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Predicted survival in patients with brain metastases from colorectal cancer: Is a current nomogram helpful?

Carsten Nieder[a,b,*], Mandy Hintz[c], Anca L. Grosu[c]

[a] Department of Oncology and Palliative Medicine, Nordland Hospital, Bodø, Norway
[b] Institute of Clinical Medicine, Faculty of Health Sciences, University of Tromsø, Tromsø, Norway
[c] Department of Radiation Oncology, University Hospital Freiburg, Freiburg, Germany

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ABSTRACT

Objective: To examine the clinical applicability of a new nomogram by comparing survival of patients with brain metastases from colorectal cancer treated with surgery and/or radiotherapy in the authors' institutions with nomogram-predicted median survival.
Methods: Retrospective analysis of 64 patients treated with comparable approaches and during the same time period as the patients in the nomogram study. Points were assigned for age, performance status, number and site of brain metastases, as required for nomogram use.
Results: In 46 patients (72%), the observed survival was shorter than the predicted median. The median deviation was −1.4 months. The nomogram underestimated the survival of patients treated with radiosurgery/surgery by a median of 4.2 months, whereas it overestimated the survival of patients treated with whole-brain radiotherapy (WBRT) by a median of 2.1 months ($p = 0.0001$). Nevertheless, all 5 patients with predicted median survival ≤3 months died within 3 months. Among 8 patients with predicted median survival >12 months, 6 (75%) survived for >12 months. Not all prognostic factors in the nomogram correlated with survival. In the multivariate Cox model, only performance status and number of brain metastases were significant, both with $p = 0.0001$.
Conclusion: Despite differences in prognostic factors and survival of many individual patients, especially those with intermediate prognosis, the nomogram performed promising in poor- and good-prognosis patients. Evaluation of separate prediction tools for patients treated with WBRT and more aggressive local approaches appears warranted in order to minimize the influence of better local control of the brain metastases.

1. Introduction

Detection of brain metastases from colorectal cancer is a serious event, which often heralds impaired quality of life and short survival [1–3]. Presence of other visceral metastases is common and most patients have already received systemic therapy [4–6]. However, a minority of patients harbor brain metastases only or present with such lesions already when diagnosed with colorectal cancer [7,8]. This inhomogeneity results in variable survival and a need for individually tailored management approaches. We have previously reported that survival was influenced by three factors: good Karnofsky performance status (KPS), limited number of brain metastases, and absence of extracranial metastases [4]. Other authors suggested prognostic models that may facilitate decision making on a case-by-case basis [9]. The most recent development has been a nomogram based on 227 patients treated in Italy between 2000 and 2013 (whole-brain radiotherapy (WBRT) in 47%, surgery in 37%, stereotactic radiosurgery (SRS) in 49%, sequence not reported) [10]. External validation was performed in 119 patients from four Italian institutions. Better survival was reported in patients with good KPS, limited number of brain metastases, younger age and supratentorial brain metastases. The purpose of the present study was to evaluate the clinical applicability of the nomogram in a different database, which includes patients treated with comparable strategies during the same time period in Germany and

* Corresponding author at: Department of Oncology and Palliative Medicine, Nordland Hospital, 8092 Bodø, Norway. Fax: +47 75 53 4975.
E-mail address: carsten.nieder@nlsh.no (C. Nieder).

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Norway. We compared each individual patient's actual survival to the nomogram-predicted result.

2. Patients and methods

Patients were identified from the previously described databases of the Radiation Oncology facilities at the authors' institutions in Bodø, Norway, and Freiburg, Germany, where new patients are added every three months, and evaluated retrospectively [11]. Baseline characteristics were extracted from the hospitals' electronic patient records. In contrast to our previous study [11], patients managed with best supportive care were excluded in order to match the Italian patient population as closely as possible. Because mature survival results were needed, we limited the study to patients who had died from their disease or were alive after more than 24 months, i.e., the maximum median survival covered by the nomogram. All patients presented initially with solid brain metastases, not with leptomeningeal spread. Treatment consisted of WBRT (10 fractions of 3 Gy in the majority of patients, or 5 fractions of 4 Gy or 14 fractions of 2.5 Gy) with or without surgical resection or SRS. Relapses were treated with one or several of the same modalities. Systemic treatment after brain-directed therapy was administered as judged appropriate by the patients' medical oncologists. Such treatment was paused during local therapy for brain metastases. Computed tomography and/or magnetic resonance imaging of the brain was used, depending on the number of lesions initially depicted if surgical resection or SRS was considered. We used the Kaplan–Meier method to generate actuarial survival curves. These were compared with the log rank test. Survival was calculated from the first day of treatment, which could have been WBRT, surgery or SRS. All but four patients had died at the time of analysis. Multivariate analysis was performed by Cox regression (forward conditional method). IBM SPSS statistics 22 was used for all analyses. A p-value <0.05 was considered statistically significant.

