# Leptomeningeal metastases of solid cancer

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**Purpose of review**
To review recent original data on leptomeningeal metastases in patients with solid cancer.

**Recent findings**
Lung and breast cancer as well as melanoma remain the most common primaries. Advanced cytological methods and targeted sequencing for candidate tumor-specific mutations may improve the sensitivity of cerebrospinal fluid diagnostics in leptomeningeal metastases. Targeted treatments like epidermal growth factor receptor tyrosine kinase inhibitors for non-small cell lung cancer, anti-human epidermal growth factor receptor-2 treatments for breast cancer or B-rapidly accelerated fibrosarcoma-targeted or immunotherapy for melanoma have an emerging role in the management of this condition.

**Summary**
Novel diagnostic approaches and the introduction of targeted agents may improve the clinical management of patients with leptomeningeal metastases from solid cancers.

**Keywords**
brain metastases, carcinomatous meningitis, cerebrospinal fluid, leptomeningeal metastasis, neoplastic meningitis

## INTRODUCTION

Leptomeningeal metastases from solid cancers result from spreading to the subarachnoid space through hematogenous spread, direct infiltration from solid brain lesions, endoneural/perineural and perivascular spread, or iatrogenic spread after neurosurgery. Leptomeningeal metastases develop in approximately 5–10% of cancer patients. Breast cancer, lung cancer, and melanoma represent the three most common primary tumors [1,2]. Diagnosis is commonly made in patients with advanced cancer. Prognosis remains poor and survival limited to months despite multimodality treatment. Here we review original data on leptomeningeal metastases from solid cancer considering original articles and case reports of special interest published in English between January 2015 and June 2016.

## EPIDEMIOLOGY

The incidence of leptomeningeal metastases is increasing because of improvements in neuroimaging and systemic control of cancer. In a retrospective cohort of 1915, consecutive breast cancer patients followed up between 1998 and 2010, only three and six patients, respectively, presented with leptomeningeal metastases at 5 and 10 years [3]. The 5 and 10 years risks were 0.3 and 0.6%.

In a cohort of 519 patients with leptomeningeal metastases, 497 had solid tumors (mainly lung cancer, $n = 334$; breast cancer, $n = 96$; or gastrointestinal cancer, $n = 39$). Median age was 56, median Karnofsky performance score (KPS) 60 [4▪]. In 124 patients with brain metastases and radiographic leptomeningeal metastases, the most common primaries were lung cancer (42.7%), breast cancer (16.9%), and melanoma (8.9%), and the median age was 52 years [5].

Some general risk factors for leptomeningeal metastases have been identified, such as surgical resection of cerebellar metastases or surgical opening of the ventricular system [2]. Strong correlation between leptomeningeal metastases and surgical opening of the ventricles was observed in glioma patients [6]. The risk of leptomeningeal metastases

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## KEY POINTS

- Leptomeningeal metastasis is a typical manifestation of advanced cancer.
- Its incidence will increase with improved systemic treatment options for the three most common primaries: NSCLC, breast cancer, and melanoma.
- Novel technologies including gene panel sequencing will improve the sensitivity of detecting malignant cells in the CSF.
- Targeted therapy administered systemically or as intra-CSF treatment may improve outcome in subgroups of cancer patients with leptomeningeal metastasis.

following stereotactic radiosurgery (SRS) was evaluated in 126 breast cancer patients with brain metastases [7]. Eighteen patients (14%) developed leptomeningeal metastases and the actuarial risk at 12 months was 9% (11 patients). The leptomeningeal metastases risk was evaluated in another cohort of 330 patients treated with SRS without whole brain radiotherapy (WBRT) as upfront treatment and at least 3 months of follow-up; 218 patients were treated with SRS alone and 112 with surgery followed by SRS [8]. After a median follow-up of 9 months, 39 patients (12%) presented with leptomeningeal metastases after a median of 6.0 months, and the incidences of leptomeningeal metastases were 5.2 versus 16.9% for patients treated with SRS alone versus surgery followed by SRS. Surgical resection ($P < 0.01$) and breast cancer ($P = 0.03$) were associated with a risk of leptomeningeal metastases. In breast cancer, leptomeningeal metastases risk factors also include infiltrating lobular carcinoma and hormonal-negative cancers [2]. In a cohort of 233 breast cancer patients with leptomeningeal metastases with a median age of 50, 35% were hormone receptor positive / human epidermal growth factor receptor 2 (HER2)-negative, 29% were HER2+, and 35% were triple-negative [9▪]. The incidence of leptomeningeal metastases may be underestimated in clinical practice because current diagnostic procedures lack sensitivity and repeated evaluations are not always performed because of limited treatment options.

