

Survival Then and Now in Patients With Surgically Resected Brain Metastasis: Major Improvement in Cases With Controlled Primary Tumor

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Abstract

Background/Aim: The aim of this study was to analyze the survival outcomes in different time periods (recent, 2016-2024; earlier, 2007-2015; historical, before 2007) for patients with brain metastasis managed with surgical resection and postoperative radiotherapy. Major changes in systemic therapy over time were hypothesized to translate into better survival.

Materials and Methods: A retrospective analysis was performed that included 174 patients, largely with single brain metastasis and Karnofsky performance status (KPS) 80-100. Uni- and multivariate analyses of actuarial overall survival were performed.

Results: Three significant prognostic factors for survival emerged: KPS, primary tumor control, and administration of systemic therapy after treatment of brain metastasis. In all patients, and also those who received systemic therapy after treatment for brain metastasis, survival remained similar (median of 16 months) for all three time periods (recent, earlier, historical). In patients with controlled primary tumor, survival increased from 17.5 (historical) to 35.8 months, $p=0.01$.

Conclusion: Patients with resected and postoperatively irradiated brain metastasis benefited from additional systemic therapy. Only one subgroup experienced major survival prolongation in more recent years: those with controlled primary tumor. Therefore, efforts to optimize primary tumor control, such as surgery and radical radiotherapy, may play an important role in multimodal treatment paradigms.

Keywords: Palliative radiation therapy, stereotactic radiotherapy, quality of care, prognosis, metastatic cancer.

Introduction

Personalized treatment options have evolved for patients with brain metastasis from solid primary tumors, *e.g.* lung, breast, bowel and kidney cancer (1-5). Guided by number, location, size and biology of the lesions, and,

in addition, well-established prognostic factors, *e.g.* performance status, primary tumor control, and presence of extracranial metastases, the initial question is whether systemic treatment alone should be offered. Alternatively, local brain-directed measures may be indicated, especially in an oligometastatic setting or if clinically symptomatic



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lesions are present (6-8). Recommended measures include stereotactic radiotherapy (SRT), whole-brain radiotherapy (WBRT), and surgical resection. The latter has advantages such as histopathological confirmation of the diagnosis and rapid relief of mass effect and edema (9, 10). It is, however, an invasive procedure and carries a considerable risk of local relapse and detection of new brain metastases distant from the resection cavity (11).

Historically, postoperative WBRT was often recommended (12). In clinical trials, early postoperative SRT has emerged as the recommended approach (13, 14). It reduced resection-site failures and preserved neurocognitive function. WBRT is now regarded as later line salvage treatment (4). Both highly efficacious brain-directed therapy and improved systemic treatment have reduced the risk of early death after the detection of brain metastasis. The aim of our study was to analyze survival by time-period and systemic therapy in patients undergoing resection and postoperative radiotherapy. We hypothesized that recently treated patients (2016-2024) have longer survival than their historical peers.

Patients and Methods

A retrospective study was performed, employing our previously described merged database from German and Norwegian institutions (15). All study patients were adults with non-hematological cancers treated in routine clinical practice outside of prospective clinical trials. They had newly diagnosed, histologically verified parenchymal brain metastasis confirmed by resection of at least one lesion. Patients with brain biopsy only were excluded. The clinical oncologists in charge prescribed both postoperative RT and state-of-the-art systemic treatment, based on tumor-specific guidelines and multidisciplinary tumor board recommendations. Shared decision-making was individualized on a case-by-case basis without employing decision support tools.

We compared three strata: 2016-2024 (recent), 2007-2015 (earlier), and before 2007 (historical). Historical patients always received WBRT (10×3 Gy, 15×2.5 Gy

or 20×2 Gy; sometimes with sequential boost). Recent patients were managed with fractionated cavity SRT (3×9 Gy, or 6-7×5 Gy; 7 fractions in the case of residual tumor on early postoperative magnetic resonance imaging. Earlier patients in the transition phase between WBRT and SRT received a large variety of approaches, which also included focal treatment with 10-13 fractions. Postoperative RT typically commenced within 3-5 weeks after resection. In the case of brain metastasis relapse during the course of the disease, further SRT, WBRT and resection were considered. Therefore, highly individualized treatment sequences were employed.

