Reports of Practical Oncology and Radiotherapy 25 (2020) 307–311

Available online at www.sciencedirect.com

Reports of Practical Oncology and Radiotherapy

journal homepage: http://www.elsevier.com/locate/rpor

Original research article

Long-term survival results after treatment for oligometastatic brain disease

Carsten Nieder[a,b,*], Mandy Hintz[c], Ilinca Popp[c,d], Angelika Bilger[c,d], Anca L. Grosu[c,d]

[a] Department of Oncology and Palliative Medicine, Nordland Hospital, 8092 Bodø, Norway
[b] Department of Clinical Medicine, Faculty of Health Sciences, University of Tromsø, 9037 Tromsø, Norway
[c] Department of Radiation Oncology, University Hospital Freiburg, 79106 Freiburg, Germany
[d] German Cancer Consortium (DKTK), Partner Site Freiburg, Germany

ARTICLE INFO

Article history:
Received 13 November 2019
Received in revised form
30 December 2019
Accepted 2 March 2020
Available online 4 March 2020

Keywords:
Brain metastases
Oligometastases
Radiotherapy
Radiosurgery
Neurosurgery

ABSTRACT

Aim: The aim of this study was to characterize the survival results of patients with up to four brain metastases after intense local therapy (primary surgery or stereotactic radiotherapy) if extracranial metastases were absent or limited to one site, e.g. the lungs.
Background: Oligometastatic disease has repeatedly been reported to convey a favorable prognosis.
Material and methods: This retrospective study included 198 German and Norwegian patients treated with individualized approaches, always including brain radiotherapy. Information about age, extracranial spread, number of brain metastases, performance status and other variables was collected. Uni- and multivariate tests were performed.
Results: Median survival was 16.5 months (single brain metastasis) and 9.8 months (2–4, comparable survival for 2, 3 and 4), respectively (p = 0.001). After 5 years, 15 and 2% of the patients were still alive. In patients alive after 2 years, added median survival was 23 months and the probability of being alive 5 years after treatment was 26%. In multivariate analysis, extracranial metastases were not significantly associated with survival, while primary tumor control was.
Conclusion: Long-term survival beyond 5 years is possible in a minority of patients with oligometastatic brain disease, in particular those with a single brain metastasis. The presence of extracranial metastases to one site should not be regarded a barrier towards maximum brain-directed therapy.

1. Background and aim

Current research has indicated that oligometastatic cancer is a disease state that should be differentiated from the more common state of disseminated distant spread, and that surgery or other ablative treatments might have a positive impact on prognosis.[1–4] In the context of oligometastases to the brain without leptomeningeal seeding it has long been recognized that effective local therapy often translates into survival beyond the typical landmark of 1–2 years.[5–8] Commonly, up to four brain metastases are regarded suitable targets for local therapy, such as stereotactic radiosurgery (SRS), stereotactic fractionated radiotherapy (SFRT) and surgical resection.[9–11] The latter is often supplemented by post-operative stereotactic radiotherapy,[12] while whole-brain radiotherapy (WBRT) is deferred until more widespread metastases become apparent. In case of negative prognostic factors, such as extensive and uncontrollable extracranial disease, WBRT or even best supportive care alone might be appropriate even in situations with up to four brain metastases.[13,14] The aim of the present study was to characterize the survival results of patients with up to four brain metastases after intense local therapy (primary surgery, SRS or SFRT) if extracranial metastases were absent or limited to one site, e.g. the lungs. We hypothesized that the combination of a favorable disease extent and efficacious local treatment would lead to detectable 5-year survival, comparable to studies of oligometastases not involving the brain.

2. Material and methods

2.1. Patients and treatment

A retrospective study based on chart review of 198 patients with 1–4 irradiated brain metastases was performed. Patients managed

* Corresponding author at: Department of Oncology and Palliative Medicine, Nordland Hospital, 8092 Bodø, Norway.
E-mail address: carsten.nieder@nlsh.no (C. Nieder).

