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Neuro-Oncology

Leptomeningeal Spread in Glioblastoma: Diagnostic and Therapeutic Challenges

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Key Words. Glioblastoma • Leptomeningeal spread • Diagnostic • Treatment

Abstract

Background. Glioblastoma (GBM) is the most common and aggressive primary malignant brain tumor. Leptomeningeal spread (LMS) is a severe complication of GBM, raising diagnostic and therapeutic challenges in clinical routine.

Methods. We performed a review of the literature focused on LMS in GBM. MEDLINE and EMBASE databases were queried from 1989 to 2019 for articles describing diagnosis and therapeutic options in GBM LMS, as well as risk factors and pathogenic mechanisms.

Results. We retrieved 155 articles, including retrospective series, case reports, and early phase clinical trials, as well as preclinical studies. These articles confirmed that LMS in GBM remains (a) a diagnostic challenge with cytological proof of LMS obtained in only 35% of cases and (b) a therapeutic challenge with a median overall survival below 2 months with best supportive care alone. For patients faced with suggestive clinical symptoms, whole neuroaxis magnetic resonance imaging and cerebrospinal fluid analysis are both recommended. Liquid biopsies are under investigation and may help prompt a reliable diagnosis. Based on the literature, a multimodal and personalized therapeutic approach of LMS, including surgery, radiotherapy, systemic cytotoxic chemotherapy, and intrathecal chemotherapies, may provide benefits to selected patients. Interestingly, molecular targeted therapies appear promising in case of actionable molecular target and should be considered.

Conclusion. As the prognosis of glioblastoma is improving over time, LMS becomes a more common complication. Our review highlights the need for translational studies and clinical trials dedicated to this challenging condition in order to improve diagnostic and therapeutic strategies. ***The Oncologist*** 2020;25:e1763–e1776

Implications for Practice: This review summarizes the diagnostic tools and applied treatments for leptomeningeal spread, a complication of glioblastoma, as well as their outcomes. The importance of exhaustive molecular testing for molecular targeted therapies is discussed. New diagnostic and therapeutic strategies are outlined, and the need for translational studies and clinical trials dedicated to this challenging condition is highlighted.

Introduction

Glioblastoma (GBM) is the most common and the most aggressive primary malignant brain tumor in adults [1–3]. Its annual incidence is close to 3 per 100,000 persons per year. The treatment of patients newly diagnosed with GBM relies on maximal safe surgical resection followed by radiotherapy with concurrent and adjuvant temozolomide chemotherapy

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[4]. Despite the intensive therapeutic regimen, the prognosis of patients with GBM remains poor with a median overall survival below 18 months and a 5-year survival rate of 5.6% [2].

The propensity of GBM to metastasize to cerebrospinal fluid (CSF) flow stream, inducing GBM leptomeningeal spread (LMS), was first described in 1931 [5]. LMS results from spreading of tumor cells from brain parenchyma to leptomeninges and CSF and is one of the most severe complications of GBM. Other severe complications of GBM include (a) intratumor hemorrhage, (b) status epilepticus, and (c) hydrocephalus. As the prognosis of patients with GBM improves, LMS becomes a more frequent clinical issue in neuro-oncology [1, 6, 7].

Considered initially a rare complication in gliomas [8], the incidence of LMS seems above the estimated rate of 4%, reaching 25% on postmortem neuropathological studies [1, 5, 6, 9, 10]. In cases of LMS, the median overall survival of patients with GBM varies between 2 and 5 months [1, 6, 7, 11, 12]. No risk factor has been clearly demonstrated, although multiple factors have been suggested: (a) age, (b) histologic features, (c) molecular alterations, (d) anatomical tumor site, and (e) therapeutic interventions (e.g., surgical opening of the ventricles or antiangiogenic therapies) [1, 6, 13–16].

Diagnosis of LMS in patients with GBM is challenging. The sensitivity of classic diagnostic investigations (i.e., magnetic resonance imaging [MRI] and cytological CSF analysis) remains low, failing to identify tumor CSF spread most of the time [17, 18].

There is no standard of care treatment for LMS in patients with GBM, although multiple groups have proposed several therapeutic options (e.g., methotrexate, cytarabine, thiotepa, and/or nimustine) with limited efficacy so far [1, 6, 7, 11, 15, 19–21]. Interestingly, treatment with intrathecal chimeric antigen receptor T cells has demonstrated dramatic efficacy in a single patient [22]. The advent of molecular targeted therapies and immunotherapies supports further exploration of the molecular landscape of CSF-circulating GBM cells [23–26].

Diagnostic and therapeutic challenges raised by LMS in patients with GBM will be presented and discussed in the current review.

Materials and Methods

We conducted a survey, from January 1, 1989, to December 31, 2019, in the PubMed database and Scopus-EMBASE using the following combination of terms connected by Boolean operators: (glioma OR high grade glioma OR glioblastoma) AND (meningeal OR leptomeningeal OR leptomeningeal dissemination OR meningeal gliomatosis OR leptomeningeal gliomatosis OR meningeal metastasis OR CSF dissemination) to identify relevant studies related to LMS and glioma.

Our search retrieved 2,043 articles. We excluded (a) duplicate articles, (b) articles in languages other than English and French, and (c) irrelevant articles (i.e., primary meningeal gliomatosis, pediatric tumors). Eighty-five full-text articles were selected. Based on this first selection and linked list of references, additional articles were identified and included in our review. Overall, 155 articles were identified as relevant to the topic. The research algorithm is schematized in Figure 1.

Epidemiology

LMS in high-grade gliomas was reported by several authors (Table 1). In a series of 600 patients with GBM, Vertosick et al. estimated the incidence rate of symptomatic LMS at 2% [1, 6, 7, 10, 11, 27–32]. This incidence rate is probably underestimated because of undiagnosed and asymptomatic cases. Indeed, in autopsy studies, LMS was identified in up to 25% of patients with high-grade glioma [1, 10, 15, 27, 28, 33].

Pathogenesis

Little is known about the pathogenesis of LMS. CSF dissemination seems to follow two patterns: (a) intense CSF seeding with limited tumor progression at initial tumor site or (b) minimal CSF seeding with massive tumor progression at initial location [1, 5, 10, 34].

GBM cells migrate from the initial tumor site along brain vessels to subpial, subarachnoid, and subependymal spaces (Fig. 2A) [5, 10, 35, 36]. The leptomeningeal seeding from cortical areas is preceded by subpial spread as an intermediary step [5, 10, 17, 35]. During this migratory process, GBM cells secrete multiple proteases degrading the extracellular matrix (e.g., MMP-1, -2, -7, -9, -14, and -19 with a critical role of MMP-2 and -9) to create a moving space [37–42] and express multiple adhesion-migration proteins (e.g., glycosylated chondroitin sulfate proteoglycans, fibronectin, fascin, and integrins) [35, 39, 41, 43]. Both molecule classes, working synergistically with cytoskeleton, allow tumor cell migration toward leptomeninges and CSF [5, 18, 28, 30, 35, 39, 41, 43–45].

Furthermore, in a mouse model, prolonged vascular endothelial growth factor (VEGF) inhibition converted tumor cell phenotype to invasive/mesenchymal, leading to tumor invasion through perivascular and subpial spaces [46]. Multiple proteins, including FGF, IGFBP2, MMP-2, Podoplanin, fascin, MET, TGF-B, and IL8, are involved in this process, but further insight is needed [44, 46–50].

The role of the glioma stem cell like cells and their cross talk with microenvironment cells in tumor cell migration remains poorly understood [41, 45]. Translational and preclinical research are shedding light on molecular and cellular mechanisms of this phenomenon and its implication in invasiveness potential of GBM and in LMS development [26, 37, 51–53].

Clinical Presentation

Two thirds of patients with GBM develop LMS within the first 2 years after diagnosis [1, 7, 11, 20, 28, 30, 33, 54]. The median delay from initial diagnosis of GBM to clinicoradiological evidence of LMS varies from 5 to 16.4 months [1, 5–7, 10, 11, 15, 20, 28, 30, 33, 55–58]. This delay is shorter in specific tumor locations, including pineal, spinal, periventricular, and infratentorial [12, 15, 59–66].

Clinical presentation of LMS is heterogeneous, from asymptomatic to severely symptomatic disease [1, 6, 11, 12, 15, 29, 31, 67]. Usually the onset and the worsening of symptoms are progressive; acute presentation is exceptional [5, 12, 27, 36, 68–70].

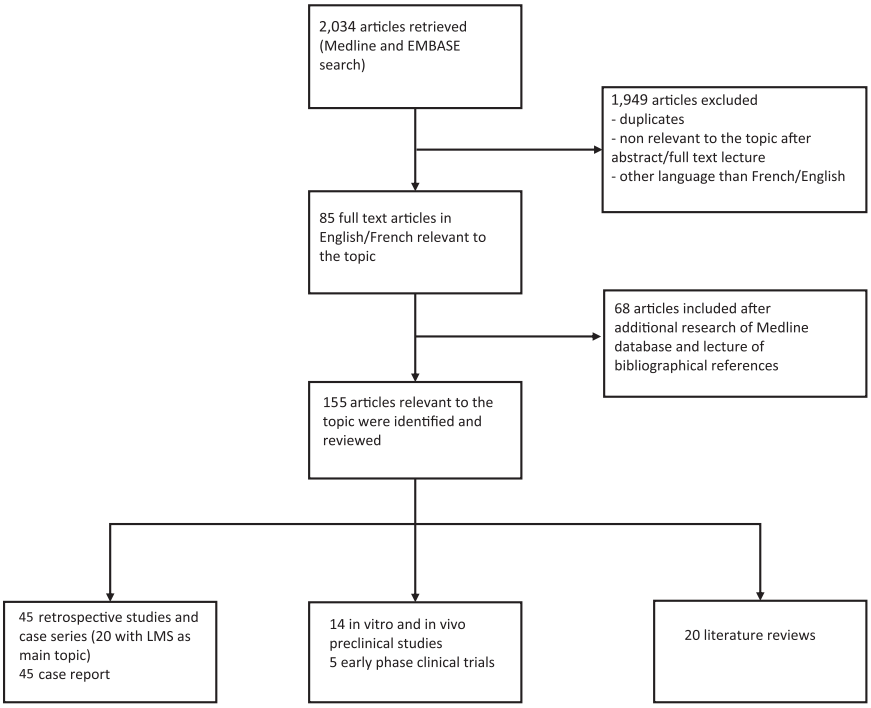

Figure 1. Literature research flow chart showing the selection of publications used in the review.
Abbreviation: LMS, leptomeningeal spread.

