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CLINICAL STUDY

Diagnosis and treatment patterns for patients with leptomeningeal metastasis from solid tumors across Europe

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Abstract Leptomeningeal metastases are a late manifestation of systemic cancer which affects up to 10% of patients with solid tumors. Prognosis is poor, and overall survival at 1 year is only approximately 10%. Management depends mainly on general and neurological condition, primary tumor, and patterns of metastasis, notably absence or presence of concurrent systemic or solid brain metastases. Here we set out to characterize current practice patterns of diagnosis and treatment of patients with leptomeningeal metastasis in Europe. We prepared a web-based survey including 25 simple or multiple choices questions on best practice supplemented by eight case vignettes with various diagnosis and management options. The survey was sent to the membership of the European Association of Neuro-Oncology and the European Organisation for Research and Treatment of Cancer Brain Tumor Group. Between April 7, 2016 and August 8, 2016, 224 colleagues from 26 countries initiated the survey, 115 colleagues completed the whole survey. There were major differences both in the general diagnostic and therapeutic approach, e.g., regarding the use of cerebrospinal fluid (CSF) flow studies, intra-CSF chemotherapy, various types of radiotherapy, and even more so when selecting decisions on diagnostic and therapeutic measures for single case vignettes. Diagnosis and treatment decisions for patients with leptomeningeal metastasis from solid tumors vary widely across Europe. Standardization of diagnosis and evaluation tools as well as controlled studies to improve the level of evidence for all therapeutic approaches to LM are required.

Keywords Leptomeningeal · Metastasis · Cerebrospinal · Chemotherapy · Intrathecal

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Introduction

Leptomeningeal metastasis is a serious complication of systemic cancer commonly occurring in later disease stages which affects approximately 10% of patients with solid tumors. The risk is highest for patients with breast cancer, lung cancer and melanoma. Survival at 1 year is approximately 10% and varies profoundly by primary tumor. Clinical evaluation, magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) analysis are the most important diagnostic measures [1]. Treatment recommendations vary mainly by primary tumor and pattern of brain and meningeal disease, that is, e.g., the absence or presence of concurrent systemic or solid brain metastasis, the radiological presentation, and the absence or presence of tumor cells in the CSF, and are typically rather individualized [2]. Many important questions regarding diagnosis and treatment of LM remain controversial and have never been explored in controlled clinical trials. Heterogeneous patterns of presentation, divergent modes of commonly heavy pretreatment, and poor prognosis are the main reasons why it has remained challenging to conduct prospective clinical trials in this patient population. Here we designed a questionnaire-based survey to explore the current routine clinical practice of diagnosing and treating LM and to identify the most important controversies to be addressed in future clinical trials across Europe.

Methods

A web-based survey containing 25 general questions on current practice patterns as well as eight case presentations with diagnosis and management questions (Supplementary Note) was sent to members of the European Association of Neuro-Oncology and of the Brain Tumor Group of the European Organisation for Research and Treatment of Cancer in April 2016 via the respective email listings of these organizations. The case vignettes are real patients from the authors' clinical practice and were selected based on their representation of primary cancers and the typical challenges associated with the diagnosis and treatment of LM from solid cancers. Responses were analysed with a focus on age and discipline of participants, physician in charge of LM at the center, and the number of LM patients seen per month. Comparisons between groups were done using Chi square or Fisher exact test. Statistical analyses were performed with SAS Software, V9.4 (Cary, NC).

Results

General information

Between April 7, 2016 and August 8, 2016, a total of 224 colleagues from 26 countries initiated the survey and 115 colleagues completed the whole survey. Fifteen colleagues only opened the file without answering any of the questions. Rates of "no response" for the general questions varied between 8.5 and 15% with the exception on the question addressing the route of administration of intra-CSF therapy to which 23% of participants did not answer (Table 1).