https://doi.org/10.1016/j.rpor.2020.03.001
1507-1367/

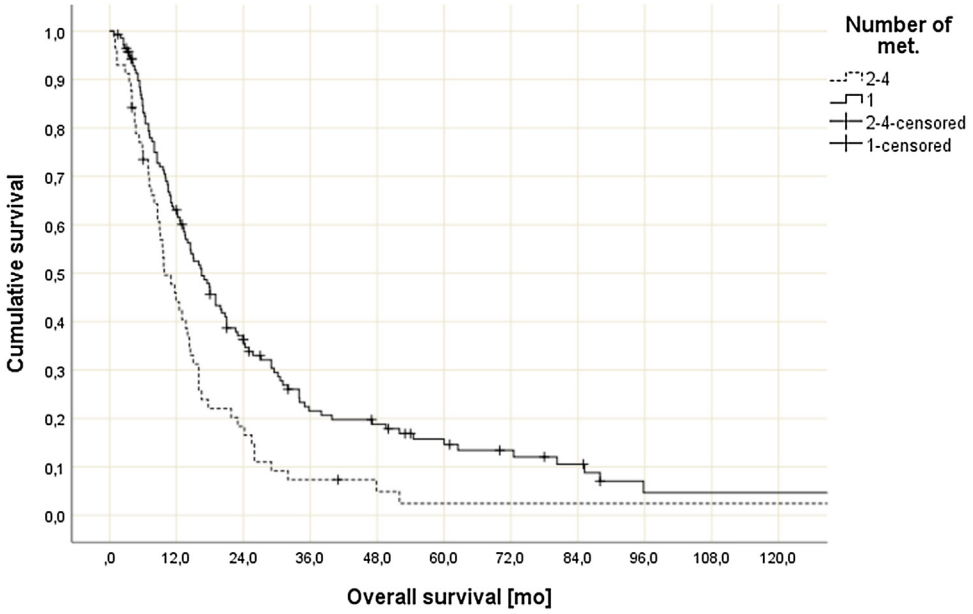

Fig. 1. Actuarial overall survival (Kaplan–Meier analysis) stratified by the number of brain metastases (one versus two, three or four), p = 0.001 (log-rank test).

with best supportive care or WBRT rather than surgery, SRS or SFRT were excluded. The same applies to patients with extracranial metastases to more than one site, meaning that those with adrenal gland metastases were eligible, while those with adrenal gland plus lung metastases were not. Patients with pleural or peritoneal metastases were not included. The number of extracranial metastases was not limited, because the imaging studies and intervals were not standardized in this real-world patient cohort. Staging was done as judged appropriate by the oncologists at the time of diagnosis of brain metastases. PET imaging was not mandatory and, therefore, the registered number of metastases might not always have been accurate enough when applying a common threshold for oligometastases, such as five metastases in total. We felt that a simple measure of extracranial disease extent, i.e. maximum one site, would be a reliable parameter to include for evaluation in this study. Moreover, in resource-limited settings extensive and advanced staging might not be feasible in a clinical routine. The vast majority of patients never received ablative treatments, such as stereotactic body radiotherapy, for extracranial metastases. Brain-directed treatment was individualized and consisted of the aforementioned focal therapies with or without WBRT, or postoperative SRS/SFRT. Sequential salvage treatment of new or progressive intracranial lesions was individualized, too. All approaches mentioned above were considered at the time of relapse or progression. Systemic treatment before and after brain-directed measures was usually prescribed as judged appropriate by the patients' medical oncologists. The patients were treated between 2000 and 2018 and identified from a previously described database, which includes data from the radiotherapy centers in Bodø and Freiburg.[8]

2.2. Statistical methods

Actuarial survival from the first day of radiotherapy or from surgery was calculated employing the Kaplan–Meier method, and different groups were compared using the log-rank test (SPSS 25, IBM Corp., Armonk, NY, USA). Date of death was known in all but 29 patients. The latter were included as censored observations after a median follow-up of 25 months (range 2–160). Uni- and multivariate Cox regression analysis was also performed (forward conditional method). The multivariate model included baseline patient characteristics that had p-values <0.05 in univariate analysis, but not treatment-related parameters.

3. Results

3.1. Patient characteristics

Most patients (73%) had brain metastases alone. In 71% a single lesion was present on the treatment planning magnetic resonance imaging scans. Treatment included surgical resection in 78%. As shown in Table 1, non-small cell lung cancer (NSCLC) and breast cancer were common primary tumors.