Patients with LMS can suffer from cranial nerve palsies, increased intracranial pressure syndrome, hydrocephalus, meningism, and/or focal neurological deficits [1, 7, 15, 20, 33, 71–76]. Seizure frequency does not seem to increase during LMS development [77]. Confusion and generalized cognitive decline are the most common features of LMS in elderly patients with GBM [15, 78, 79]. Although rare, aseptic fever, central neurogenic hyperventilation, and cardiac arrest are reported [5, 11, 12, 70, 80]

Intractable vomiting may be an early symptom of CSF seeding to the fourth ventricle [81]. Cranial nerve deficits, including of the second, third, fourth, sixth, and/or seventh, are observed in 6% of cases [8, 78]. The fourth and seventh cranial nerves are the most frequently involved [78, 82]. Once installed, cranial nerve palsies are often irreversible [5, 27].

Progressive paraplegia [9, 27, 36, 69, 73, 83, 84], sphincter incontinence [1, 11, 36, 55, 80, 84], and spinal ataxia [20, 29, 80] were described when the spinal cord or cauda equina are involved [9, 29, 30, 33, 69, 73, 85, 86]. Isolated symptoms such as paresthesia, ataxia, back pain, and leg or shoulder pain are rare [27, 29, 87, 88]. Radicular pain has been described with various topography: the upper limbs, interscapular [89], thoracic, or lumbar level as well as sciatalgia [1, 5, 11, 15, 20, 33, 55, 90].

Of note, although LMS may manifest as communicating hydrocephalus [33], only 25%–40% of patients with LMS present this complication [75, 91].

Risk Factors

A number of risk factors of LMS have been investigated in patients with GBM. Young age (around 35–45 years), brain location, male gender, long survival after initial diagnosis, and tumor volume seem to be associated with a greater risk of LMS in patients with GBM [1, 6, 27, 78].

The initial tumor location seems to be of importance. Indeed, infratentorial location (in 45%–100% of cases) [1, 5, 10, 13, 62, 63] and GBM of the pineal region [59] are associated with a higher frequency of LMS. The spatial proximity to ventricles and the tumor size were considered as risk factor of LMS, but existing data are conflicting [1, 6, 7, 11]. Indeed, invasive behavior of tumor cells and the environment of the subventricular zone have been pinpointed [1, 14, 15, 30, 85, 92, 93].

Ventricular opening during surgery and repeated surgeries, even more in patients treated with radiotherapy or chemotherapy [5, 89], have been proposed as risk factors of LMS [15, 65, 94, 95]. However, none has been clearly validated [1, 14, 29, 75, 92–97], and prophylactic radiotherapy in these cases does not bring supplementary benefit [98]. Persistence of preoperative leptomeningeal enhancement after initial surgical resection was also correlated with a higher LMS incidence in recurrence [99].

Hydrocephalus with subsequent ependymal fissuring has also been suggested as a potential but not formally validated risk factor [89, 100].

Histological and molecular characteristics of initial tumor were also investigated. Astrocytic phenotype, high Ki67/Mib1 expression index [1, 29, 60, 85, 101, 102], and GFAP loss of expression either at initial diagnosis [10] or at recurrence [28, 29] were correlated with higher risk of LMS. Epithelioid GBM [26, 103, 104] and GBM with a neuronal component or primitive neuroectodermal tumor–like GBM [56, 74] disseminate more frequently to CSF.

Table 1. Leptomeningeal spread in glioblastoma: Retrospective studies and case series

Study	*n*	Mean age, years	Histology	Status of primary at time of LMS presentation	Latency, mean, months	Mean KPS	LMS treatment	Mean OS after LMS diagnosis, months
Mandel et al. 2014 [1]	36	45	GBM		4.9–12	<70 (34%)	Focal RT, surgery, CT, CT + RT	2.2–4.7
Noh et al. 2015 [6]	75	47	GBM	NA	12	60	RT CT-TMZ, OT-GKS, i.t. MTX	3–6.6
Autran et al. 2019 [7]	31	45	20 GBM, 10 LGG	NA	8	<70 (71%)	BCNU-TMZ ± Beva	5.7 combo 0.6 with palliative care
Onda et al. 1989 [10]	14	53	11 GBM, 3 AG	PD	NA	NA	NA	NA after LMS diagnosis
Andersen et al. 2019 [11]	128	58	GBM	NA	11	70	RT, CT, antiangiogenic Targeted Palliative care	3.2 1.6–7.6 1.6 with palliative care
Bae et al. 2011 [15]	7	50	GBM	PD	12	55 40–80	i.t. MTX, palliative care	2.3
Burger et al. 2016 [55]	9	46	4 GBM, 5 AG	PD	17	70	IFXRT + CT (Iri/CCNU) + Beva	3.8
Pradat et al. 1999 [20]	20	51	8 GBM	PD 41%	9.5	65	Spinal RT, i.v. Thio-PCB, Thio-5FU-VP16-CCNU i.t. MTX/ Thio	3 0.2–10.5
Vertosick et al. 1990 [27]	11	39	GBM	PD	14.1	NA	RT, Surgery	2.8
Arita et al. 1994 [28]	22	31	10 GBM, 11 AA	PD 64%	22	NA	RT, CT (i.t./i.v.), RT-CT	6.5
Dardis et al. 2014 [30]	34	50	24 GBM, 10 AA	PD 57%	7.9	70	RT, CT, i.t. (Depocyt/ MTX)	3.7–9.9
Delattre et al. 1989 [33]	5	31	3 GBM, 2 AA	PD 33%	8.6	NA	Spinal RT, CT CBDCA, i.t. IFN	5.3
Chamberlain et al. 2003 [57]	18	38	8 GBM, 10 AA	PD 70%	5.6	60	RT, systemic CT, MTX i.t.	3
Witham et al. 1999 [58]	14	42	9 GBM, 5 AA	NA	7.7	NA	RT, systemic CT (BCNU): Thiotepa i.t.	10.1
Amitendu et al. 2012 [83]	4	53	3 GBM	NA	7.1	NA	RT, surgery	4
Saito et al. 2003 [86]	11	47	5 GBM, 6 AA	PD	12.7	80	RT, CT, MTX i.t.	8
Karaca et al. 2006 [87]	3	37	GBM	NA	10	NA	Spinal RT, Adjuvant CT	4
Roelz et al. 2015 [94]	27	56	22 GBM, 5 AG	PD 78%	12.1	NA	RT, Surgery, Chemotherapy, RT and CT	7.9

Abbreviations: 5FU, fluorouracil; AA, anaplastic astrocytoma; AG, anaplastic glioma; BCNU, carmustine; Beva, bevacizumab; CBDCA, carboplatin 175 mg/m^2 every week for 4 weeks repeated after 2 weeks; CCNU, lomustine; CT, chemotherapy; GBM, glioblastoma; GKS, gamma knife surgery; IFN, interferon; IFXRT, involved-field radiation therapy; Iri, irinotecan; i.t., intrathecal; i.v., intravenous; KPS, Karnofsky performance status; LGG, low grade glioma; LMS, leptomeningeal spread; MTX, methotrexate; NA, not available; OS, overall survival; PCB, procarbazine; PD, progressive disease; RT, radiotherapy; Thio, thiotepa; TMZ, temozolomide; VP16, etoposide.

Some molecular alterations have been also suggested as risk factors of LMS [85]. Gain of 1p36 [105], *PTEN* mutation [102, 106], and *PIK3CA* mutations [107] seem to predispose to meningeal seeding [102, 105, 106]. O6-methylguanine-DNA methyltransferase promoter methylation was also proposed as a risk factor by isolated studies [65, 108] The suspected mechanisms is increased survival in patients with *MGMT* promoter methylation GBM, giving time for tumor cells to reach CSF [65]. This was not confirmed by larger studies [11, 109], and to date, no molecular signature has been validated as risk factor of LMS in high-grade glioma.

Antiangiogenic therapies (VEGF and COX2 inhibitors) have been suggested as promoters of distant recurrence including LMS [44, 48], but available data are conflicting. Further studies are needed [1, 49, 50, 110].

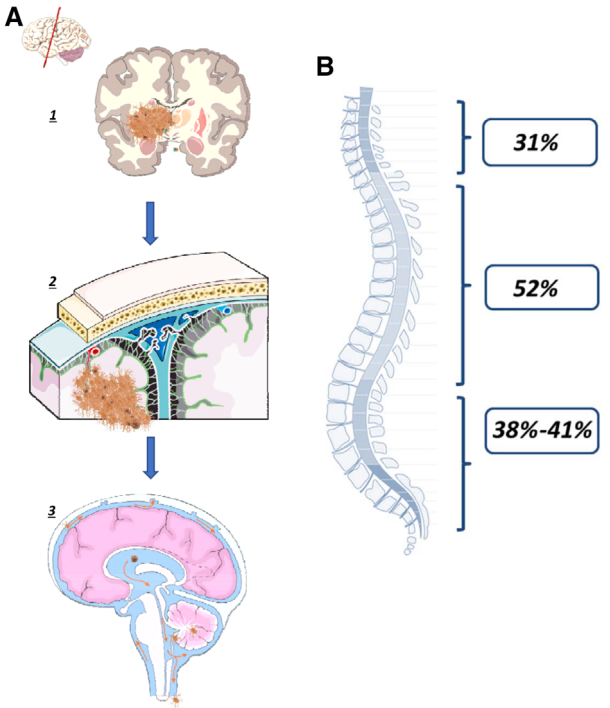

Figure 2. Leptomeningeal spread (LMS) in glioblastoma: routes of migration and spatial distribution of spinal LMS. **(A):** Routes of migration of glioblastoma cells from initial tumor site to meningeal spaces. **(1, 2):** Migration of glioblastoma (GBM) cells from the initial tumor site along brain vessels to subpial and subarachnoid spaces. **(3):** GBM cells circulating via the cerebrospinal fluid. **(B):** Distribution of leptomeningeal and spinal dissemination of intracranial glioblastoma.