## DIAGNOSIS

Diagnosis remains challenging. Contemporary clinical trials base inclusion on positive cerebrospinal fluid (CSF) cytology, or, in its absence, on suggestive clinical and neuroimaging findings. Clinical features can be pleomorphic and depend on the CNS region involved [2]. Both neuroimaging and standard CSF cytology lack sensitivity. Among 529 patients with leptomeningeal metastases, 22% of patients were diagnosed with cytology alone, 35% by MRI alone, and 42% by both [4▪]. Craniospinal MRI represents the gold standard for a neuroimaging diagnosis of leptomeningeal metastases. The most frequent MRI signs include subarachnoid or ventricular nodules, focal or diffuse pial enhancement, and ependymal, sulcal, and cranial or spinal nerve root enhancement (Fig. 1). Rarely, leptomeningeal metastases may be visible on fluid-attenuated inversion recovery or T2-weighted imaging only [10].

Despite low sensitivity, CSF cytology remains the gold diagnostic standard. New analytical methods may improve the identification of tumor cells. A higher detection rate was observed with thin-layer preparation (Thinprep) than cytospin coupled Wright-Giemsa stain in 45 fresh CSF samples of patients with leptomeningeal metastases (73.3 vs. 57.8%, $P < 0.01$) [11].

CellSearch, an epithelial-cell adhesion molecule (EpCAM)-based method involving immunomagnetic enrichment followed by flow cytometry, which was designed for peripheral blood studies, has been adapted for the detection of malignant cells in the CSF by using the 'control mode' [12], addition of blood to the CSF [13], or coloration of the outside tube with a black felt-tip [14]. The value of the 'control mode' was confirmed on 38 CSF samples from breast cancer with a suspicion of leptomeningeal metastases [15]. Another case series of 18 leptomeningeal metastases lung cancer patients reported 77.8% sensitivity with an adaptation of the CellSearch method with a coloration of the outside of the tube versus 44.4% for standard cytology [16].

The contribution of flow cytometry immunophenotyping (FCI) using EpCAM for epithelial cell identification was evaluated in 144 patients with carcinomas, including 94 patients with confirmed leptomeningeal metastases [17]. The sensitivity was 79.79 versus 50% using FCI and standard cytology, and the negative predictive value was 68.85 versus 51.55%. Specificity and positive predictive value, however, were lower for FCI (84 versus 100%, 90.36 versus 100%). The prognostic value was evaluated in 72 patients with leptomeningeal metastases eligible for therapy. A cut-off value of 8% EpCAM-positive cells at baseline distinguished two statistically significant groups for overall survival ($P = 0.018$).

The value of EpCAM-based flow cytometry versus CSF cytology was also shown in 29 patients with clinical suspicion of leptomeningeal metastases [18]. The feasibility of counting tumor cells by 'tumor marker immunofluorescent *in situ* hybridization'