3.2. Survival

Median survival was 16.5 months after treatment for single brain metastases (two: 9.6 months, three: 11.9 months, four: 9.8 months, pooled 9.8 months). As shown in Fig. 1, five-year survival was 15 and 2%, respectively (log-rank test p = 0.001). The differences regarding two, three or four brain metastases were not statistically significant (all p-values >0.11). Conditional survival was evaluated, too (based on 54 patients who were alive two years after treatment). Their probability of being alive five years after treatment was 26%, and added median survival was 23 months.

The presence of extracranial metastases worsened median survival (16.0 versus 10.5 months, p = 0.01). These results were obtained for the subgroup with a single metastasis (18.0 versus 13.2 months) and 2–4 metastases (14.0 versus 9.5 months). However, different sites of extracranial metastases had different impact on survival, as shown in Fig. 2. Survival was the worst in patients with hepatic metastases (median 5.3 months), intermediate in those with pulmonal, lymphatic or osseous metastases (median 11.9 months) and the best in those with adrenal, cutaneous or subcutaneous/soft tissue metastases (median 16.3 months). The latter figure was similar to that seen in the absence of extracranial metastases (median 16.0 months, p = 0.19).

Controlled primary tumors were associated with a better median survival (16.0 versus 11.0 months, p = 0.02). Primary disease type was also associated with survival, as shown in Table 2. Prognostic factors also included age (p = 0.002 in the univariate Cox

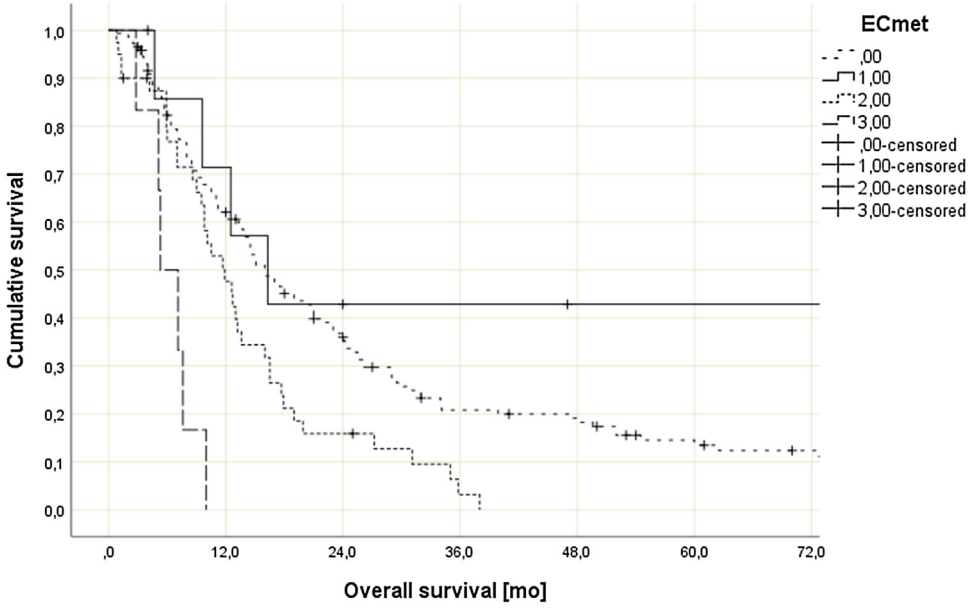

Fig. 2. Actuarial overall survival (Kaplan–Meier analysis) stratified by extracranial metastases: none, favourable (adrenal, cutaneous, subcutaneous/soft tissue), intermediate (pulmonal, osseous, lymphatic), unfavourable (hepatic), p = 0.19 (none versus favourable), p < 0.05 for unfavourable versus each of the remaining groups and also for intermediate versus each of the remaining groups. Number of patients: 144 (none), 8 (favourable), 40 (intermediate), 6 (unfavourable).

Table 1
Baseline characteristics in 198 patients.

Parameter	Number	Percent
Single brain metastasis	141	71
Two brain metastases	29	15
Three brain metastases	22	11
Four brain metastases	6	3
No extracranial metastases	144	73
One extracranial site involved	54	27
Controlled primary tumor	134	68
Uncontrolled primary tumor	62	31
Unknown status of the primary tumor	2	1
Surgical resection	154	78
Stereotactic radiosurgery	30	15
Stereotactic fractionated radiotherapy	14	7
Non-small cell lung cancer	90[a]	45
Breast cancer	21	11
Kidney cancer	18	9
Colon cancer	14	7
Malignant melanoma	13	7
Rectal cancer	10	5
Unknown primary tumor	7	4
Small cell lung cancer	6	3
Ovarian cancer	5	3
Others	14	7
Female sex	106	54
Male sex	92	46
Synchronous brain metastases	63	32
Presentation within 12 months	46	23
Interval 13–35 months	46	23
Interval at least 36 months	26	13
Metachronous, undocumented interval	17	9
Systemic treatment after local therapy	65	33
No systemic treatment	36	18
Lack of definitive information	97	49
Median age, years, range	63	25–85
Median Karnofsky performance status	80	60–100

[a] 46 adenocarcinoma, 16 squamous cell carcinoma, 28 others/mixed/unspecified.