Diagnostic Approach

Imaging

Currently, the standard examination for LMS diagnosis is contrast MRI with a sensitivity reported between 90% and 100% for brain [1, 6, 11, 99, 111–114] and between 56% and 95% for spinal LMS in symptomatic patients [1, 6, 11, 114]. Radiological screening of the neuraxis is required in patients with GBM and suspected LMS symptoms [31, 71, 111].

However, the benefit of neuraxis screening for patients with GBM without LMS symptoms remains unclear. This could be considered because the presentation can be asymptomatic and LMS can occur with stable disease at initial tumor site, particularly in subgroups at high risk of LMS [1, 29, 56, 59, 63, 103, 111]. Exceptional cases of asymptomatic LMS-like leptomeningeal enhancement on MRI were reported in the setting of radio-induced pseudoprogression [115].

Typically, LMS appears on MRI as linear and/or nodular foci with high signal intensity on T2 weighted images, low signal intensity on T1 weighted images, and enhanced after gadolinium injection [111]. An MRI LMS pattern was proposed using enhancement characteristics: (a) nodular, type Ia (Fig. 3); (b) diffuse, type Ib (Fig. 4) in the subarachnoid space [18, 34]; and (c) subependymal dissemination, type II (Figs. 3, 5) is also described regardless CSF cytology status [34]. Mixed pattern is also possible (Fig. 5) [1, 34]. Distribution of LMS varies, commonly involving the anterior parts of brain stem and cranial nerves [101]. Still, the expanded use of antiangiogenic agents seems to modify this pattern making it more difficult to distinguish, in these cases a potential interest of contrast-enhanced fluid-attenuated inversion-recovery sequences can be discussed [34, 55].

In intracranial LMS, brain MRI can show multiple aspects: (a) nodular enhancement, 38% (subarachnoid or ventricular; Fig. 4) and (b) pial enhancement, 47% (focal or diffuse) [1, 11, 34]. Nerve roots enhancement can be seen in some cases (57%) as well as cranial nerve infiltration (11%–19%) [1, 34, 78]. Exceptional presentation mimicking chronic subdural hematoma or empyema has been reported [116, 117].

Spinal LMS has been reported to be more frequently in lower thoracic, upper lumbar (most often posterior) [36, 101], lumbosacral regions, cauda equina, and dural sac [36]. Thirty-one percent of lesions are described on the cervical level, 52% on the thoracic level, and 41% at the lumbar level (Fig. 2B) [1, 34, 101, 111]. Cauda equina and conus medullaris were involved in up to 38% of cases [1, 111].

Intraoperative detection of LMS using 5-aminolevulinic acid was reported as useful in anaplastic astrocytoma (histone K27M mutated) [9], but its benefit is inconsistent [66]. Nuclear imaging detecting hypermetabolic foci using ^{18}F-fluorodeoxyglucose [22, 23] or translocator protein with ^{18}flutriciclamide [118, 119] can be helpful.

CSF Study

CSF analysis is often negative for detection of tumor cells; only 25%–45% are positive after a first assay [1, 11, 30, 65]. Repeated lumbar puncture increases the diagnostic sensitivity to 86% with three consecutive lumbar punctures [65, 71, 78] and to 93% with more than three lumbar punctures [6]. Nevertheless, even in cases of radiologically confirmed LMS, CSF cytological results were positive in only 4%–75% of cases, making an abnormal neuropathological CSF study sufficient but not necessary for diagnosis of LMS in gliomas [1, 6, 11, 28, 65, 85]. Indirect aspects can be observed as high intracranial pressure (>15 cm H_2O), high protein level (>50–100 mg/dL) with or without low glucose, and high lactate with an acellular aspect [15, 85, 120], although a mild pleocytosis with presence of macrophages has been described [94].

On cytological examination, GBM cells were noted most often to be singly dispersed in the CSF (Fig. 2A). The main challenge is their distinction from monocytes (Fig. 6) [18].

The input of liquid biopsies in diagnosis and monitoring of LMS in patients with GBM has been explored with increasing interest over the last years [121–123]. Collecting and analyzing tumor components floating in CSF (i.e., circulating tumor cells [CTCs], cell-free tumor DNA RNAs [circulating tumor RNA, microRNA, and exosomes]) may help noninvasive diagnosis of central nervous system tumors and heighten the sensitivity of LMS detection [121, 122, 124]. CTCs and ctDNA seem to be of clinical interest [125]. In systemic malignancies CSF CTC assay has a reported sensitivity between 81% and 100% and a specificity of 85%–97%. However, for

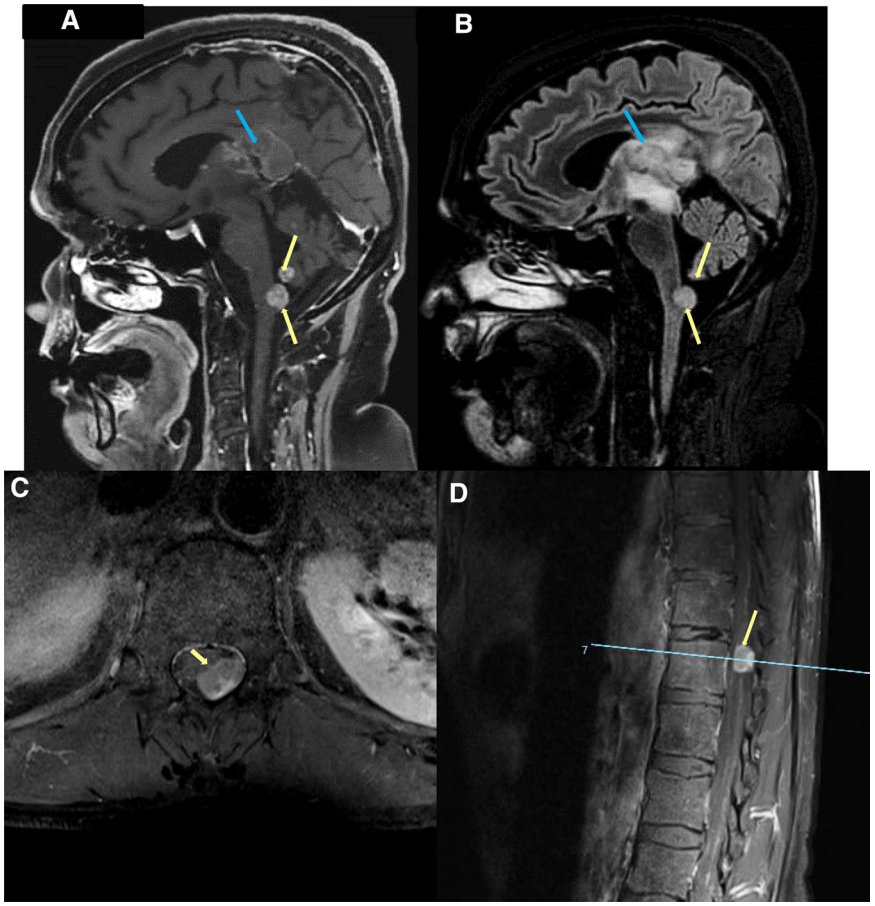

Figure 3. Nodular leptomeningeal spread in glioblastoma. **(A, B):** Subependymal. **(C, D):** Spinal. Blue arrow indicates initial location; yellow arrow indicates nodular leptomeningeal spread.

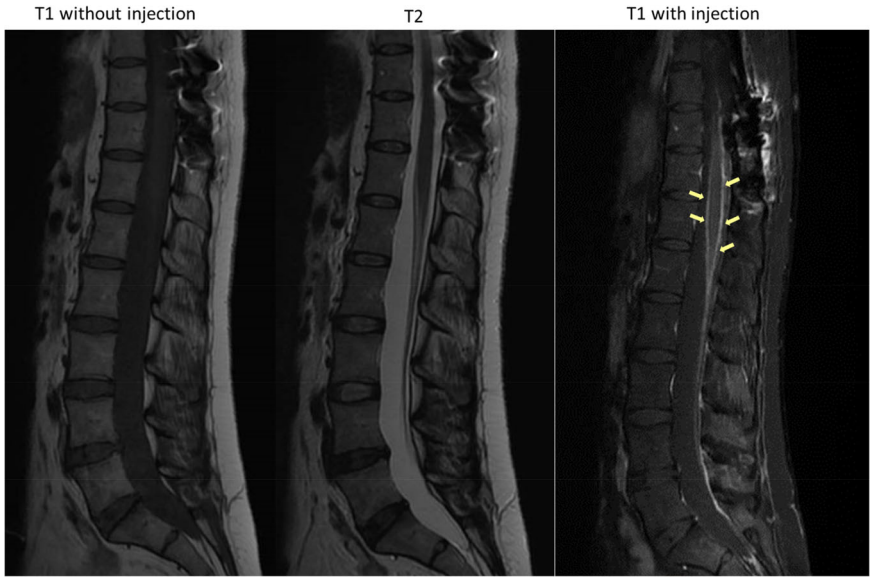

Figure 4. Linear (diffuse) leptomeningeal spread in glioblastoma.

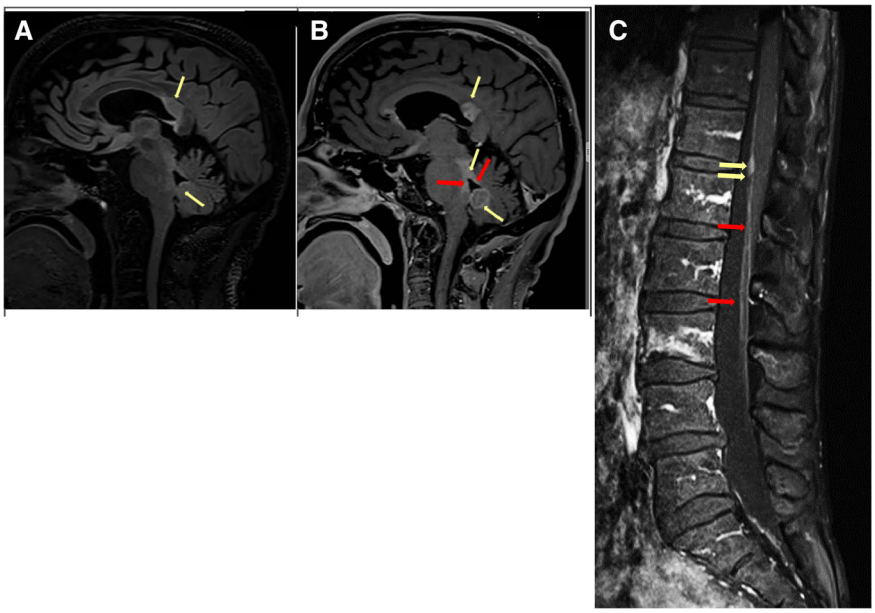

Figure 5. Mixed leptomeningeal spread in glioblastoma. **(A, B):** Subependymal. **(C):** Spinal. Yellow arrows indicate nodular aspects; red arrows indicate linear aspects.