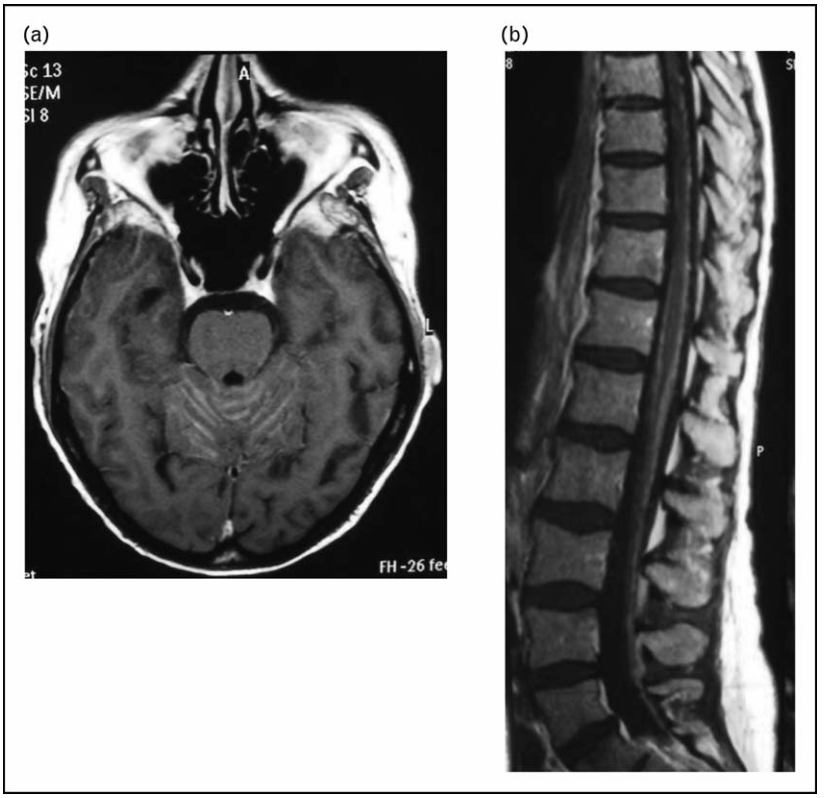


**FIGURE 1.** (a) Axial post T1 gadolinium image of the brain with typical meningeal contrast enhancement. (b) Sagittal post T1 gadolinium of the spine showing a characteristic perimedullar contrast enhancement, in a patient with leptomeningeal metastases from breast cancer.

was demonstrated in the CSF of lung cancer patients with leptomeningeal metastases [19]. These approaches, once prospectively validated, may improve the diagnostic yield of CSF analysis.

The feasibility of identifying cell-free DNA using whole exome sequencing to monitor response to treatment in CSF was shown in a patient with B-rapidly accelerated fibrosarcoma-mutated melanoma [20]. Digital PCR and targeted amplicon sequencing have also been reported in seven patients with solid primary and metastatic brain tumors [21]. The detection of epidermal growth factor receptor (EGFR) mutation including the resistance-associated mutation T790M in the CSF using real-time PCR was analyzed in seven patients with non-small cell lung cancer (NSCLC)-associated leptomeningeal metastases [22▪]. In all cases, EGFR mutations were identified in the CSF, although tumor cells were identified in only two CSF samples. EGFR mutations were identical in CSF and primary tumor, and no additional T790M mutations were observed in the CSF.

## PROGNOSIS

Median overall survival (OS) was 3 months in a large cohort of 519 patients with various primaries [4▪]. In another cohort of 124 patients with various primaries with brain metastases and radiographic signs of leptomeningeal metastases, median OS was 2.3 months [5]. In a systematic review on 851 patients with breast cancer leptomeningeal metastases, three groups of studies were identified [23]. In group A, five prospective trials, 129 breast cancer patients were identified among 300 leptomeningeal metastases cases [24–28]. Breast cancer–specific survival data were available for 71 patients. Intra-CSF treatment, given in 86%, was associated with a mean survival of 14.94 weeks. A study on prospective systemic treatment alone reported a median OS of 30.3 weeks. Group B1 included 10 retrospective studies with overall 693 patients including 259 patients with breast cancer with mean OS for breast cancer patients of 15.3 weeks. Group B2 included eight retrospective cohort studies dedicated to breast cancer and including 446 patients, median OS was 18.1 weeks. In a cohort of 233 breast cancer patients with leptomeningeal metastases, median OS was 4.4 months for HER2+, 3.7 months for HR+/HER2−, and 2.2 months for triple-negative breast cancer [9▪]. Among eight retrospective studies on various primaries, patients with breast cancer had longer survival than patients with other primaries, with survival of 15 weeks in

breast cancer versus 8.3 or 8.7 weeks for solid tumor excluding breast cancer or for lung cancer [23].

In a retrospective cohort of 32 EGFR-mutant NSCLC, median OS was 3.1 months [29▪]. Median OS of 2.9 and 16.9 weeks for untreated and treated patients were reported for patients with leptomeningeal metastases with melanoma [30▪]. Median OS was 239 days in 27 grade III/IV glioma patients with leptomeningeal metastases [6].