Participants came mainly from France (n = 35, 15.5%), Italy (n = 28, 12.5%), Netherlands (n = 22, 10%) and Spain (n = 19, 8.5%) (Fig. 1a), and the leading disciplines were neurology (n = 77, 34%), medical oncology (n = 52, 23%), radiation oncology (n = 42, 19%) and neurosurgery (n = 23, 10%) (Fig. 1b). The age distribution was as follows: 31–40 years (n = 56, 25%), 41–50 (n = 69, 31%), 51–65 (n = 76, 34%) (Supplementary Fig. 1). 119 participants (53%) indicated to see not more than 1 LM patient per month, 78 participants (35%) indicated to see 2–4 patients per month, and nine participants (4%) indicated to see five patients per month or more (Supplementary Fig. 2). Almost no differences were observed between physicians in charge of 0–1 LM patients per month and physicians in charge of at least two patients per month among the different items of the survey.

One hundred-twenty nine participants (58%) felt that they were in charge of LM at their institution (Supplementary Fig. 3). Medical oncologists (54.5%) or neurologists (48%) were most often reported to be responsible for the diagnosis of LM, whereas medical oncologists (63%) were more often in charge of treatment than neurologists (32%) or radiation oncologists (11%) (Fig. 1c).

Diagnosis of LM

Only 36 participants (16%) indicated that a neurological scale was used to score the results of the neurological examination (Table 1). No difference was observed between neurologists and participants from other specialties (Supplementary Table). Only 51 colleagues (23%) reported that cerebrospinal MRI was not always done in patients with suspected LM. Similarly, only 64 participants (28.5%) reported that CSF flow studies were never done in the diagnostic work-up. However, a CSF flow study was reported to be always performed at LM diagnosis by significantly more participants not in charge of LM (24.5%) than by participants in charge of LM (13%) ($p = 0.043$).

Only 125 participants (56%) indicated that CSF analysis was always performed as part of the diagnostic work-up in case of suspected LM from solid tumors whereas

Table 1 Responses to the general questions on current practice of diagnosing and treating LM

Diagnosis	Number (% of participants)
At your institution, a standardized neurological scale to score neurological symptoms/signs is performed for the management of LM?	Yes: 36 (16) No: 165 (74) No response: 23 (10)
At your institution, a cerebrospinal MRI is always performed regardless of localizing neurologic symptoms/signs in suspected LM	Yes: 153 (68) No: 51 (23) No response: 20 (9)
At your institution, a CSF flow study is performed for the diagnosis of LM from solid tumors other than gliomas:[a]	Always: 36 (16%) Depending on patient's characteristics: 62 (27.5) Depending on disease's characteristics: 69 (31) In case of toxicity of the intra-CSF treatment: 6 (2.5) Never: 64 (28.5) No response: 21 (9.5)
At your institution, a CSF analysis is done (in cases without contra-indication):[a]	Always in case of suspicion of LM from solid tumors other than glioma: 125 (56) Always in case of suspicion of LM from glioma (not other solid tumors): 39 (17.5) Only in case of doubt after clinical and MRI evaluation for solid tumors other than glioma: 78 (35) Only in case of doubt after clinical and MRI evaluation for glioma: 40 (18) No response: 19 (8.5)
At your institution, what is the median volume of CSF sample collected?	0–2 ml: 3 (1.5) 2–5 ml: 68 (30.5) 5–10 ml: 86 (38) >10 ml: 39 (17.5) No response: 28 (12.5)
At your institution, what is the median time between CSF sampling and processing?	<30 min: 36 (16) 30–60 min: 91 (40.5) 60–90 min: 47 (21) >90 min: 20 (9) No response: 30 (13.5)
At your institution, a CSF cytology defined as "atypical" is usually considered	Positive: 100 (44.5) Negative: 91 (40.5) No response: 33 (15)
At your institution, a CSF cytology defined as "suspicious" is usually considered	Positive: 167 (74.5) Negative: 28 (12.5) No response: 29 (13)
At your institution, is positive CSF cytology is always required to diagnose LM?	Yes: 21 (9) No: 181 (81) No response: 22 (10)
In case of negative CSF cytology, a combination of clinical and radiological findings is considered sufficient to diagnose LM?	Yes: 191 (85) No: 11 (5) No response: 22 (10)
Treatment—follow up	**Number (%)**
At your institution, systemic treatment for LM is administered:[a]	Always when feasible: 71 (31.5) Never: 2 (1) Depending on CSF and MRI findings: 66 (29.5) Depending on the primary cancer: 126 (56) Depending on molecular data of the primary cancer: 35 (15.5) Only in combination with intra-CSF treatment: 10 (4.5) No response: 23 (10.5)