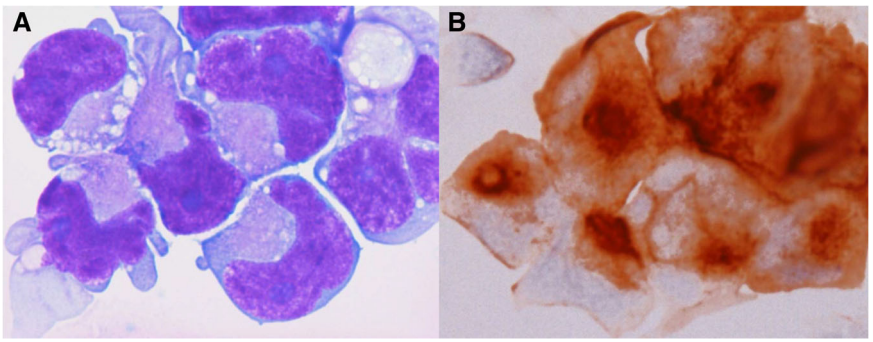

Figure 6. Cytopathological aspects of leptomeningeal spread in glioblastoma. **(A)**: Cerebrospinal fluid obtained from lumbar puncture was studied by cytocentrifugation and May-Grünwald-Giemsa staining. Microscopic examination showed large tumor cells with marked atypia (high nucleocytoplasmic ratio, irregular nuclear borders, prominent nucleoli, basophilic cytoplasm). **(B):** GFAP immunostaining (brown signal) showed cytoplasmic positivity confirming the glial lineage of the tumor cells.

nonepithelial malignancies such as GBM, the appropriate detection technique needs to be established [121, 125].

As for the CSF ctDNA, analysis can be particularly useful for detection of clonal mutations (*BRAF*^{V600E}, *IDH1*, *IDH2*, *TERT* promoter, *ATRX* and *TP53* mutations, *EGFR* amplification) [23, 121, 122, 126]. Of note, although there is a clear correlation between CSF ctDNA and survival, the CSF detection of ctDNA does not systematically mean LMS; its clinical value in this context remains to be established [121].

Therapeutic Approach

In most cases, LMS in patients with glioma is considered an untreatable end stage complication of the disease [34]. There is no consensus or standard of care regarding treatments [81]. Multiple treatment modalities, such as intrathecal chemotherapeutics and radiation therapy, seem to have improved median survival from 4–6 weeks to 3–6 months in high-grade gliomas [127]. Survival of patients with LMS and GBM in studies is reported at 0.2–9.7 months with a mean of 4.7 months [1, 28, 128].

Progression of the disease or treatment-related complications (such as hemorrhage [129] and infections [20, 33] after intrathecal administrated treatment or ventriculoperitoneal shunting [20, 130, 131]) may sometimes contribute to the fatal outcome [82, 129].

Surgery

Because of the multifocal character of LMS, a surgical approach is not suitable [87]. Surgical resection of compressive nodular focal leptomeningeal lesions may provide symptomatic benefit without affecting survival [9, 68, 83]. Another use for surgery in LMS is placement of a ventriculo-peritoneal (VP) shunt in

Table 2. Molecular targeted therapies for leptomeningeal spread in patients with glioblastoma

Study	*n*	Age (years), sex	Histology	Latency, months	Location LMS	Targeted therapy	CSF	PFS (FD)	OS, months
Woo et al. 2019 [23]	1	22, F	Epithelioid: GBM *BRAF*^{V600E}	0	Intracranial and spinal	First line: Dabra + Trame Second line: Nivolumab Spinal RT	Y NGS Y HML 17.1/mb Cell-free DNA	3	7
	1	23, M	Epithelioid: GBM *BRAF*^{V600E}	1	Intracranial NA for spinal	First line: Vemu + Cobi Second line: TMZ CCRT + Vemu + Palbo	Cell-free DNA in CSF *BRAF*^{V600E} 35.7%	1.5 2	7.5
Abadal et al. 2017 [24]	1	34, F	Nonepithelioid GBM *BRAF*^{V600E}	11	Cranial and spinal	Prior to LMS: CCRT and adjuvant TMZ and switch to bevacizumab alone First recurrence with LMS: Vemu	NA	>11	>22
Burger et al. 2017 [25]	1	25, M	Nonepithelioid: *BRAF*^{V600E}	9	Cranial	First line, prior to LMS TMZ CCRT and adjuvant TMZ Second line post LMS development: lomustin Third line: Dabra	NA	>3	NA
Kanemaru et al. 2019 [26]	1	57, M	Epithelioid: GBM *BRAF*^{V600E}	<2	Cranial and spinal	First line: TMZ CCRT Second line: Dabra + Trame + spinal RT	NA	NA	8 mo
Leaver et al. 2016 [76]	1	26, M	Epithelioid GBM *BRAF*^{V600E}	1	Intracranial LMS and extra-axial (lung)	Vemu	NA	1	<2

Abbreviations: CCRT, concomitant chemoradiotherapy; CSF, cerebrospinal fluid; Cobi, cobimetinib; Dabra, dabrafenib; F, female; FD, follow-up duration; GBM, glioblastoma; HML, high mutational load; LMS, leptomeningeal spread; M, male; NA, not available; NGS, next-generation sequencing; OS, overall survival; RT, radiotherapy; Palbo, palbociclib; PFS, progression-free survival; TMZ, temozolomide; Trame, trametinib; Vemu, vemurafenib; Y, yes.

case of hydrocephalus [11, 14, 20, 72, 130, 132]. This seems to be necessary in up 20%–30% of patients [11]. The main complications are shunt occlusion caused by high fibrinogen CSF concentration [131, 133], VP valve malfunction [133], hemorrhage, and meningitis [20, 130, 133] as well as extracranial dissemination in peritoneal cavity [111, 133]. The latter is exceedingly rare, although postmortem diagnosis in asymptomatic patients is possible [111, 133]. In case of shunt occlusion, the use of urokinase can be considered [131], and careful monitoring should be ensured [20, 130].

Radiotherapy

Palliative radiation therapy is the most commonly used treatment modality. Doses between 20 to 40 Gy are usually delivered allowing a good symptomatic control, especially for pain relief [27, 68, 87, 31, 134], compressive symptomatology [83, 87], or intractable vomiting caused by seeding to fourth ventricle [81]. Although focal LMS from systemic cancers is sometimes treated by stereotactic radiosurgery, its use in GBM LMS is rarely reported [1, 6, 60]. The clinical benefit is limited in terms of neurological deficit recovery or survival when administered alone [27, 33, 68, 84, 87, 135], and it improves slightly when added to surgery [27, 68, 69]. Isolated trials of radiolabeled monoclonal antibodies failed to significantly improve the survival of patients with LMS [136].

Pharmacological Treatment

Multiple chemotherapeutic regimens have been investigated: (a) temozolomide alone or combined with carmustine [7] or lomustine [55], (b) thiotepa alone [57, 58] or combined with procarbazine [20, 58, 64], (c) methotrexate [6, 15, 20, 57, 137], (d) cytarabine [19, 57, 128, 138, 139], (e) topotecan or irinotecan [15, 140, 141], and (f) platinum-based agents with or without etoposide [56, 74]. Drug administration was either oral [7], intravenous [1, 6, 11, 15, 64, 142] intrathecal via Ommaya reservoir or lumbar puncture [6, 11, 19, 21, 57, 58, 138, 140, 141] or subcutaneous port [137], or combined [1, 6, 7, 11, 20, 110].

Antiangiogenic drugs (e.g., bevacizumab) alone [1, 44, 117, 142] or combined with cytotoxic agents (e.g., irinotecan) were used with inconsistent clinical benefit [15, 55, 64, 85, 110, 134, 143]. Concurrent radiochemotherapy can be proposed in selected cases, eventually in association with antiangiogenic agents [15, 31, 55, 134].

Targeted therapy can be advised in selected cases (Table 2); for example, the MAPK pathway inhibitors

Table 3. Early phase clinical trials for LMS

Study	*n*	Targeted tumors	Mean age, years	Histology	Prior treatments	LMS treatment	Administration	Response	Toxicity	Mean PFS, days	Mean OS, days
Brown et al. 1996 [136] Phase I	31	Glioma LMS	48	17 GBM (rest: other-grade glioma, pediatric glioma)	RT and CT × 13 No prior treatments × 4	^{131}I labeled 81C6 mAb (anti-tenascin)	i.t. (Ommaya/ Rickham)	5 SD (clinical and radiological) 1 radiological PR 12 PD	41% Gr 3–4 neutropenia and thrombopenia	56	171 (5–393 +)
Gammon et al. 2006 [140] Phase I–II	11	Glioma LMS	57	6 GBM 5 other-grade glioma	CT ± gefitinb	Topotecan Added to systemic CT	i.t.	6 CSF clearance after first dose 2 after second dose 1 after the fifth	Mild meningeal irritation 2/11 Gr 2 rash Gr 1–2 fatigue	NA	NA
Chamberlain et al. 2003 [57] Phase II	18	Glioma LMS	52.5	8 GBM AA	RT and CT	Methotrexate	i.t.	PR 25%	Transient aseptic arachnoiditis Myelosuppression 22%	NA	90 days
Levin et al. 1989 [21] Phase I/II	1	Agnostic		2 GBM	CT	i.t. ACNU Systemic CT	i.t.	1 SD 1 month response followed by recurrence	Radiculopathy Fatigue Nausea, vomiting	30 SD in one patient	NA
Glantz et al. 1999 [139]	59	Agnostic	49	7 primary CNS tumors	NA	Methotrexate vs. Depocyt	i.t.	5/7 response for Depocyt 2/7 MTX	Hematological CNS infections	NA	NA

Abbreviations: × number of patients having received RT; AA, anaplastic astrocytoma; ACNU, nimustine; CNS, central nervous system; CSF, cerebrospinal fluid; CT, chemotherapy; GBM, glioblastoma; Gr, grade; i.t., intrathecal; LMS, leptomeningeal spread; mAb, monoclonal antibody; MTX, methotrexate; NA, Not available; PD, progressive disease; PR, partial response; RT, radiotherapy; SD, stable disease.