Favorable prognostic factors include KPS of 60 or more, absence of major neurologic deficits, minimal systemic disease, and reasonable systemic treatment options [31]. Previous studies confirmed the prognostic role of general status, age at leptomeningeal metastases diagnosis, treatment, and clinical improvement in response to treatment [2]. Similarly, high KPS, absence of brain metastases, CSF protein $\leq$ 50 mg/dl, and systemic treatment were positive prognostic factors [4▪,5,32]. The role of WBRT remains doubtful, with positive [5] and negative reports, albeit specifically in lung cancer [33], and no data from randomized trials.

## TREATMENT

Only six randomized trials have been published, all focusing on intra-CSF chemotherapy. A critical review of endpoints and response criteria showed a lack of standardization with respect to methodology and response criteria [34▪▪], a deficiency that ongoing efforts by the Response Assessment in Neurooncology Group (RANO) are trying to overcome. Large trials evaluating the role of systemic treatment in the management of leptomeningeal metastases are lacking. A review on interventional drug trials for adult patients with advanced NSCLC identified 413 open studies, of whom 78 (19%) excluded patients with leptomeningeal metastases, and 59 (14%) excluded patients with CNS metastases. CNS metastases were permitted after local treatment in 169 trials (41%), and CNS disease was not mentioned in 79 trials (19%) [35]. Despite a high incidence of CNS metastases, no direct evidence of efficacy can, therefore, be obtained in most trials for NSCLC. Of 519 patients, 28% received supportive care only, 45% chemotherapy alone (intra-CSF therapy alone in 84%, systemic therapy alone in 3%, and both in 13%), 10% radiotherapy alone, and only 17% chemotherapy combined with radiation [4▪]. Therapeutic options may vary according to histological subtype of the primary, general health status, presence and prior treatment for systemic and solid brain metastases, and clinical and imaging presentation.

Ventriculoperitoneal shunting (VPS) was evaluated in 59 patients (34% with leptomeningeal metastases) presenting with hydrocephalus (40 patients with brain metastases and 19 with primary brain tumors) [36]. The mean surgery time was 50.4 min. Symptoms were improved in 93% of patients. After a median follow-up of 6.3 months, complications had occurred in seven patients (11.8%), mean OS from shunt placement was 6.4 months. VPS remained functional in 93.5 and 87% at 3 and 12 months. Lumboperitoneal shunting, which is less invasive, may also be an option to treat leptomeningeal metastases-associated intracranial hypertension [37,38].

Craniospinal irradiation is rarely indicated in leptomeningeal metastases because of major bone marrow toxicity. Focal radiotherapy is mainly recommended in case of bulky disease and symptomatic or obstructive lesions. Durable response after SRS or cyberknife therapy have been reported in patients with a bulky or nodular disease previously treated with WBRT [39,40]. This approach should be considered for patients with bulky or nodular disease especially with negative CSF cytology.

Four partial responses and three stable diseases were reported in a retrospective series of 13 patients with breast cancer leptomeningeal metastases treated with i.v. thiotepa (40 mg/m$^2$ $\times$ 21 days) [41]. Survival rates at 6 and 12 months were 69 and 31%, respectively.

A prolonged response to bi-weekly high-dose lapatinib was reported in a patient with leptomeningeal metastases with HER2+ breast cancer [42]. Several dramatic clinical responses on the efficacy of bevacizumab combined with various chemotherapeutic agents were reported in patients with breast cancer with leptomeningeal metastases [43,44]. Median OS among eight patients in a pilot study (NCT 01281696) on bevacizumab combined with etoposide and cisplatin was 4.7 months, and neurological response or stability were observed in three and one patient, respectively [45]. In another recently reported phase I/II trial, ANG1005 (a paclitaxel/Angiopep-2 drug conjugate) with excellent BBB penetration was administered to 130 patients with breast cancer with recurrent brain metastases and/or leptomeningeal metastases. The clinical benefit rate in the 23 patients with leptomeningeal metastases was 74%, which included a 22% partial response and a 52% stable disease rate. In addition, a median OS of 8 months was observed in these patients versus the expected 3–3.5 months in historic controls [46▪]. A randomized phase II trial of this approach in patients with leptomeningeal metastases with metastatic breast cancer is in the planning stages.