Table 1 (continued)

Treatment—follow up	Number (%)
At your institution, intra-CSF treatment for LM is administered:[a]	Always: 8 (3.5) Never: 23 (10.5) Depending on CSF and MRI findings: 81 (36) Depending on the primary cancer: 126 (56) Depending on molecular data of the primary cancer: 28 (12.5) Depending on the systemic treatment: 68 (30.5) Only in combination with a systemic treatment: 12 (5.5) No response: 25 (10.5)
At your institution, intraventricular intra-CSF chemotherapy is preferred over intralumbar intra-CSF chemotherapy:[a]	For most patients: 50 (22.5) Only in patients with regular CSF flow studies: 15 (6.5) Only when no WBRT is given: 9 (4) Only if repeated lumbar punctures are not feasible: 103 (46) Only if patients require anticoagulation: 10 (4.5) No response: 51 (23)
At your institution, WBRT is performed:[a]	Always: 35 (15.5) In case of concomitant BM only: 108 (48) In case of nodular/bulky LM disease: 115 (51.5) Never: 4 (2) No response: 27 (12)
At your institution, in a patient with a diagnosis of LM and a predominant symptomatic site (i.e. cauda equina, posterior fossa, skull base) you perform focal RT based on	Neurological symptoms only: 30 (13.5) Neurological symptoms only when associated with MRI Abnormalities: 164 (73) No response: 30 (13.5)
At your institution, a cerebro-spinal MRI is always performed in the follow-up regardless of signs	Yes: 108 (48) No: 92 (41) No response: 24 (11)
At your institution, what is the frequency of MRI examination in the follow-up?	Every 2 months: 30 (13.5) Every 2 months initially, then every 3 months: 54 (24) Every 3 months: 51 (23) Only depending on the clinical course: 64 (28.5) No response: 25 (11)
At your institution, the change of steroid doses following antineoplastic treatment is part of criteria for defining response or progression (as in brain metastases and malignant gliomas)	Yes: 120 (53.5) No: 79 (35.5) No response: 25 (11)

[a]Multiple answers were allowed

78 participants (35%) indicated that CSF analysis was only done in case of doubt after clinical and MRI evaluation (Table 1). These numbers were much lower for suspected LM from gliomas, 39 participants (17.5%) versus 40 participants (18%). Radiation oncologists declared less often always performing a CSF cytology in case of suspicion of LM from solid tumors (26%) than neurologists (61%), medical oncologists (79%) or neurosurgeons (61%) ($p < 0.0001$). Radiation oncologists also declared less frequently to perform CSF analysis (5%) in case of suspected LM from gliomas than other specialists (neurologists: 17%, medical oncologists: 23%, neurosurgeons: 17%) ($p = 0.044$). The indication for CSF analysis for the diagnosis of LM varied significantly also by age (Supplementary Table).

More than half (56.5%) of participants reported that CSF was processed within 1 h. Interestingly, similar numbers of participants felt that a CSF cytology defined as atypical should be considered negative (40.5%) or positive (44.5%). In contrast, a CSF cytology defined as suspicious was considered positive by 167 participants (74.5%). Only 21 participants (9%) felt that a positive cytology was always required to diagnose LM (Table 1).