3. Results

We evaluated 64 patients. Of these, 61% were treated with initial WBRT. The same proportion had intermediate prognostic features, i.e. recursive partitioning analysis (RPA) class II [12]. Table 1 shows the patient characteristics, also compared to the Italian data. Due to different methods of data display, not all parameters could be extracted from the Italian study. The median survival was 3.8 months (1-year survival rate 20%). Points were assigned for age, KPS, brain metastases site and number, as described by Pietrantonio et al. [10]. Total points ranged from 26 to 248, median 142.5. Actual survival was compared to the nomogram-predicted median survival. Agreement was excellent, i.e., within one month, in 11 patients (17%). The difference was 1.1–2 months in 13 patients (20%), 2.1–3 months in 5 patients (8%), 3.1–4 months in 9 patients (14%), 4.1–5 months in 8 patients (12.5%) and more than 5 months in 18 patients (28%). In 46 cases (72%), the observed survival was shorter than the predicted median. The median deviation was −1.4 months (mean 2.5 months, standard deviation 14 months), Fig. 1. The nomogram underestimated the survival of patients treated with SRS/surgery by a median of 4.2 months, whereas it overestimated the survival of patients treated with WBRT by a median of 2.1 months ($p = 0.0001$). Table 2 shows the results for 4 groups of patients with unfavorable, intermediate-unfavorable, intermediate-favorable and favorable survival (arbitrarily defined as ≤3 months, 3.1–6 months, 6.1–12 months, >12 months). Despite obvious disagreement in many groups, all 5 patients with predicted median survival ≤3 months died within 3 months. Among 8 patients with predicted median survival >12 months, 6 (75%) survived for >12 months.

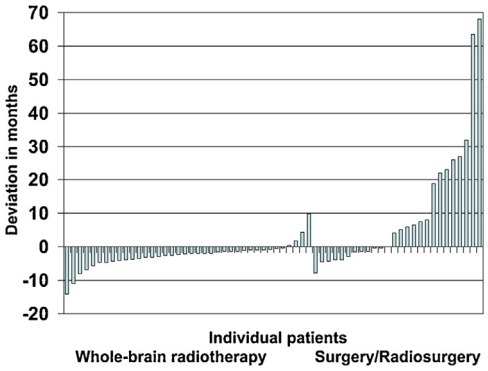

Fig. 1. Difference in observed survival and nomogram-predicted survival in months for all 64 patients. Left side: patients treated with initial whole-brain radiotherapy, survival was often shorter than predicted. Right side: patients treated with initial surgery or radiosurgery, survival was often longer than predicted.

Not all prognostic factors in the nomogram correlated with survival in our patients. Univariately, extracranial metastases ($p = 0.015$), KPS ($p = 0.0001$) and number of brain metastases ($p = 0.0001$) were significant. In the multivariate Cox model, only KPS (3-tiered categorical as in the Italian study) and number of brain metastases (also 3-tiered categorical as in the Italian study) were retained, both with $p = 0.0001$. For age and brain metastases site not even a trend emerged. For example, median survival was 4.0 months in patients with supratentorial lesions as compared to 3.6 months in those with infratentorial lesions or at both sites, $p = 0.84$. After WBRT, median survival was 3.0 months as compared to 11.4 months in patients managed with SRS/surgery.

4. Discussion

Brain metastases from colorectal cancer are less common than lung and liver metastases, but their clinical implications are very serious [13,14]. As reported by various groups, brain metastases usually develop late in the disease trajectory, when few treatment options remain [1,3,7,8]. The large multi-center analysis resulting in the disease-specific graded prognostic assessment (DS-GPA) score found that only KPS significantly predicted survival in patients with colorectal cancer [15]. Inconsistent results were reported by different other groups, largely in small retrospective analyses. The recently published nomogram was derived from a larger database and based on KPS, age, number and site of brain metastases [10]. It was validated in a multi-institutional Italian dataset. We were interested in its clinical applicability, because it is challenging to assign the right treatment to the right patient [16]. For example, patients with very short expected survival should not spent most of their remaining life span on multi-fraction radiotherapy, while patients with favorable prognosis usually benefit from local control of their brain metastases and should be considered for surgery or SRS [17–23]. The potential impact of intensified local treatment on survival was also described by Hammoud et al. [7], where WBRT alone resulted in median overall survival of 3 months, while surgical resection resulted in 9 months (steroids alone 1 month). Other surgical series reported 5.5–15.2 months [19,20] and the WBRT alone group by Amichetti et al. survived for a median of 3 months [5], comparable to the present results. Median overall survival in patients managed with SRS was 6–8 months [21–23]. Even in the absence of randomized trials for patients with colorectal cancer, these data support the use of surgery or SRS in adequately selected patients.