Descriptive statistics were employed for statistical analyses in IBM SPSS Statistics (Version 29; Armonk, NY, USA). Survival data were obtained in November 2025 by use of our electronic patient records, which also provided baseline characteristics such as age, sex *etc.* Twenty-five out of 174 patients were still alive when analyzing the data (censored observations in Kaplan–Meier analyses; median follow-up of 26 months). Actuarial survival curves were calculated according to the Kaplan–Meier method and analyzed by log-rank tests (start date: first day of postoperative radiotherapy). Furthermore, forward conditional Cox regression analysis was employed. Statistical significance was defined as *p*-value of less than 0.05. In the Cox regression analysis, parameters with univariate *p*-value <0.1 in the log-rank tests were included.

Results

Among all patients who received active treatment for brain metastases 15% were managed with surgical resection and included in this study. Most study patients were treated before 2007 (n=103), while 33 and 38 belonged to the 2007-2015 and 2016-2024 cohorts, respectively. Regarding all 174 study patients, their median age was 63 years (range=33-85 years) and 89 (51%) were females (Table I). Typical patients had a single brain metastasis (79%), no extracranial metastasis (79%), and intermediate prognostic features (class 2) according to

Table 1. Baseline and treatment parameters in 174 patients postoperatively irradiated for brain metastasis.

| Parameter | Subgroup | Value |
|--------------------------------|---------------------------------------|-------------|
| Sex, n (%) | Female | 89 (51) |
| | Male | 85 (49) |
| Age, years | Median (range) | 63 (33-85) |
| Time interval, months | Median (range) | 8 (0-216) |
| KPS) | Median (range) | 80 (60-100) |
| Primary disease, n (%) | Breast cancer | 19 (11) |
| | NSCLC | 80 (46) |
| | SCLC | 6 (3) |
| | Kidney cancer | 14 (8) |
| | Colorectal cancer | 19 (11) |
| | Malignant melanoma | 12 (7) |
| | Ovarian cancer | 5 (3) |
| | Bladder cancer | 4 (2) |
| | Undetected primary tumor | 7 (4) |
| | Other | 8 (5) |
| Primary tumor status, n (%) | Controlled | 115 (66) |
| | Uncontrolled | 58 (33) |
| | Not recorded | 1 (1) |
| Extracranial metastases, n (%) | Absent | 137 (73) |
| | Present | 47 (27) |
| | Lung | 22 (13) |
| | Liver | 4 (2) |
| | Bone | 4 (2) |
| Number of BM, n (%) | Single | 137 (79) |
| | Two | 19 (11) |
| | Three | 15 (9) |
| | Four | 3 (2) |
| Time to BM detection, n (%) | Synchronous at first cancer diagnosis | 59 (34) |
| | >2 Years | 35 (20) |
| | ≤2 Years | 80 (46) |
| RPA, n (%) | Class 1 | 50 (29) |
| | Class 2 | 117 (67) |
| | Class 3 | 7 (4) |
| | None | 33 (19) |
| Systemic therapy, n (%) | ICI | 10 (6) |
| | Not containing ICI | 58 (33) |
| | Not recorded | 73 (42) |

BM: Brain metastases; ICI: immune checkpoint inhibitor; KPS: Karnofsky performance status; NSCLC: non-small-cell lung cancer; RPA: recursive partitioning analysis; SCLC: small-cell lung cancer.

the recursive partitioning analysis (RPA) 3-tiered model (67%): Class 1 is defined as age <65 years with Karnofsky performance status (KPS) ≥70, no extracranial metastases, and controlled primary tumor (16); class 3 is defined as KPS <70%. Regarding patients with non-small-cell lung cancer, the majority had adenocarcinoma histology,

and only two had targetable molecular alterations, *e.g.* epidermal growth factor receptor (*EGFR*) mutations.

Actuarial survival was similar for the major primary disease types (breast, lung, colorectal, kidney cancer, malignant melanoma). Considering all patients, median actuarial survival was 16.0 months (95% confidence interval=12.9-19.1 months). The 2- and 5-year survival rates were 35% and 12%, respectively. There was no statistically significant difference between recent, earlier and historical cohorts (Table II). Synchronous presentation and time to detection of brain metastasis were not associated with survival. RPA class was highly prognostic (medians of 24.2, 13.3, and 4.5 months, for class 1, 2 and 3, respectively, $p<0.001$). Further prognostic factors included younger age, primary tumor control, good KPS (80-100), and administration of systemic therapy after treatment for brain metastasis. With a univariate p -value of 0.08, systemic therapy did not meet the definition of statistical significance. The multivariate Cox regression analysis was limited to age, primary tumor control, KPS, and systemic therapy. RPA class was not included because it is based on three of these parameters, leading to redundancy. While age lost its significance, primary tumor control, good KPS and administration of additional systemic therapy were confirmed as independent prognostic factors for overall survival.