Table 2
Median overall survival (OS) stratified by primary tumor.

Tumor	Median OS
Small cell lung cancer	19.0
Ovarian cancer	19.0
Rectal cancer	17.5
Malignant melanoma	16.3
Kidney cancer	16.0
Non-small cell lung cancer (others, mixed, unspecified)	15.0
Non-small cell lung cancer (squamous cell)	14.0
Non-small cell lung cancer (adenocarcinoma)	13.7
Breast cancer	13.0
Unknown primary	6.4
Bladder cancer	5.4
Colon cancer	4.2

model) and Karnofsky performance status (KPS, p = 0.0001 in the univariate Cox model), whereas time interval (p = 0.29, log-rank test) and gender were not significant (p = 0.78, log-rank test).

Systemic therapy after local treatment was associated with improved survival (median 14.5 versus 9.0 months, p = 0.04). Surgery and SRS resulted in comparable outcome (median 16.0 versus 13.3 months, p = 0.98).

The multivariate model (Table 3) identified better KPS (p = 0.0001), single brain metastasis (p = 0.0001), primary tumor other than colon, bladder or unknown (p = 0.008), younger age (p = 0.009), and controlled primary tumor (p = 0.014) as independent prognostic factors for survival. Irrespective of different ways of stratification, extracranial metastases were not significant in the multivariate model.

4. Discussion

This study mainly included patients with a single brain metastasis (71%) whose management included surgical resection with or without post-operative radiotherapy (78%). Seventy-three percent had brain metastases alone, the others extracranial metastases to one site without peritoneal or pleural involvement. In 25 cases (13%), these extracranial lesions were located in the lungs. The exact number of extracranial metastases was not included in this analysis, due to considerations and limitations already outlined. We believe this simple and straightforward approach towards the definition of limited extracranial spread facilitates evaluation of retrospective databases that include information from staging methods, which evolved over time. In addition, it limits the

Table 3
Prognostic factors for overall survival.

Parameter	Univariate p-value	Multivariate p-value	Hazard ratio
Age, continuous	0.002	0.009	1.02
KPS, continuous	0.0001	0.0001	0.61
Single brain metastasis	0.001	0.0001	0.52
Any extracranial metastases present	0.01	0.09	n.s.
Controlled primary tumor	0.02	0.014	0.62
Primary tumor colon, bladder or unknown	0.001	0.008	1.72
Gender	0.78		
Time interval	0.29		

KPS: Karnofsky performance status, n.s.: not significant.

resource utilization during staging or re-staging of these patients in clinical practice where the diagnosis, e.g., of small lung nodules that are difficult to biopsy or characterize on PET scans, poses challenges. The study cohort was heterogeneous regarding the type of primary tumor, time interval between cancer diagnosis and detection of brain metastases, age, etc., and included a real-world population managed at two academic hospitals (all comers).

In line with our hypothesis, a subgroup of patients survived five or more years, in particular if single brain metastases were treated. Otherwise, the number of brain metastases (2, 3 or 4) did not significantly influence survival. Interestingly, multivariate analysis revealed that the apparent role of extracranial metastases diminished if other prognostic factors were considered as well. Eventually, primary tumor type and control were more important, beside well-established parameters, such as KPS and age. Unknown primary tumors (4%) were classified as uncontrolled. Seemingly, the pattern of extracranial spread impacted survival (worst in the case of liver involvement). However, since these results were derived from small subgroups and did not persist in multivariate analysis additional work is needed to draw firm conclusions. At present, we recommend to consider surgery, SRS or SFRT also in patients with limited extracranial metastases, as defined in this study. In parallel, WBRT with simultaneous integrated dose escalation on multiple brain metastases is under investigation.[15]