(i.e., BRAF and/or MEK inhibitor) can be considered in *BRAF*^{V600E} mutant GBM [23]. Dramatic clinical and radiological response were reported with a survival benefit from 1 to 11 months [23–25, 76]. This motivates to extensive molecular testing [23–25].

As the brain-blood barrier breakdown is low and given the potential resistance mechanism, combined therapy with anti-MEK should be considered from the start as it seems associated with longer survival [23, 26]. Radiotherapy can be discussed to increase survival while balancing the treatment benefit and its toxicity [144, 145]. Because of the rarity of druggable targets in GBM, this option is available for about 6% of patients with LMS GBM [11].

Immunotherapy

Immune checkpoint inhibitors were proposed in cases of high mutational load and with microsatellite instability, alone or in combination with molecular targeted therapies [23, 146]. Nevertheless, there is no clear evidence of their efficacy in LMS [6, 22, 85, 146]. The use of adoptive cell therapy seems to be of interest. The IL13R α2–targeted chimeric antigen receptor (CAR) T cells (with 4-1BB as costimulatory domain and tCD19 as a marker for transduction) had encouraging results with no high-grade therapy-related side effects when used in a LMS of *IDH* wild type, *MGMT* methylated GBM [22, 147]. After repeated intraventricular administration of IL13BBζ CAR T cells, a clinical and radiologic response was sustained up to 7.5 months [22]. Other constructs targeting EGFRvIII and HER2 having different costimulatory domains were explored, but their impact on LMS is not reported [148, 149]. However, the difficulty in finding an adequate target, the immunosuppressive microenvironment, and the consequent toxicities are the limitations of immunotherapy in GBM, including in patients with LMS [147].

Among other approaches, we count gene therapy using engineered mesenchymal stem cells transduced with herpes simplex virus–thymidine kinase gene followed by systemic ganciclovir in a rat experimental leptomeningeal glioma model that seems to have encouraging results [150] and oncolytic viruses tested in transgenic mice inoculated with GBM cells [151]. Intrathecal immunoconjugates have also been advocated [90, 152] as well as intratumoral/intrathecal targeted therapy [153].

The completed clinical trials (Table 3) explored the use of multiple intrathecal chemotherapies including topotecan, methotrexate, and cytarabine in LMS. Although the safety profile was satisfactory, none of them showed significant improvement of survival in patients with LMS [21, 57, 139, 140]. Of note, the ongoing disease-agnostic clinical trials (Table 4) allow inclusion of patients with LMS and GBM. Nonetheless, their severe neurological impairment and their poor prognosis limit their enrollment.

After the literature review, a management algorithm is proposed in Figure 7.

Survival

LMS in primary malignant central nervous system tumor implies more aggressive behavior and a worse prognosis.

Table 4. Ongoing clinical trials for LMS (as identified on clinicaltrials.gov)

Ongoing trial	Phase	Histology	Title	Drug
NCT03719768	Phase I	Agnostic	Avelumab with Radiotherapy in Patients with Leptomeningeal Disease	Avelumab and RT
NCT03091478	Phase II	Agnostic	Pembrolizumab in Leptomeningeal Disease	Pembrolizumab
NCT03423628	Phase I	GBM and GBM LMS	A Study to Assess the Safety and Tolerability of AZD1390 Given with Radiation Therapy in Patients with Brain Cancer	AZD 1390 RT
NCT00445965	Phase II	Agnostic	Iodine I 131 Monoclonal Antibody 3F8 in Treating Patients with Central Nervous System Cancer or Leptomeningeal Cancer	131I-3F8
NCT00089245	Phase I	AGNOSTIC	Radiolabeled Monoclonal Antibody Therapy in Treating Patients with Refractory, Recurrent, or Advanced CNS or Leptomeningeal Cancer	Iodine I 131 MOAB 8H9
NCT02939300	Phase II	agnostic	Ipilimumab and Nivolumab in Leptomeningeal Metastases	Ipilimumab, nivolumab

Abbreviations: CNS, central nervous system; GBM, glioblastoma; LMS, leptomeningeal spread; RT, radiotherapy.

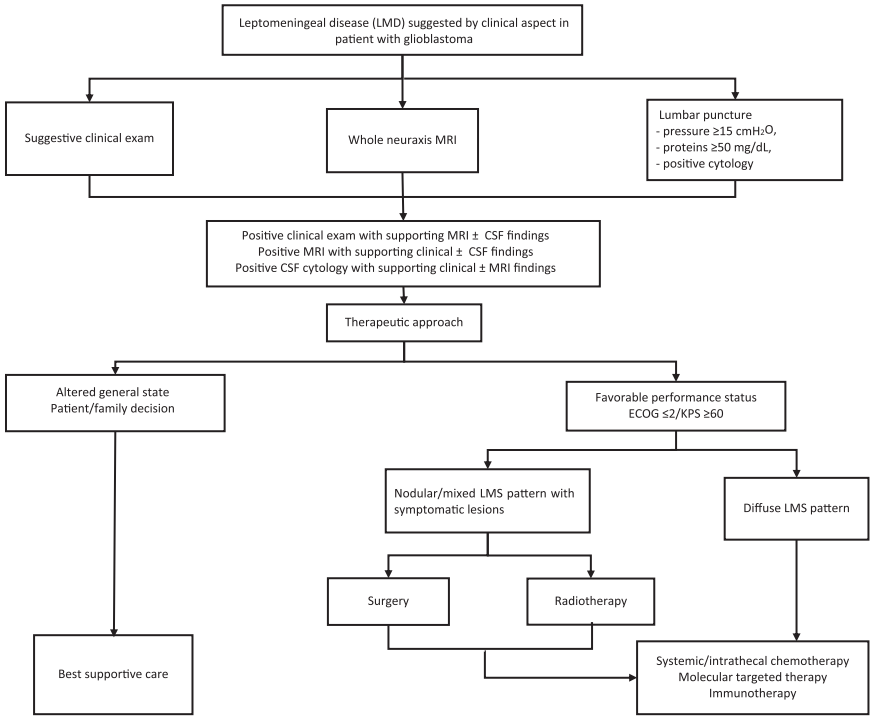

Figure 7. Proposed algorithm for management leptomeningeal spread in glioblastoma.
Abbreviations: CSF, cerebrospinal fluid; ECOG, Eastern Cooperative Oncology Group performance status; KPS, Karnofsky performance status; LMD, leptomeningeal disease; LMS, leptomeningeal spread; MRI, magnetic resonance imaging.

Mean overall survival after diagnosis of treated LMS in high-grade gliomas is 4.94 months (2–9 months) [1, 6, 7, 27, 44, 60, 86, 142]. Exceptional overall survival up to 12 months was reported in cases with nodular LMS for which surgical resection was possible [83].

Among treated patients, the median overall survival was higher regardless chemotherapeutic regimen, but the bias of delivering more intensive treatments in patients in better performance status should be taken into account [1, 6, 7, 11, 58, 73, 138, 140]. Among studies, there seems to be a tendency of better survival for patients having received intrathecal chemotherapy (either Depocyt or thiotepa) with mean survival up to 10 months [20, 30]. A better survival seems associated with antiangiogenic (6–-7.6 months mean survival) [11, 55, 142] and molecular targeted therapy when appropriate [11, 24, 25]. Nevertheless, all these data need to be validated in prospective trials.

Despite significant efforts to standardize the response assessment in LMS, this has proven challenging [154], and it varies according to clinical trial outcome measures. The main criteria for assessing objective response in LMS treatments are the improvement of CSF cytology [139, 140] and radiological decrease of LMS extent [1, 6, 7, 11, 15].

Up to 50% of patients with LMS are treated only by best supportive care, and considering the symptom severity, we

need to underline importance of palliative care guidelines in LMS management [155].

Prognostic Factors

Although the reserved prognosis of LMS is well known, data on the prognostic factors are limited. The interval time from the initial glioma diagnosis to the LMS diagnosis is a potential prognostic factor [7] as well as Karnofsky performance status [30, 82]. Male patients seem to have shorter progression-free survival, although the impact on overall survival does not seem significant [30]. Of note, the extent of LMS does not seem to have a predictive value [1].

Conclusion

Data on LMS in patients with GBM remain scarce although it has become more common in neuro-oncology clinics. The main problems are the lack of reliable early diagnostic tools and consensual standard of care.

Based on our review of the literature, multimodal treatment of LMS, including surgery, radiotherapy, chemotherapy and/or best supportive care, is a suitable approach to be discussed during multidisciplinary brain tumor board.

Interestingly, given the advances in glioma therapeutics, including molecular targeted therapies and immunotherapies, the landscape of LMS treatment is evolving. However, investigation of these innovative treatments remains limited in the setting of LMS and needs further studies. Given the dismal prognosis and increasing incidence of this GBM complication, identification of risk factors, biomarkers, and efficient therapeutic options in large prospective studies and clinical trials is warranted.

Acknowledgments

The research leading to these results has received funding from the Investissements d'avenir program (ANR-10-IAIHU-06) and the Institut Universitaire de Cancérologie (INCA-DGOS Inserm 12560 SiRIC Curamus). SiRIC CURAMUS is financially supported by the French National Cancer Institute, the French Ministry of Solidarity and Health, and Inserm.

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Disclosures

Franck Bielle: Bristol-Myers Squibb (E), Abbvie (RF), Crossject (OI); **Mehdi Touat:** Agios Pharmaceutical (SAB), Integragen, Taiho Oncology (C/A); **Ahmed Idbaih:** Carthera (Travel funding, RF), Transgene, Sanofi, Air Liquide, Leo Pharma, Nutritheragene (RF). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

References

1. Mandel JJ, Yust-Katz S, Cachia D et al. Leptomeningeal dissemination in glioblastoma; an inspection of risk factors, treatment, and outcomes at a single institution. J Neurooncol 2014; 120:597–605.

2. Ostrom QT, Gittleman H, Truitt G et al. CBTRUS statistical report: Primary brain and other central nervous system tumors diagnosed in the United States in 2011–2015. Neuro Oncol 2018;20(suppl 4):iv1–iv86.