Treatment of LM

The decision for systemic treatment was based on the primary cancer according to 126 participants (56%), but on CSF and MRI findings according to only 66 participants (29.5%), although multiple answers were allowed. Systemic treatment was declared being always administered when feasible by only 71 participants (31.5%) (Table 1). Systemic treatment was always recommended when feasible by medical oncologists in 50% and by neurosurgeons in 48%, as opposed to only 26% of radiation oncologists and 22% of neurologists ($p = 0.0029$). The role of the primary

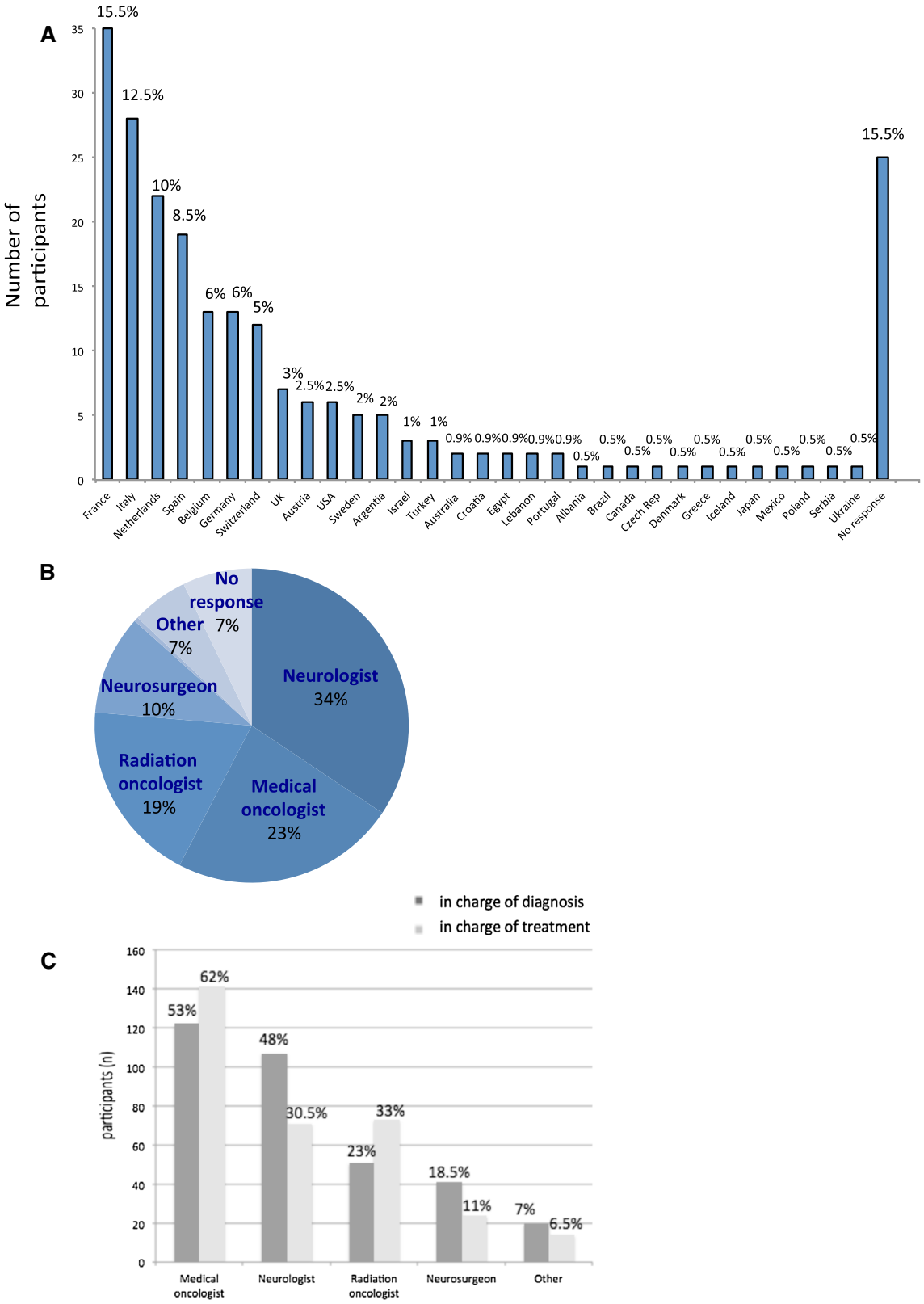

Fig. 1 Characteristics of participants. Distribution per country (**a**), per discipline (**b**) and per self-assessed role in the management of LM per discipline (**c**). In (**b**), other disciplines indicated were: biologists (n = 1, 0.5%), neuro-oncologists (n = 3, 1%), neuropathologist (n = 2, 1%); pediatric neurologist (n = 2, 1%), radiologist (n = 1, 0.5%). For C, there are no responses for diagnosis by 24 participants (11%) and for treatment by 22 participants (10%)

tumor for systemic treatment was judged similar across disciplines (Supplementary Table).