In patients who received systemic therapy after treatment for brain metastasis, survival remained similar for all three time periods (recent, earlier, historical). The small subgroup of 10 patients who received immune checkpoint inhibitor (ICI)-based systemic therapy had numerically longer survival than patients who had non-ICI regimens (median of 34.2 *versus* 16.5 months, $p=0.12$).

In patients with good KPS, median survival was increased from 19.9 months in historical patients to 23.0 months in the two remaining cohorts ($p=0.13$). A larger and statistically significant difference between time cohorts was observed in patients with controlled primary tumor, in whom survival increased from 17.5 to 35.8 months ($p=0.01$) (Figure 1).

Table II. Analyses of prognostic factors for survival.

| Parameter | Subgroup | Median survival (range), months | Univariate | Multivariate | |
|-------------------------|--------------|---------------------------------|------------|-------------------|---------|
| | | | p-value | HR (95% CI) | p-Value |
| Cohort | Recent | 13.3 (1.3-81.4) | 0.3 | | NA |
| | Earlier | 17.7 (3.5-156.0) | | | |
| | Historical | 16.0 (2.0-150.0) | | | |
| Sex | Female | 16.0 (2.5-95.8) | 0.7 | | NA |
| | Male | 15.1 (1.3-156.0) | | | |
| Extracranial metastases | No | 18.0 (2.0-150.0) | 0.2 | | NA |
| | Yes | 12.7 (1.3-156.0) | | | |
| Primary tumor | Controlled | 19.9 (2.0-156.0) | 0.03 | 0.47 (0.26-0.68) | 0.001 |
| | Uncontrolled | 11.0 (1.3-85.0) | | | |
| Age | <65 Years | 18.0 (2.0-156.0) | 0.02 | 1 | 0.5 |
| | ≥65 Years | 12.0 (1.3-88.0) | | | |
| No. of brain metastases | Single | 16.5 (2.0-150.0) | 0.7 | NA | NA |
| | Two | 3.7 (3.5-156.0) | | | |
| | Three | 16.5 (1.3-52.0) | | | |
| | Four | 9.8 (3.0-24.5) | | | |
| KPS | 100 | 38.0 (6.3-88.0) | <0.001 | 0.61 (0.50-0.72)* | <0.001 |
| | 90 | 21.0 (2.0-156.0) | | | |
| | 80 | 16.3 (2.5-85.2) | | | |
| | 70 | 9.8 (2.5-58.1) | | | |
| | 60 | 4.5 (1.3-16.0) | | | |
| Systemic therapy | None | 8.6 (1.3-88.0) | 0.08 | 1 | 0.04 |
| | Any | 17.7 (3.2-156.0) | | | |

HR: Hazard ratio; CI: confidence interval; KPS: Karnofsky performance status; NA: not applicable. *Dichotomized 80-100 vs. <80.

Discussion

This study compared three cohorts of patients who underwent resection for brain metastasis and received RT postoperatively between 2016-2024 (recent), 2007-2015 (earlier), and before 2007 (historical). Given that treatment paradigms have changed due to availability of new systemic therapies, e.g. ICI, and a transition from WBRT to cavity SRT, we were interested in potential changes of overall survival over time. Compared to all-comers with a diagnosis of brain metastasis, patients undergoing surgical resection represent a selected subgroup with better prognostic features and *a priori* longer overall survival. In our database, 15% of all actively treated patients were selected for surgical resection. Notable baseline features included the common presence of a single brain metastasis and the absence of extracranial metastases. It should also be noted that not

all brain metastases are surgically accessible and nor are all patients medically operable.