3. Ricard D, Idbaih A, Ducray F et al. Primary brain tumours in adults. Lancet 2012;379:1984–1996.

4. Stupp R, Mason WP, van den Bent MJ et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005;352:987–996.

5. Alatakis S, Malham GM, Thien C. Spinal leptomeningeal metastasis from cerebral glioblastoma multiforme presenting with radicular pain: Case report and literature review. Surg Neurol 2001;56:33–37.

6. Noh JH, Lee MH, Kim WS et al. Optimal treatment of leptomeningeal spread in glioblastoma: Analysis of risk factors and outcome. Acta Neurochir (Wien) 2015;157(4):569–576.

7. Autran D, Barrie M, Matta M et al. Leptomeningeal gliomatosis: A single institution study of 31 patients. Anticancer Res 2019;39: 1035–1041.

8. Yung WKA, Horten BC, Shapiro WR. Meningeal gliomatosis: A review of 12 cases. Ann Neurol 1980;8:605–608.

9. Krause Molle Z, Gierga K, Turowski B et al. 5-ALA-Induced fluorescence in leptomeningeal dissemination of spinal malignant glioma. World Neurosurg 2018;110:345–348.

10. Onda K, Tanaka R, Takahashi H et al. Cerebral glioblastoma with cerebrospinal fluid dissemination: A clinicopathological study of 14 cases examined by complete autopsy. Neurosurgery 1989;25: 533–540.

11. Andersen BM, Miranda C, Hatzoglou V et al. Leptomeningeal metastases in glioma: The Memorial Sloan Kettering Cancer Center experience. Neurology 2019;92:e2483–e2491.

12. Ammerman JM, Kerr PB, Roberti F. Acute tetraplegia and cardiac arrest following high cervical leptomeningeal metastasis of giant cell glioblastoma. J Clin Neurosci 2011;18:1133–1135.

13. Jafri NF, Clarke JL, Weinberg V et al. Relationship of glioblastoma multiforme to the subventricular zone is associated with survival. Neuro Oncol 2013;15:91–96.

14. Mistry AM, Kelly PD, Gallant JN et al. Comparative analysis of subventricular zone glioblastoma contact and ventricular entry during resection in predicting dissemination, hydrocephalus, and survival. Neurosurgery 2019;85:E924–E932.

15. Bae JS, Yang SH, Yoon WS et al. The clinical features of spinal leptomeningeal dissemination from malignant gliomas. J Korean Neurosurg Soc 2011;49:334.

16. Falchetti ML, D'Alessandris QG, Pacioni S et al. Glioblastoma endothelium drives bevacizumab-induced infiltrative growth via modulation of PLXDC1. Int J Cancer 2019;144: 1331–1344.

17. Burger PC, Kleihues P. Cytologic composition of the untreated glioblastoma with implications for evaluation of needle biopsies. Cancer 1989;63:2014–2023.

18. Ho CY, VandenBussche CJ, Huppman AR et al. Cytomorphologic and clinicoradiologic analysis of primary nonhematologic central nervous system tumors with positive cerebrospinal fluid. Cancer Cytopathol 2015;123:123–135.

19. Beauchesne P, Blonski M, Brissart H. Response to intrathecal infusions of Depocyt in secondary diffuse leptomeningeal gliomatosis. A case report. In Vivo 2011;25:991–993.

20. Pradat PF, Hoang-Xuan K, Cornu P et al. Treatment of meningeal gliomatosis. J Neurooncol 1999;44:163–168.

21. Levin VA, Chamberlain M, Silver P et al. Phase I/II study of intraventricular and intrathecal ACNU for leptomeningeal neoplasia. Cancer Chemother Pharmacol 1989;23:301–307.

22. Brown CE, Alizadeh D, Starr R et al. Regression of glioblastoma after chimeric antigen receptor T-cell therapy. N Engl J Med 2016;375: 2561–2569.

23. Woo PYM, Lam TC, Pu JKS et al. Regression of BRAFV600E mutant adult glioblastoma after primary combined BRAF-MEK inhibitor targeted therapy: A report of two cases. Oncotarget 2019; 10:3818–3826.

24. Abadal KB, Walsh MA, Yachnis AT et al. Eleven month progression-free survival on

vemurafenib monotherapy in a patient with recurrent and metastatic *BRAF* V600E–mutated glioblastoma WHO grade 4. JCO Precis Oncol 2017. DOI: https://doi.org/10.1200/PO.17.00055.

25. Burger MC, Ronellenfitsch MW, Lorenz NI et al. Dabrafenib in patients with recurrent, BRAF V600E mutated malignant glioma and leptomeningeal disease. Oncol Rep 2017;38: 3291–3296.

26. Kanemaru Y, Natsumeda M, Okada M et al. Dramatic response of BRAF V600E-mutant epithelioid glioblastoma to combination therapy with BRAF and MEK inhibitor: Establishment and xenograft of a cell line to predict clinical efficacy. Acta Neuropathol Commun 2019;7:119.

27. Vertosick FT, Selker RG. Brain stem and spinal metastases of supratentorial glioblastoma multiforme: A clinical series. Neurosurgery 1990; 27:516–522.

28. Arita N, Taneda M, Hayakawa T. Leptomeningeal dissemination of malignant gliomas. Incidence, diagnosis and outcome. Acta Neurochir (Wien) 1994;126:84–92.

29. Maslehaty H, Cordovi S, Hefti M. Symptomatic spinal metastases of intracranial glioblastoma: Clinical characteristics and pathomechanism relating to GFAP expression. J Neurooncol 2011;101: 329–333.

30. Dardis C, Milton K, Ashby L et al. Leptomeningeal metastases in high-grade adult glioma: Development, diagnosis, management, and outcomes in a series of 34 patients. Front Neurol 2014;5:220.

31. Lindsay A, Holthouse D, Robbins P et al. Spinal leptomeningeal metastases following glioblastoma multiforme treated with radiotherapy. J Clin Neurosci 2002;9:725–728.

32. Roh TH, Park HH, Kang SG et al. Long-term outcomes of concomitant chemoradiotherapy with temozolomide for newly diagnosed glioblastoma patients: A single-center analysis. Medicine (Baltimore) 2017;96:e7422.

33. Delattre JY, Walker RW, Rosenblum MK. Leptomeningeal gliomatosis with spinal cord or cauda equina compression: A complication of supratentorial gliomas in adults. Acta Neurol Scand 1989;79:133–139.

34. Bordignon KC, Neto MC, Ramina R et al. Patterns of neuroaxis dissemination of gliomas: Suggestion of a classification based on magnetic resonance imaging findings. Surg Neurol 2006; 65:472–477; discussion 477.

35. Giesexs A, Westphal M. Glioma invasion in the central nervous system. Neurosurgery 1996; 39:235–252.

36. Chen-Zhao X, Aznar-García L. Diagnosis and management of spinal metastasis of primary brain tumours. AME Case Rep 2018;2:26.

37. Wasita B, Kamitani H, Kinoshita Y et al. A rat glioblastoma model with diffuse leptomeningeal gliomatosis induced by intracarotid injection of C6 glioma cells. Neurol Res 2009;31:453–462.

38. Rooprai HK, Rucklidge GJ, Panou C et al. The effects of exogenous growth factors on matrix metalloproteinase secretion by human brain tumour cells. Br J Cancer 2000;82:52–55.

39. Enam SA, Klaus E. Role of extracellular matrix in tumor invasion: Migration of glioma cells along fibronectin-positive mesenchymal cell processes. Neurosurgery 1998;42:599–608.

40. Zhang H, Kelly G, Zerillo C et al. Expression of a cleaved brain-specific extracellular matrix protein mediates glioma cell invasion In vivo. J Neurosci 1998;18:2370–2376.

41. Velásquez C, Mansouri S, Mora C et al. Molecular and clinical insights into the invasive capacity of glioblastoma cells. J Oncol 2019; 2019:1–16.

42. Pullen N, Pickford A, Perry M et al. Current insights into matrix metalloproteinases and glioma progression: Transcending the degradation boundary. Met Med 2018;5:13–30.

43. Paulus W, Tonn JC. Basement membrane invasion of glioma cells mediated by integrin receptors. J Neurosurg 1994;80:515–519.

44. Ruff MW, Kizilbash SH. Glioblastoma with bilateral extraocular muscle infiltration preceded by evidence of vascular tropism. J Clin Neurosci 2019;61:277–8.

45. Roos A, Ding Z, Loftus JC et al. Molecular and microenvironmental determinants of glioma stem-like cell survival and invasion. Front Oncol 2017;7:120.

46. de Groot JF, Fuller G, Kumar AJ et al. Tumor invasion after treatment of glioblastoma with bevacizumab: Radiographic and pathologic correlation in humans and mice. Neuro Oncol 2010; 12:233–242.

47. Otani Y, Ichikawa T, Kurozumi K et al. Fibroblast growth factor 13 regulates glioma cell invasion and is important for bevacizumab-induced glioma invasion. Oncogene 2018;37:777–786.

48. Seiz M, Nölte I, Pechlivanis I et al. Far-distant metastases along the CSF pathway of glioblastoma multiforme during continuous low-dose chemotherapy with temozolomide and celecoxib. Neurosurg Rev 2010;33:375–381.

49. Yamamoto Y, Tamura R, Tanaka T et al. "Paradoxical" findings of tumor vascularity and oxygenation in recurrent glioblastomas refractory to bevacizumab. Oncotarget 2017;8:103890–103899.

50. Tamura R, Tanaka T, Miyake K et al. Histopathological investigation of glioblastomas resected under bevacizumab treatment. Oncotarget 2016;7: 52423–52435.

51. Tamura R, Miyoshi H, Sampetrean O et al. Visualization of spatiotemporal dynamics of human glioma stem cell invasion. Mol Brain 2019;12:45.

52. Xiao W, Sohrabi A, Seidlits SK. Integrating the glioblastoma microenvironment into engineered experimental models. Future Sci OA 2017;3:FSO189.

53. da Hora CC, Schweiger MW, Wurdinger T et al. Patient-derived glioma models: From patients to dish to animals. Cells 2019;8:1177.

54. Shibahara I, Saito R, Osada Y et al. Incidence of initial spinal metastasis in glioblastoma patients and the importance of spinal screening using MRI. J Neurooncol 2019;141:337–345.

55. Burger MC, Zeiner PS, Jahnke K et al. Addition of anti-angiogenetic therapy with bevacizumab to chemo- and radiotherapy for leptomeningeal metastases in primary brain tumors. PLoS One 2016;11:e0155315.

