whether the outcome of intraoperative stimulation is due to interference with linguistic knowledge shared by all languages or specific for the language tested during stimulation. Moreover, given that neuroanatomical findings are highly inconsistent across studies, the present review highlights that the outcome of the neurosurgical procedure relies on an accurate planning of preoperative and intraoperative testing. Especially, this work illustrates the relevance of an objective and accurate description of both the linguistic profile of multilingual patients and the specific properties of the languages under scrutiny.

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APPENDIX

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