We recorded a median overall survival of 16 months. Furthermore, we confirmed that long-term survival beyond 5 years is achievable in a subset of patients, as also reported previously (7, 17), and showed that the well-established RPA prognostic classes (16) continue to predict survival. Primary tumor control, good KPS, and additional systemic therapy were confirmed as independent prognostic factors for overall survival in multivariate analysis. Unexpectedly, there was no statistically significant survival difference between recent, earlier and historical patients, except for the subgroup with controlled primary tumor (recent was better than earlier and historical, but no significant difference was seen between earlier and historical). Even when the main analysis was restricted to patients who received additional systemic therapy after brain

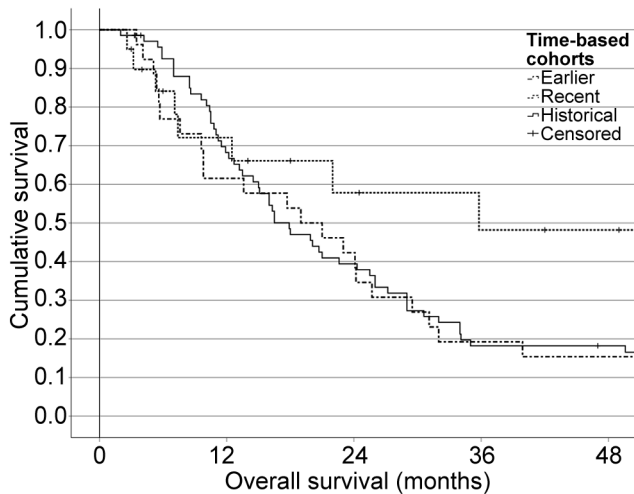


Figure 1. Actuarial overall survival (Kaplan-Meier curves) for patients with controlled primary tumor is displayed and stratified by time period. Recent: 2016-2024 (n=20); earlier: 2007-2015 (n=26); historical: before 2007 (n=69). Significantly different at $p=0.01$ (pooled over all three strata).

metastasis treatment, no meaningful difference emerged. Despite this finding, survival of ICI-treated patients was much longer than that of patients managed with non-ICI regimens. However, only 10 out of 174 patients had received an ICI after brain metastasis treatment. Possibly, an increase in the proportion of patients treated with ICI may lead to measurable prolongation of survival in larger studies of recently treated patients. The fact that systemic therapy improves survival has previously been reported by several groups (18-22). In prospective trials that included surgical resection as part of the treatment concept, median survival was 11 months [(23), published in 1998], 12 months [(13), published in 2017], and 17 months [(14), published in 2017]. Our own result of 16 months is comparable to these data from the literature.

KPS has long been recognized as a crucial prognostic factor in all patients with brain metastasis, irrespective of treatment strategy (4, 16, 23). Its impact was also obvious in the present study. Due to the considerable likelihood of long-term survival in patients with good KPS and controlled intracranial disease after resection and irradiation, survivorship issues such as preserved cognitive function,

quality of life, rehabilitation, psycho-oncological support and, in younger patients, return to work are gaining importance (24). Patients with KPS <70 (RPA class 3) had a short median survival of 4.5 months. Thus, a general recommendation for surgical resection and postoperative radiotherapy is not justified for this subgroup.

It appears possible that blood test results may contribute to better assessment of the prognosis than KPS, primary tumor control, and eligibility for additional systemic therapy alone. Previous work suggests that the LabBM score, which is based on inexpensive routine tests (serum hemoglobin, platelet count, albumin, lactate dehydrogenase and C-reactive protein) deserves further validation (25-27). This score reflects aspects of nutrition, inflammation and overall cancer burden. Due to unavailability of blood test results for the historical cohort, this score was not assessed in the present study. Further limitations include the relatively small size of the recent and earlier cohorts, and number of ICI-treated patients. As a consequence, statistical power was limited. For this reason, we did not attempt to perform primary tumor-specific analyses, *e.g.* for breast or kidney cancer. To fully elucidate temporal trends in all subgroups, larger studies are needed.

Our results suggest that, when offering highly efficacious combined local treatment for brain metastasis, the same effort is warranted to achieve definitive control of the primary tumor site. By also adding tumor biology-adapted systemic therapy, the highest possible chance of long-term survival can be ensured.

Conclusion

Patients with brain metastasis treated with resection and postoperatively RT benefited from additional systemic therapy. Only one subgroup experienced major survival prolongation in more recent years: those with controlled primary tumor. Therefore, efforts to optimize primary tumor control, such as surgery and radical radiotherapy, may play an important role in multimodal treatment paradigms.

Conflicts of Interest

The Authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Authors' Contributions

All Authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by C.N. The first draft of the manuscript was written by C.N. and all Authors commented on previous versions of the manuscript. All Authors have read and agreed to the published version of the manuscript.

Artificial Intelligence (AI) Disclosure

No artificial intelligence (AI) tools, including large language models or machine learning software, were used in the preparation, analysis, or presentation of this manuscript.

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