The decision for intra-CSF treatment was again most often based on the primary cancer (n = 126, 56%) but also on CSF and MRI findings (n = 81, 36%) and depending on systemic treatment (n = 68, 30.5%). Intra-CSF treatment was declared as being never administered by only 23 participants (10.5%) (Table 1). The indication for intra-CSF was determined by CSF and MRI characteristics for 47% of neurologists and 42% of medical oncologists, but only 30.5% of neurosurgeons and 21.5% of radiation oncologists (p = 0.039) (Supplementary Table). Almost half of the participants (103, 46%) selected intraventricular intra-CSF chemotherapy over intralumbar therapy *only* if repeated lumbar punctures were not feasible whereas 50 participants (22.5%) generally preferred intraventricular chemotherapy. Intraventricular intra-CSF chemotherapy was preferred over intralumbar administration for most patients by 31% of the participants in charge of LM versus only 12% of participants not in charge of LM (p = 0.0025) (Table 1). No significant difference was observed between participants according to their specialties regarding the route of administration of intra-CSF chemotherapy (Supplementary Table).

Only 35 participants (15.5%) felt that WBRT should always be performed. WBRT was always recommended by 35% of neurosurgeons and 28.5% of radiation oncologists, but by only 14.5% of neurologists and 4% of medical oncologists (p = 0.0012). WBRT was proposed in case of multifocal nodular disease by 73% of medical oncologists, 56% of neurologists, 50% of radiation oncologists and 39% of neurosurgeons (p = 0.0248) (Supplementary Table).

Most participants (n = 164, 73%) declared performing focal radiotherapy in LM patients in case of neurological symptoms only when these could be linked to MRI abnormalities. Only 30 participants (13.5%) agreed to opt for focal RT based on neurological symptoms only in LM patients (Table 1). Focal radiotherapy based on neurological symptoms in the presence of MRI abnormalities only was proposed mainly by radiation oncologists (90.5%) and medical oncologists (86.5%) as compared to neurologists (71.5%) and neurosurgeons (74%) (p = 0.0401) (Supplementary Table).

Cerebrospinal MRI for follow-up was reported to be done routinely by 108 participants (48%), commonly in 2–3 months intervals (60.5%) (Table 1). Standardized MRI follow-up was done more often when participants were in charge of LM (0.0406), whereas 25.5% of participants in charge of LM and 45% of participants not in charge planned MRI only depending on clinical course. No significant difference was observed among participants from different specialties regarding the imaging follow-up. To define the response status, 120 participants (53.5%) reported that they considered changes in steroid dose. Change of steroids dose was considered as part of criteria for response assessment of LM by 81% of medical oncologists, 62.5% of radiation oncologists, 56.5% of neurosurgeons and 50.5% of neurologists (p = 0.0071) (Supplementary Table).

Case vignettes

Eight cases were proposed to explore the diagnosis and treatment strategies in distinct situations (Supplementary Note 1): non-small cell lung cancer, epidermal growth factor receptor (EGFR) wildtype (case 1) and EGFR mutated (case 5); melanoma, BRAF mutated (case 2); breast cancer, HER2-negative (case 3) and HER2-positive (case 4); medulloblastoma (case 6); glioblastoma (case 7) and ependymoma (case 8). The completion rate was lower than for the general questionnaire with the following percentages of "no response": case 1: 37.5%; case 2: 40–47.5%; case 3: 46–61%; case 4: 48–50.5%; case 5: 55–66%; case 6: 59–64.5%, case 7: 57–60.5% and case 8: 55.5–60%). The highest rates of non-response within each case were observed when participants had to select a systemic agent.