56. Perry A, Miller CR, Gujrati M et al. Malignant gliomas with primitive neuroectodermal tumor-like components: A clinicopathologic and genetic study of 53 cases. Brain Pathol 2009;19: 81–90.

57. Chamberlain MC. Combined-modality treatment of leptomeningeal gliomatosis. Neurosurgery 2003;52:324–329; discussion 330.

58. Witham TF, Fukui MB, Meltzer CC et al. Survival of patients with high grade glioma treated with intrathecal thiotriethylenephosphoramide for ependymal or leptomeningeal gliomatosis. Cancer 1999;86:1347–1353.

59. Amini A, Schmidt RH, Salzman K et al. Glioblastoma multiforme of the pineal region. J Neurooncol 2006;79:307–314.

60. Endo H, Kumabe T, Jokura H et al. Leptomeningeal dissemination of cerebellar malignant astrocytomas. J Neurooncol 2003;63: 191–199.

61. Pande S, Pavithran K. Drop metastases to the spinal cord from infratentorial glioblastoma multiforme in post-temozolomide era. J Cancer Res Ther 2015;11:1039.

62. Picart T, Barritault M, Berthillier J et al. Characteristics of cerebellar glioblastomas in adults. J Neurooncol 2018;136:555–563.

63. Tsung AJ, Prabhu SS, Lei X et al. Cerebellar glioblastoma: A retrospective review of 21 patients at a single institution. J Neurooncol 2011;105: 555–562.

64. Linsenmann T, Monoranu CM, Vince GH et al. Long-term tumor control of spinal dissemination of cerebellar glioblastoma multiforme by combined adjuvant bevacizumab antibody therapy: A case report. BMC Res Notes 2014;7:496.

65. Chan DTM, Hsieh SYP, Kam MKM et al. Pattern of recurrence and factors associated with cerebrospinal fluid dissemination of glioblastoma in Chinese patients. Surg Neurol Int 2016;7:92.

66. Nunn A, Polyzoidis S, Piechowski-Jozwiak B et al. Primary glioblastoma multiforme of the conus medullaris with leptomeningeal metastasis. J Neurol Sci 2017;381:315–317.

67. Begemann M, Tsiouris AJ, Malkin MG. Leptomeningeal and ependymal invasion by glioblastoma multiforme. Neurology 2004;63(3):E8.

68. Khan MB, Riaz M, Bari ME. Is surgical spinal decompression for supratentorial GBM symptomatic drop down metastasis warranted? A case report and review of literature. Surg Neurol Int 2014;5:40.

69. Tinchon A, Oberndorfer S, Marosi C et al. Malignant spinal cord compression in cerebral glioblastoma multiforme: A multicenter case series and review of the literature. J Neurooncol 2012;110:221–226.

70. Toyooka T, Miyazawa T, Fukui S et al. Central neurogenic hyperventilation in a conscious man with CSF dissemination from a pineal glioblastoma. J Clin Neurosci 2005;12:834–837.

71. Witoonpanich P, Bamrungrak K, Jinawath A et al. Glioblastoma multiforme at the corpus callosum with spinal leptomeningeal metastasis. Clin Neurol Neurosurg 2011;113:407–410.

72. Fischer CM, Neidert MC, Péus D et al. Hydrocephalus after resection and adjuvant radiochemotherapy in patients with glioblastoma. Clin Neurol Neurosurg 2014;120:27–31.

73. Bae JY, Choi BO, SunWoo IN et al. Diffuse cerebrospinal gliomatosis with extensive leptomeningeal spread. Yonsei Med J 2000;41: 517–521.

74. Prelaj A, Rebuzzi SE, Caffarena G et al. Therapeutic approach in glioblastoma multiforme

with primitive neuroectodermal tumor components: Case report and review of the literature. Oncology Letters 2008;15:6641–6647.

75. Onuma K, Ishikawa E, Matsuda M et al. Clinical characteristics and neuroimaging findings in 12 cases of recurrent glioblastoma with communicating hydrocephalus. Neurol Med Chir (Tokyo) 2013;53:474–481.

76. Leaver KE, Zhang N, Ziskin JL et al. Response of metastatic glioma to vemurafenib. Neuro Oncol Pract 2016;3:268–271.

77. Zima LA, Tulpule S, Samson K et al. Seizure prevalence, contributing factors, and prognostic factors in patients with leptomeningeal disease. J Neurol Sci 2019;403:19–23.

78. Trivedi RA, Nichols P, Coley S et al. Leptomeningeal glioblastoma presenting with multiple cranial neuropathies and confusion. Clin Neurol Neurosurg 2000;102:223–226.

79. Faivre G, Pentsova E, Demopoulos A et al. Clinical reasoning: Worsening neurologic symptoms in a brain tumor patient. Neurology 2015; 85:e57–e61.

80. Goel A, Shah A, Redhu R et al. Supratentorial glioblastoma multiforme with spinal metastases. J Craniovertebral Junction Spine 2010;1:126.

81. Cohen ZR, Hassenbusch SJ, Maor MH et al. Intractable vomiting from glioblastoma metastatic to the fourth ventricle: Three case studies. Neuro Oncol 2002;4:129–133.

82. Montes de Oca Delgado M, Cacho Díaz B, Santos Zambrano J et al. The comparative treatment of intraventricular chemotherapy by ommaya reservoir vs. lumbar puncture in patients with leptomeningeal carcinomatosis. Front Oncol. 2018;8:509.

83. Amitendu S, Mak SKD, Ling JM et al. A single institution experience of the incidence of extracranial metastasis in glioma. J Clin Neurosci 2012;19:1511–1515.

84. Hübner F, Braun V, Richter HP. Case reports of symptomatic metastases in four patients with primary intracranial gliomas. Acta Neurochir (Wien) 2001;143:25–29.

85. Schwartz C, Romagna A, Machegger L et al. Extensive leptomeningeal intracranial and spinal metastases in a patient with a supratentorial glioblastoma multiforme, IDH-wildtype. World Neurosurg 2018;120:442–447.

86. Saito R, Kumabe T, Jokura H et al. Symptomatic spinal dissemination of malignant astrocytoma. J Neurooncol 2003;61:227–235.

87. Karaca M, Andrieu MN, Hicsonmez A et al. Cases of glioblastoma multiforme metastasizing to spinal cord. Neurol India 2006;54:428–430.

88. Kuo LT, Tsai SY, Yang CY et al. Meningeal seeding from glioblastoma multiforme treated with radiotherapy and temozolomide. Asian J Surg 2017;40:61–65.

89. Grabb PA, Albright AL, Pang D. Dissemination of supratentorial malignant gliomas via the cerebrospinal fluid in children. Neurosurgery 1992;30:64–71.

90. Lin L, Innerfield CE, Cuccurullo SJ. Symptomatic spinal leptomeningeal metastasis from intracranial glioblastoma multiforme. Am J Phys Med Rehabil 2014;93:838–839.

91. Inamasu J, Nakamura Y, Saito R et al. Postoperative communicating hydrocephalus in patients with supratentorial malignant glioma. Clin Neurol Neurosurg 2003;106:9–15.

92. Matsuda M, Kohzuki H, Ishikawa E et al. Prognostic analysis of patients who underwent gross total resection of newly diagnosed glioblastoma. J Clin Neurosci 2018;50:172–176.

93. Sonoda Y, Saito R, Kanamori M et al. The association of subventricular zone involvement at recurrence with survival after repeat surgery in patients with recurrent glioblastoma. Neurol Med Chir (Tokyo) 2014;54:302–309.

94. Roelz R, Reinacher P, Jabbarli R et al. Surgical ventricular entry is a key risk factor for leptomeningeal metastasis of high grade gliomas. Sci Rep 2015;5:17758.

95. Mistry AM, Kelly PD, Thompson RC et al. Cancer dissemination, hydrocephalus, and survival after cerebral ventricular entry during high-grade glioma surgery: A meta-analysis. Neurosurgery 2018;83:1119–1127.

96. Adeberg S, König L, Bostel T et al. Glioblastoma recurrence patterns after radiation therapy with regard to the subventricular zone. Int J Radiat Oncol Biol Phys 2014;90:886–893.

97. Elliott JP, Keles GE, Waite M et al. Ventricular entry during resection of malignant gliomas: effect on intracranial cerebrospinal fluid tumor dissemination. J Neurosurg. 1994 May;80(5): 834–9.

98. Adeberg S, Diehl C, Jung CS et al. Is a modification of the radiotherapeutic target volume necessary after resection of glioblastomas with opening of the ventricles? J Neurooncol 2016; 127:581–587.

99. Kim H, Lim DH, Kim TG et al. Leptomeningeal enhancement on preoperative brain MRI in patients with glioblastoma and its clinical impact. Asia Pac J Clin Oncol 2018;14: e366–e373.

100. D'Haene N, Coen N, Neugroschl C et al. Leptomeningeal dissemination of low-grade intramedullary gliomas: About one case and review. Clin Neurol Neurosurg 2009;111: 390–394.

101. Lam CH, Cosgrove GR, Drislane FW et al. Spinal leptomeningeal metastasis from cerebral glioblastoma. Appearance on magnetic resonance imaging. Surg Neurol 1991;35:377–380.

102. Kato H, Fujimura M, Kumabe T et al. PTEN gene mutation and high MIB-1 labeling index may contribute to dissemination in patients with glioblastoma. J Clin Neurosci 2004;11:37–41.

103. Broniscer A, Tatevossian RG, Sabin ND et al. Clinical, radiological, histological and molecular characteristics of paediatric epithelioid glioblastoma: Epithelioid glioblastoma in children. Neuropathol Appl Neurobiol 2014;40: 327–336.

104. Babu R, Hatef J, McLendon RE et al. Clinicopathological characteristics and treatment of rhabdoid glioblastoma. J Neurosurg 2013;119: 412–419.

105. Korshunov A, Sycheva R, Golanov A et al. Gains at the 1p36 chromosomal region are associated with symptomatic leptomeningeal dissemination of supratentorial glioblastomas. Am J Clin Pathol 2007;127:585–590.

106. Izumoto S, Ohnishi T, Kanemura H et al. PTEN mutations in malignant gliomas and their relation with meningeal gliomatosis. J Neurooncol 2001;53:21–26.