It is important to note that few patients received local treatment of their extracranial metastases. Rather, systemic therapy was administered. Unfortunately, the latter was not documented sufficiently in a considerable number of cases. In those with available information, systemic therapy was associated with better survival, comparable to a previous study that included patients treated with WBRT.[16] Most patients were treated before immune checkpoint inhibitors became clinically available. Compared to other parts of the world, few of our patients with NSCLC were eligible for targeted therapy, due to the absence of relevant targets. It is, therefore, tempting to speculate that contemporary management might be able to further improve the long-term survival results.[17]

There is additional evidence from other studies supporting the present findings. For example, a multi-center study from the United States and Canada (SRS, 2083 patients, many (46%) with lung primaries, 14% without extracranial metastases) demonstrated a median survival of 14.6 months (single brain metastasis) and 9.5 months (2–4 metastases).[18] Patients with 2–4 metastases had a significantly higher risk of distant brain failure. This endpoint was not included in our analysis. Compared to no extracranial metastases, oligometastases (max.5) were associated with significantly worse survival (HR 1.47 in multivariate analysis). However, this definition does not take into account the number of involved organs or sites and is not directly comparable to our approach and eligibility criteria. In the future, additional strategies might improve identification of patients with limited extracranial disease burden, e.g. liquid biomarkers and surrogates of impaired organ function.[19,20]

For patients with breast cancer, a Polish study reported median survival of 20 months in the setting of a solitary brain metastasis (i.e., no extracranial spread) and 11 months for patients with single brain metastases.[21] In our combined group (n = 21, too small to stratify), the corresponding figure was 13 months. Kotecha et al. have also shown that 5–10 year survival is possible, especially if solitary or single brain lesions were present.[22] Despite these encouraging data, non-brain oligometastases seemingly fare better. After stereotactic radiotherapy of pulmonary oligometastases (max.5, max.2 organs) median survival was 33 months and 5-year survival 30%.[23] In a different study (surgery or radiotherapy, lung oligometastases) 5-year survival was about 40% for both modalities.[24] A 5-year survival rate of 32% was reported by Wong et al. (max.5 metastases, stereotactic radiotherapy).[25] Possibly, differences in tumor biology might explain these results (predominant brain seeding vs. affinity to other sites).[26] Even if retrospective studies suffer from limitations and possible selection bias, the aggregate data suggests that it is important for clinicians to perform a comprehensive assessment of management options in patients with brain metastases who have the potential to survive for many years, both in synchronous and metachronous settings.

Conflict of interest

None declared.

Financial disclosure

None declared.

References

1. Stenman M, Sinclair G, Paavola P, Wersäll P, Harmenberg U, Lindskog M. Overall survival after stereotactic radiotherapy or surgical metastasectomy in oligometastatic renal cell carcinoma patients treated at two Swedish centres 2005–2014. *Radiother Oncol*. 2018;127:501–506.
2. Pitroda SP, Chmura SJ, Weichselbaum RR. Integration of radiotherapy and immunotherapy for treatment of oligometastases. *Lancet Oncol*. 2019;20:e434–e442.
3. Massaut E, Bohlok A, Lucidi V, Hendlisz A, Klastersky JA, Donckier V. The concept of oligometastases in colorectal cancer: from the clinical evidences to new therapeutic strategies. *Curr Opin Oncol*. 2018;30:262–268.
4. Scorsetti M, Franceschini D, De Rose F, et al. The role of SBRT in oligometastatic patients with liver metastases from breast cancer. *Rep Pract Oncol Radiother*. 2017;22:163–169.
5. Nowak-Sadzikowska J, Walasek T, Jakubowicz J, Blecharz P, Reinfuss M. Current treatment options of brain metastases and outcomes in patients with malignant melanoma. *Rep Pract Oncol Radiother*. 2016;21:271–277.
6. Gray PJ, Mak RH, Yeap BY, et al. Aggressive therapy for patients with non-small cell lung carcinoma and synchronous brain-only oligometastatic disease is associated with long-term survival. *Lung Cancer*. 2014;85:239–244.
7. Füreder LM, Widhalm G, Gatterbauer B, et al. Brain metastases as first manifestation of advanced cancer: exploratory analysis of 459 patients at a tertiary care center. *Clin Exp Metastasis*. 2018;35:727–738.
8. Nieder C, Hintz M, Oehlke O, Bilger A, Grosu AL. The TNM 8 M1b and M1c classification for non-small cell lung cancer in a cohort of patients with brain metastases. *Clin Transl Oncol*. 2017;19:1141–1146.
9. Thiagarajan A, Yamada Y. Radiobiology and radiotherapy of brain metastases. *Clin Exp Metastasis*. 2017;34:411–419.
10. de la Peña C, Guajardo JH, Gonzalez MF, González C, Cruz B. CyberKnife stereotactic radiosurgery in brain metastases: a report from Latin America with literature review. *Rep Pract Oncol Radiother*. 2018;23:161–167.