Cases 2 and 5 addressed the initial evaluation of LM. Most participants agreed on the role of completing the initial evaluation of LM with an entire spinal MRI when lesions were first diagnosed in the brain. Only a minority of participants performed CSF flow studies at diagnosis. For most cases, no clear consensus was observed for treatment recommendations. However, most participants agreed on the value of combining therapeutic options. WBRT was recommended most of the time in combination with systemic treatment and/or intra-CSF in case of diffuse linear cerebral involvement (cases 2 and 3). However, WBRT was not recommended in the absence of brain involvement on cerebral MRI (case 4). Systemic treatment was widely proposed in almost all cases, with the exception of ependymoma (case 8), but without consensus on the choice of agent (cases 2, 5, 6, 8), with the exception of capecitabine for LM from breast cancer LM (case 3) and of a nitrosourea for LM from glioblastoma (case 7). Half of the participants recommended intra-CSF chemotherapy in non-brain primary tumors with LM, but almost no intra-CSF therapy was suggested for LM from medulloblastoma (case 6), glioblastoma (case 7) or ependymoma (case 8). Intra-CSF chemotherapy was mostly recommended in the presence of tumor cells in the CSF, but also when CSF cytology was negative (case 1). Liposomal cytarabine and methotrexate were the two intra-CSF drugs most commonly chosen.

Discussion

The diagnosis of LM remains difficult and is defined in most recent cohorts by the presence of malignant cells

in the CSF or, in the absence of malignant cells in the CSF, by concomitant characteristic clinical symptoms or signs and typical MRI findings [3–16]. However, clinical symptoms and signs vary according to areas of the CNS involved by tumor cells and may be difficult to distinguish from other neurological signs in cancer patients that are not related to LM.

In this survey, we observed that only a minority (16%) of participants used a scale for the neurological evaluation, although recommended by the Response Assessment in Neuro-Oncology (RANO)–Leptomeningeal Metastasis (LM) group [1]. We also noted that neurologists or medical oncologists do not use a neurological scale more frequently than neurosurgeons or radiation oncologists for the clinical evaluation. Such a scale could help defining the neurological signs related to LM and to detect changes in the neurological status during follow-up and should be considered for clinical practice.

Surprisingly, 23% of the participants declared not to perform a cerebrospinal MRI in case of suspicion of LM, although LM may involve both brain and spine and although the radiological presentation should have an impact on the clinical decision making [2]. Moreover, not performing a complete baseline evaluation renders response assessment difficult. 64 participants (28.5%) declared that an evaluation of CSF flow was never done at diagnosis. Mainly physicians who had declared not being in charge of LM in their respective hospitals proposed CSF flow studies. In most recent cohorts, including patients receiving intra-CSF chemotherapy, no CSF flow data are reported [3–21] although recommended by the RANO–LM group for patients considered for intra-CSF treatment [1].

Only half of the participants (56%) reported that CSF analysis was always done when LM from solid tumors except glioma is suspected, and up to 80% reported to perform CSF analyses only in case of doubt after clinical and MRI evaluation. Until now, despite a sensitivity rate of only 66–90% in recent cohorts of LM patients [4–9, 15, 22], the gold standard for the diagnosis of LM remains the demonstration of tumor cells in the CSF since clinical and MRI findings can be typical, but never specific. The prognostic role of malignant cells in the CSF at baseline and their role in the response assessment has not been clearly defined [1]. However, the identification of malignant cells in the CSF may influence the therapeutic decision, especially for intra-CSF treatment, which has a 1–2 mm limited penetration into tumoral nodules and acts probably mainly on floating cells and linear contrast enhancement. Only 17.5% of participants declared to perform always a CSF analysis in case of suspicion of LM in glioma patients. This may be explained by the limited role of intra-CSF chemotherapy within the overall treatment strategy.

Radiation oncologists declared to perform less often CSF analyses when LM is suspected. CSF volume and time between sampling and processing determine the quality of CSF samples and impact the sensitivity of CSF analysis [1, 23–25]. When CSF analysis was performed, the median volume of CSF was declared as more than 5 ml by 55.5% of participants and between 2 and 5 ml by 30.5% of participants, and the median time between CSF sampling and processing was declared as less than 60 min in 56.5%, and in less than 90 min in 77.5%, which reflects broad acceptance of these recommendations.