107. Tanaka S, Batchelor TT, Iafrate AJ et al. PIK3CA activating mutations are associated with more disseminated disease at presentation and earlier recurrence in glioblastoma. Acta Neuropathol Commun 2019;7:66.

108. Brandes AA, Tosoni A, Franceschi E et al. Recurrence pattern after temozolomide concomitant with and adjuvant to radiotherapy in newly diagnosed patients with glioblastoma: correlation with MGMT promoter methylation status. J Clin Oncol 2009;27:1275–1279.

109. Zhao YH, Wang ZF, Cao CJ et al. The clinical significance of O6-methylguanine-DNA methyltransferase promoter methylation status in adult patients with glioblastoma: A meta-analysis. Front Neurol 2018;9:127.

110. Okita Y, Nonaka M, Umehara T et al. Efficacy of temozolomide and bevacizumab for the treatment of leptomeningeal dissemination of recurrent glioblastoma: A case report. Oncol Lett 2015;9:1885–1888.

111. Ginat DT, Schaefer PW. Imaging guidelines and findings of extracranial glioblastoma. J Neurooncol 2014;118:9–18.

112. Shah LM, Salzman KL. Imaging of spinal metastatic disease. Int J Surg Oncol 2011;2011: 769753.

113. Singh SK, Agris JM, Leeds NE et al. Intracranial leptomeningeal metastases: Comparison of depiction at FLAIR and contrast-enhanced MR imaging. Radiology 2000;217:50–53.

114. Harris P, Diouf A, Guilbert F et al. Diagnostic reliability of leptomeningeal disease using magnetic resonance imaging. Cureus 2019;11: e4416.

115. Kinger N, Hoch MJ, Shu HKG et al. Glioblastoma with brainstem leptomeningeal pseudoprogression following radiation therapy. Radiol Case Rep 2019;14: 613–617.

116. Lee J, Kim MS, Kim YZ. Extensive pachymeningeal dissemination of glioblastoma mimicking chronic subdural hematoma: A case report. Brain Tumor Res Treat 2019;7:39.

117. Alvarado A, Salacz M, Chamoun R. Malignant glioma-primitive neuroectodermal tumor recurring as PNET-like only subdural collection: Case report. Surg Neurol Int 2017;8:243.

118. Intriago B, Danús M, Añaños M et al. 18F-FDG PET detection of spinal leptomeningeal metastases from cerebral glioblastoma multiforme. Eur J Nucl Med Mol Imaging 2011; 38:1392.

119. Unterrainer M, Fleischmann DF, Lindner S et al. Detection of cerebrospinal fluid dissemination of recurrent glioblastoma using TSPO-PET with 18F-GE-180. Clin Nucl Med 2018;43: 518–519.

120. Lombardi G, Zustovich F, Farina P et al. Neoplastic meningitis from solid tumors: New diagnostic and therapeutic approaches. ***The Oncologist*** 2011;16:1175–1188.

121. Miller AM, Shah RH, Pentsova EI et al. Tracking tumour evolution in glioma through liquid biopsies of cerebrospinal fluid. Nature 2019; 565:654–658.

122. Wang J, Bettegowda C. Applications of DNA-based liquid biopsy for central nervous system neoplasms. J Mol Diagn 2017;19:24–34.

123. Seoane J, De Mattos-Arruda L, Le Rhun E et al. Cerebrospinal fluid cell-free tumour DNA as a liquid biopsy for primary brain tumours and

central nervous system metastases. Ann Oncol 2019;30:211–218.

124. Boire A, Brandsma D, Brastianos PK et al. Liquid biopsy in central nervous system metastases: A RANO review and proposals for clinical applications. Neuro Oncol 2019;21:571–584.

125. Nevel KS, Wilcox JA, Robell LJ et al. The utility of liquid biopsy in central nervous system malignancies. Curr Oncol Rep 2018;20:60.

126. Heitzer E, Haque IS, Roberts CES et al. Current and future perspectives of liquid biopsies in genomics-driven oncology. Nat Rev Genet 2019; 20:71–88.

127. Nayak L, Fleisher M, Gonzalez-Espinoza R et al. Rare cell capture technology for the diagnosis of leptomeningeal metastasis in solid tumors. Neurology 2013;80:1598–1605.

128. Zhao KH, Zhang C, Bai Y et al. Antiglioma effects of cytarabine on leptomeningeal metastasis of high-grade glioma by targeting the PI3K/Akt/mTOR pathway. Drug Des Devel Ther 2017;11:1905–1915.

129. Saito R, Kumabe T, Jokura H et al. Fatal hemorrhage after radiochemotherapy for leptomeningeal dissemination of glioma: Report of two cases. Surg Neurol 2002;57:46–48.

130. Castro BA, Imber BS, Chen R et al. Ventriculoperitoneal shunting for glioblastoma: Risk factors, indications, and efficacy. Neurosurgery 2017;80:421–430.

131. Woo PYM, Zhuang JTF, Ho JMK et al. Intraventricular urokinase to treat a blocked ventriculoperitoneal shunt in a glioblastoma patient with leptomeningeal spread. Acta Neurochir (Wien) 2018;160:1073–1077.

132. de la Fuente MI, DeAngelis LM. The role of ventriculoperitoneal shunting in patients with supratentorial glioma. Ann Clin Transl Neurol 2014;1:45–48.

133. Hong B, Polemikos M, Heissler HE et al. Challenges in cerebrospinal fluid shunting in patients with glioblastoma. Fluids Barriers CNS 2018;15:16.

134. Fiorentino A, Caivano R, Chiumento C et al. Radiotherapy and bevacizumab for intramedullary and leptomenigeal metastatic glioblastoma: A case report and review of the literature. Int J Neurosci 2012;122:691–694.

135. Scoccianti S, Detti B, Meattini I et al. Symptomatic leptomeningeal and intramedullary metastases from intracranial glioblastoma multiforme: A case report. Tumori 2008;94: 877–881.

136. Brown MT, Coleman RE, Friedman AH et al. Intrathecal 131I-labeled antitenascin monoclonal antibody 81C6 treatment of patients with leptomeningeal neoplasms or primary brain tumor resection cavities with subarachnoid communication: Phase I trial results. Clin Cancer Res 1996;2:963–972.

137. Shinoura N, Tabei Y, Yamada R et al. Continuous intrathecal treatment with methotrexate via subcutaneous port: Implication for leptomeningeal dissemination of malignant tumors. J Neurooncol 2008;87:309–316.

138. Scott BJ, van Vugt VA, Rush T et al. Concurrent intrathecal methotrexate and liposomal cytarabine for leptomeningeal metastasis from solid tumors: A retrospective cohort study. J Neurooncol 2014;119:361–368.

139. Glantz MJ, Jaeckle KA, Chamberlain MC et al. A Randomized controlled trial comparing intrathecal sustained-release cytarabine (DepoCyt) to intrathecal methotrexate in patients with neoplastic meningitis from solid tumors. Clin Cancer Res 1999;5:3394–3402.

140. Gammon DC, Bhatt MS, Tran L et al. Intrathecal topotecan in adult patients with neoplastic meningitis. Am J Health Syst Pharm 2006;63: 2083–2086.

141. Gil MJ, de Las Peñas R, Reynés G et al. Bevacizumab plus irinotecan in recurrent malignant glioma shows high overall survival in a multicenter retrospective pooled series of the Spanish Neuro-Oncology Research Group (GEINO). Anticancer Drugs 2012;23:659–665.

142. Matsuda M, Ishikawa E, Yamamoto T et al. Efficacy of bevacizumab therapy in recurrent malignant gliomas in relation to the prior recurrence pattern or tumor location. J Clin Neurosci 2017;40:115–119.

143. Kaloshi G, Roji A, Seferi A et al. Spinal dissemination of intracranial glioblastoma in bevacizumab era: A potential bevacizumab-induced mechanism. Acta Inform Medica 2014;22: 142–144.

144. Dasgupta T, Olow AK, Yang X et al. Survival advantage combining a BRAF inhibitor and radiation in BRAF V600E-mutant glioma. J Neurooncol 2016;126:385–393.

145. Behling F, Schittenhelm J. Oncogenic BRAF alterations and their role in brain tumors. Cancers 2019;11:794.

146. Johanns TM, Miller CA, Dorward IG et al. Immunogenomics of hypermutated glioblastoma: A patient with germline POLE deficiency treated with checkpoint blockade immunotherapy. Cancer Discov 2016;6:1230–1236.

147. Brown MP, Ebert LM, Gargett T. Clinical chimeric antigen receptor-T cell therapy: A new and promising treatment modality for glioblastoma. Clin Transl Immunology 2019;8:e1050.

148. Ahmed N, Brawley V, Hegde M et al. HER2-specific chimeric antigen receptor–modified virus-specific T cells for progressive glioblastoma. JAMA Oncol 2017;3:1094–1101.

149. O'Rourke DM, Nasrallah MP, Desai A et al. A single dose of peripherally infused EGFRvIII-directed CAR T cells mediates antigen loss and induces adaptive resistance in patients with recurrent glioblastoma. Sci Transl Med 2017;9: eaaa0984.

150. Gu C, Li S, Tokuyama T et al. Therapeutic effect of genetically engineered mesenchymal stem cells in rat experimental leptomeningeal glioma model. Cancer Lett 2010;291:256–262.

151. Ochiai H. Targeted therapy for glioblastoma multiforme neoplastic meningitis with intrathecal delivery of an oncolytic recombinant poliovirus. Clin Cancer Res 2006;12:1349–1354.

152. Johnson VG, Wrobel C, Wilson D et al. Improved tumor-specific immunotoxins in the treatment of CNS and leptomeningeal neoplasia. J Neurosurg 1989;70:240–248.

153. Asano K, Ohkuma H. Epithelial growth factor receptor tyrosine kinase inhibitor prevents infiltration and cerebrospinal fluid dissemination in malignant glioma: An experimental study. Neurosurgery 2011;69:399–411.

154. Le Rhun E, Devos P, Boulanger T et al. The RANO Leptomeningeal Metastasis Group proposal to assess response to treatment: Lack of feasibility and clinical utility and a revised proposal. Neuro Oncol 2019;21: 648–658.

155. Pace A, Dirven L, Koekkoek JAF et al. European Association for Neuro-Oncology (EANO) guidelines for palliative care in adults with glioma. Lancet Oncol 2017;18:e330–e340.