11. van der Meer PB, Habets EJJ, Wiggenraad RG, et al. Individual changes in neurocognitive functioning and health-related quality of life in patients with brain oligometastases treated with stereotactic radiotherapy. *J Neurooncol*. 2018;139:359–368.
12. Bilger A, Milanovic D, Lorenz H, et al. Stereotactic fractionated radiotherapy of the resection cavity in patients with one to three brain metastases. *Clin Neurol Neurosurg*. 2016;142:81–86.
13. Nieder C, Guckenberger M, Gaspar LE, et al. Management of patients with brain metastases from non-small cell lung cancer and adverse prognostic features: multi-national radiation treatment recommendations are heterogeneous. *Radiat Oncol*. 2019;14:33.
14. Nieder C, Norum J, Dalhaug A, Aandahl G, Pawinski A. Radiotherapy versus best supportive care in patients with brain metastases and adverse prognostic factors. *Clin Exp Metastasis*. 2013;30:723–729.
15. Oehlke O, Wucherpfennig D, Fels F, et al. Whole brain irradiation with hippocampal sparing and dose escalation on multiple brain metastases: local tumour control and survival. *Strahlenther Onkol*. 2015;191:461–469.
16. Nieder C, Marienhagen K, Dalhaug A, Aandahl G, Haukland E, Pawinski A. Impact of systemic treatment on survival after whole brain radiotherapy in patients with brain metastases. *Med Oncol*. 2014;31:927.
17. Luke JJ, Lemons JM, Karrison TG, et al. Safety and clinical activity of pembrolizumab and multisite stereotactic body radiotherapy in patients with advanced solid tumors. *J Clin Oncol*. 2018;36:1611–1618.
18. Hughes RT, Masters AH, McTyre ER, et al. Initial SRS for patients with 5 to 15 brain metastases: results of a multi-institutional experience. *Int J Radiat Oncol Biol Phys*. 2019;104:1091–1098.
19. Nieder C, Dalhaug A, Pawinski A. Serum lactate dehydrogenase contributes to prognostic assessment in patients with oligometastatic cancer and brain involvement. *In Vivo*. 2019;33:229–232.
20. Hanssen A, Riebensahm C, Mohme M, et al. Frequency of circulating tumor cells (CTC) in patients with brain metastases: implications as a risk assessment marker in oligo-metastatic disease. *Cancers (Basel)*. 2018;10(12).
21. Niwińska A, Pogoda K, Murawska M, Niwiński P. Factors influencing survival in patients with breast cancer and single or solitary brain metastasis. *Eur J Surg Oncol*. 2011;37:635–642.
22. Kotecha R, Vogel S, Suh JH, et al. A cure is possible: a study of 10-year survivors of brain metastases. *Neurooncol*. 2016;129:545–555.
23. Sharma A, Duijm M, Oomen-de Hoop E, et al. Survival and prognostic factors of pulmonary oligometastases treated with stereotactic body radiotherapy. *Acta Oncol*. 2019;58:74–80.
24. Lodeweges JE, Klinkenberg TJ, Ubbels JF, Groen HJM, Langendijk JA, Widder J. Long-term outcome of surgery or stereotactic radiotherapy for lung oligometastases. *J Thorac Oncol*. 2017;2:1442–1445.
25. Wong AC, Watson SP, Pitroda SP, et al. Clinical and molecular markers of long-term survival after oligometastasis-directed stereotactic body radiotherapy (SBRT). *Cancer*. 2016;122:2242–2250.
26. Prasanna T, Karapetis CS, Roder D, et al. The survival outcome of patients with metastatic colorectal cancer based on the site of metastases and the impact of molecular markers and site of primary cancer on metastatic pattern. *Acta Oncol*. 2018;57:1438–1444.