Another important point concerns the interpretation of the results of CSF analyses. For 44.5% of participants, "atypical" CSF is usually considered as positive and for 74.5% of participants, "suspicious" CSF is considered as positive. In the RANO–LM recommendations, an "atypical" CSF should be considered as negative and a "suspicious" CSF as positive [1]. These definitions have not been clearly defined by pathologists and have not been integrated into routine practice yet.

Several approaches can be combined for the treatment of LM. Systemic treatment is always administered by 31.5% of participants, and intra-CSF treatment is always given only by a minority or participants (3.5%). For others, decisions for systemic or intra-CSF treatment mainly depend on the primary cancer or on CSF and MRI findings. Intraventricular administration of chemotherapy was preferred over intralumbar administration for most patients only by 22.5% of participants whereas the majority reported to use a ventricular device only when lumbar punctures are not feasible. No difference was observed for the route of administration of intra-CSF treatment according to the specialty of participants, but intraventricular route of administration was preferred by participants declared as being in charge of LM. This is probably because ventricular devices permit, through a rapid painless and safe procedure, a homogeneous distribution of the drug into the CSF [26–28].

WBRT was proposed for all LM cases by 15.5% of participants and most participants suggested WBRT in case of concomitant brain metastases or multifocal nodular disease. Importantly, participants declared to administer focal radiotherapy mainly when neurological symptoms were associated with MRI abnormalities and not for neurological symptoms or signs alone.

In this survey, treatment approach varied significantly according to specialty by training. Half of the medical oncologists recommended systemic treatment whenever feasible versus a quarter of radiation oncologists. Moreover, a third of radiation oncologists always recommended WBRT versus less than 5% of medical oncologists.

Until now, only a few randomized trials in LM have been published, the last one more than 10 years ago [29–34]. Pretreatment evaluation, response assessment

and the reporting of treatment-related toxicity varied widely in these studies [35]. Thus no strong recommendations can be established for the management of LM, and treatment options remain mainly based on expert opinion.

In this survey, only 48% of the participants declared performing a cerebrospinal MRI for the follow-up of their patients regularly, and in up to 28.5% only depending on the clinical course. More cerebrospinal MRI were recommended during the follow-up of patients by participants in charge of LM presumably because these colleagues recognize the significance of the craniospinal extension of LM. No difference by specialty was observed for the frequency of MRI evaluation during follow-up.

Steroid doses were used as part of criteria to define the response to treatment as in brain metastases and gliomas for 53.5% of participants. The efficacy of steroids in the management of LM remains controversial, and the RANO-LM group proposed to not consider steroids in the response criteria for LM related to solid tumors [1].

The optimal management of LM requires multidisciplinary care and diagnosis and treatment strategies should ideally be developed in tumor boards. Although we did not ask specifically for that, we suspect that LM patients are often no finally discussed in such boards because organ specialists for the most common primary tumors breast, lung and melanoma may not share tumor boards with the dedicated neuro-oncology teams. This is why individual physicians and their attitudes as explored here are very important.

We are aware of several limitations of this study: The number of participants was limited, 51% colleagues terminated after opening the survey, presumably because of the length of the survey. The poor response rate for some questions may also reflect uncertainties of many collegues and the, the lack of consensus for the management of the disease. That mainly physicians treating only one patient per month participated, may seem to challenge the validity of the results, but their responses did overall not differ from responses of colleagues who reported to see more patients. Since participants were not systematically approached, the validity of the answers still remains uncertain as the results represent what clinical report [36]. Finally, the survey focused on diagnosis and therapeutic options and missed the opportunity to explore the current practice of palliative care for LM patients.

Nevertheless, this survey addresses important topics for preparing institutional or national guidelines for the diagnosis and management of patients with LM from solid tumors and helps to identify areas of controversies which can be addressed in future clinical trials.

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Compliance with ethical standards

Conflict of interest Emilie Le Rhun: research funding (Mundipharma); Dieta Brandsma: research funding (BBB pharmaceuticals); Roberta Rudà, Patrick Devos, Riccardo Soffietti, Michael Weller: no conflict of interest.

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