Among a cohort 212 patients with NSCLC with leptomeningeal metastases of whom 60.9% were

treated with at least one regimen of tyrosine kinase inhibitors (TKI) before the leptomeningeal metastases diagnosis [47], 101 had a EGFR mutation status assessed, and 75 were positive. Leptomeningeal metastases treatment was EGFR TKI in 58.5% and WBRT in 60.4%. Median OS was 4.5 months, patients treated with EGFR inhibitors after leptomeningeal metastases had a better prognosis, with a median OS of 10.2 months with versus 1.2 months without. In a cohort of 32 patients with EGFR-mutant NSCLC [29▪], mutational status was identical in CSF with the primary biopsy in all six patients examined.

In a retrospective case series of 35 EGFR-mutant NSCLC patients diagnosed with leptomeningeal metastases after failure while on standard-dose EGFR TKI, 12 were treated with high-dose erlotinib and 23 with standard-dose EGFR-TKI [48]. High dose was well tolerated. Median OS were 6.2 months in the high dose and 5.9 months in the standard-dose group. A phase I trial with high dose of gefitinib in NSCLC with EGFR mutation or prior response to EGFR TKI and presenting with leptomeningeal metastases enrolled seven patients. No DLT was observed at 750 mg and one DLT was noted at 1000 mg dose level (toxic epidermal necrolysis). The study was closed due to slow accrual, median OS was 3.5 months [49].

Afatinib was evaluated in 35 patients pretreated with at least one line of chemotherapy and one line of EGFR-TKI and presenting with brain metastases and/or leptomeningeal metastases within a compassionate use program [50]. A cerebral response was reported in 35%, and cerebral control was obtained in 66% of the patients. Overall survival was estimated at 9.8 months.

The efficacy of icotinib was evaluated in 21 patients with NSCLC with leptomeningeal metastases treated at a standard dose in 16 patients or at double dose for patients developing leptomeningeal metastases on icotinib. Median OS was 10.1 months [51].

Potential efficacy of high-dose treatment with the third-generation EGFR-TKI AZD929 has been shown in an in-vivo model of leptomeningeal metastases from EGFR-mutant lung cancer [52].

The CSF concentration of crizotinib was evaluated in two patients with ALK positive NSCLC presenting with leptomeningeal metastases [53]. The CSF blood ratio was measured at 0.0006 in a first patient with a CNS response during 5 months and at 0.001 at leptomeningeal metastases diagnosis in a second patient. Durable responses were reported with alectinib in ALK-positive NSCLC after failure of crizotinib [54]. Only a few recent cohorts of melanoma patients with leptomeningeal metastases have been reported. A series of 39 consecutive melanoma patients with leptomeningeal metastases diagnosed between 2010 and 2015 experienced a median OS of 6.9 weeks [30▪]. Fourteen patients were not treated, because of poor general status or rapidly progressive disease. The median OS were 2.9 and 16.9 weeks for untreated and treated patients. The median survival of 21 patients treated with targeted therapy or immunotherapy or both was 21.7 weeks.

The diffusion of vemurafenib into CSF was investigated in six patients treated with vemurafenib 960 mg twice daily for brain metastases and suspicion of leptomeningeal metastases. The mean CSF : plasma concentration ratio was $0.98 \pm 0.84\%$ and no relationship was found between plasma and CSF vemurafenib concentrations [55].

There are no randomized trials establishing a definitive role for intra-CSF treatment for leptomeningeal metastases. The addition of intra-CSF treatment to systemic treatment should take into account the MRI presentation since the penetration into nodules is limited with intra-CSF therapy and because of potential neurotoxicity in patients with leptomeningeal metastases with hydrocephalus. A randomized phase III trial is currently evaluating the role of the intra-CSF route of administration in breast cancer patients with leptomeningeal metastases (NCT01645839).

Intraventricular devices are often used for the administration of intra-CSF therapy. In 109 consecutive patients who underwent a stereotatic Ommaya catheter placement (68% with normal or small ventricles), accurate placement was obtained in 99%. The revision rate was 7.3% [56]. Another study evaluated frameless stereotactic neuronavigation ($n = 88$) or fluoroscopic guidance with pneumoencephalograms ($n = 57$) for placement of Ommaya reservoirs in 145 patients [57]. The median time for the procedure was 39.2 min with frameless stereotaxy and 47.8 min with fluoroscopy. The device revision rate was similar in both groups (3.5 versus 5.5%), and early surgical complications were observed in 6.8% in the frameless stereotaxy group and 1.8% in the fluoroscopy group, which was interpreted as nonsignificant. In another prospective cohort of 112 patients, the placement of ventricular access devices was performed in a median surgery time of 15 min [58]. The revision rate was 7%. A new implantable pump able to deliver intra-CSF therapy in a metronomic fashion with electronic feedback was evaluated in an animal model [59]. The objective is to ensure a continuous drug exposure while minimizing toxic drug levels. No surgical procedure can be recommended as superior, and the experience of the surgical team should guide the choice.

**Table 1.** Overall survival in the main contemporary cohorts of more than 10 patients with leptomeningeal metastases according to the primary type of tumor published in the last 10 years

| Type of primary | Number of patients, time of enrollment | Median overall survival | Authors |
|---|---|---|---|
| Various solid tumors and hematological malignancies | $n=32$, between 1999 and 2003 | 19.9 weeks | Lassman *et al.* [71] |
| | $n=187$, between 2002 and 2004 | 2.4 months | Clarke *et al.* [72] |
| | $n=85$, between 1995 and 2005 | 51 days | Waki *et al.* [73] |
| | $n=135$, between 1989 and 2005 | 2.5 months | Oechsle *et al.* [74] |
| | $n=37$, between 1990 and 2008 | 12.6 weeks | Jiménez Mateos *et al.* [75] |
| | $n=27$, time of enrollment not detailed | 8.1 weeks | Gani *et al.* [76] |
| | $n=19$, time of enrollment not detailed | 43 days | Segura *et al.* [77] |
| | $n=51$, between 2004 and 2011 | 11 months | Jahn *et al.* [60] |
| | $n=529$, between 2005 and 2014 | 3 months | Hyun *et al.* [4▪] |
| | $n=124$, between 1999 and 2014 | 2.3 months | Brower *et al.* [5] |
| Breast cancer | $n=67$, between 2000 and 2005 | 4 months | Rudnicka *et al.* [78] |
| | $n=24$, between 1999 and 2008 | 5 months | Clatot *et al.* [79] |
| | $n=80$, between 2000 and 2007 | 4.5 months | Gauthier *et al.* [80] |
| | $n=60$, between 2003 and 2009 | 4 months | de Azevedo *et al.* [81] |
| | $n=112$, between 2007 and 2011 | 3.8 months | Le Rhun *et al.* [82] |
| | $n=233$, between 1997 and 2012 | HER2+ tumors: 4.4 months | Abouharb *et al.* [9▪] |
| | $n=149$, between 1999 and 2011 | HR+/HER2− tumors: 3.7 months | Niwińska [61] |
| | Prospective trials, $n=129$ | Triple-negative tumors: 2.2 months | Scott *et al.* [23] |
| | Retrospective studies, $n=259$ | 4.2 months | Chahal *et al.* [41] |
| | Retrospective cohort studies and prospective studies, $n=446$ | 19.94 weeks | |
| | $n=13$ | 15.3 weeks | |
| | | 18.1 weeks | |
| | | 4.7 months | |
| Lung cancer | $n=26$, time of enrollment not detailed | 57 weeks | Hammerer *et al.* [83] |
| | $n=50$, between 2003 and 2009 | 3 months | Morris *et al.* [33] |
| | $n=125$, between 2002 and 2009 | 4.3 months | Park *et al.* [84] |
| | $n=105$, between 2002 and 2010 | 3.0 months | Gwak *et al.* [85] |
| | $n=149$ (NSCLC), between 2001 and 2009 | 14 weeks | Lee *et al.* [86] |
| | $n=32$ (NSCLC), between 2000 and 2014 | 3.1 months | Kuiper *et al.* [29▪] |
| | $n=212$ (NSCLC), between 2003 and 2010 | 4.5 months | Liao *et al.* [47] |
| | $n=35$ (NSCLC), between 2007 and 2013 | Standard-dose EGFR TKI: 6.2 months high-dose EGFR TKI: 5.9 months | Kawamura *et al.* [48] |
| | $n=83$, between 2007 and 2012 | 8.7 weeks | Scott *et al.* [23] |
| | $n=51$ (NSCLC), between 2007 and 2014 | 3.9 months | Ozdemir *et al.* [32] |
| Melanoma | $n=110$, between 1994 and 2002 | 10 weeks | Harstad *et al.* [87] |
| | $n=39$, between 2010 and 2015 | Untreated patients ($n=14$): 2.9 weeks | Geukes Foppen *et al.* [30▪] |
| | | Treated patients ($n=25$): 16.9 weeks | |
| WHO grade III/IV gliomas | $n=27$, between 2008 and 2012 | 239 days | Roelz *et al.* [6] |

EGFR, epidermal growth factor receptor; NSCLC, non–small cell lung cancer; TKI, tyrosine kinase inhibitors.

Three chemotherapy agents are mainly used for intrathecal administration: (liposomal) cytarabine, methotrexate, and thiotepa. In a retrospective review of 51 patients with leptomeningeal metastases from solid tumors and hematological malignancies, treated with liposomal cytarabine, responses were reported in 81.8% and median OS was 11 months. NCTC V4.0 Grade 3–4 adverse events were observed in 35.3% [60]. Another prospective case series of 149 consecutive patients reported on the efficacy of a multimodality approach with systemic therapy ($n = 77$), radiotherapy ($n = 92$), intrathecal liposomal cytarabine ($n = 15$), and methotrexate ($n = 81$) in breast cancer patients with leptomeningeal metastases [61]. Median OS was 4.2 months; no difference in OS was observed between patients treated with intra-CSF liposomal cytarabine or methotrexate.

The efficacy and safety of concomitant intrathecal methotrexate + dexamethasone and concomitant involved-field radiotherapy for treating patients with leptomeningeal metastases was evaluated in a phase II trial enrolling 59 patients with leptomeningeal metastases with lung cancer ($n = 42$), breast cancer ($n = 11$) or others (n = 6), with a median KPS of 40. The overall response was 86.7%; median OS was 6.5 months. Toxicities included acute meningitis, chronic delayed encephalopathy, radiculitis, myelosuppression, and mucositis, with 20.3% of grade 3–4 adverse events [62].

Intrathecal thiotepa was retrospectively evaluated as salvage therapy at progression on intrathecal methotrexate alone or methotrexate and cytarabine in 40 selected patients with leptomeningeal metastases from various primaries [63], with a median OS of 19.2 weeks.

The feasibility of subcutaneous and intrathecal immunotherapy with CpG-ODN in leptomeningeal metastases was assessed in a phase I trial with leptomeningeal metastases from various primaries. Median OS was 15 weeks [64]. A potential value of intrathecal trastuzumab used as single agent or in combination with intrathecal methotrexate and in combination with various systemic therapies (including trastuzumab) in breast cancer HER2+ patients with leptomeningeal metastases has been reported [65–68]. Two trials evaluating the role of intrathecal trastuzumab are ongoing (NCT01325207, NCT01373710). A durable response after intrathecal etoposide was reported in a breast cancer patient with leptomeningeal metastases [69]. Experience on intrathecal administration of autologous tumor-infiltrating lymphocytes has been reported in a melanoma patient [70]. No toxicity was observed and increased inflammatory cytokines were observed in the CSF. After 5 months, brain and systemic progression were observed, but no leptomeningeal metastases progression.

## CONCLUSION

Lung and breast cancer as well as melanoma remain the most common primary tumors in patients diagnosed with leptomeningeal metastases. As shown in Table 1, the overall survival has not improved over the last 10 years. Advanced cytological methods and targeted sequencing for candidate tumor-specific mutations may improve the sensitivity of CSF diagnostics in leptomeningeal metastases. The role of targeted treatments in leptomeningeal metastases is emerging. Novel diagnostic approaches and the introduction of targeted agents may improve the clinical management of patients with leptomeningeal metastases.

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