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A Tool to Predict the Probability of Intracerebral Recurrence or New Cerebral Metastases After Whole-brain Irradiation in Patients with Head-and-Neck Cancer

CHRISTIAN STAACKMANN[1], STEFAN JANSSEN[1,2], STEVEN E. SCHILD[3] and DIRK RADES[1]

[1]*Department of Radiation Oncology, University of Lübeck, Lübeck, Germany;*
[2]*Private Practice of Radiation Oncology, Hannover, Germany;*
[3]*Department of Radiation Oncology, Mayo Clinic, Scottsdale, AZ, U.S.A.*

Abstract. *Background/Aim: Patients with metastatic head-and-neck cancer require individual therapies facilitated by prognostic tools. A tool to estimate the risk of recurrent or new cerebral metastases following whole-brain irradiation (WBI) is presented. Patients and Methods: Age, gender, performance status, cancer site, number of cerebral lesions, extracerebral metastases, and time between cancer diagnosis and treatment of cerebral metastases were evaluated for intracerebral control in 23 patients. For characteristics showing a trend ($p<0.07$), points for these characteristics were created by dividing 6-month intracerebral control rates by 10. Patient scores were obtained by adding these points. Results: Better intracerebral control was significantly associated with oropharyngeal and laryngeal cancer ($p=0.014$). Absence of extra-cerebral metastases ($p=0.069$) and longer time between cancer diagnosis and treatment of cerebral metastases ($p=0.053$) showed trends. Three groups were identified, namely with 3-11, 13-18 and 20-24 points. Six-month intracerebral control rates were 0%, 50% and 100% ($p=0.003$), respectively, for these groups. Conclusion: A new tool was created to predict intracerebral control following WBI and should contribute to personalization of treatment for patients with cerebral metastases of head-and-neck cancer.*

Patients with cerebral metastases from head-and-neck cancer generally have poor prognoses (1). Many systemic anticancer drugs pass through the blood–brain barrier poorly and are not as effective for brain metastases (2-4). Thus, radiotherapy is the most common treatment modality for cerebral metastases from head-and-neck cancer. Radiotherapy options include local techniques, such as radiosurgery and fractionated stereotactic radiotherapy (5). However, local techniques are reasonable in patients with a limited number of cerebral lesions (5-8). Therefore, the most frequently administered type of radiotherapy in patients with metastases from head-and-neck cancer is whole-brain irradiation (WBI) (5). WBI may be combined with local radiotherapy or upfront neurosurgical resection in selected cases, particularly in patients with very few lesions (9, 10). For WBI, a variety of dose-fractionation regimens are in use worldwide, also depending on national preferences and standards (5). Usually these regimens are administered with one fraction per day and five fractions per week. They include shorter programs that take one week (*e.g.* 5×4 Gy) and longer programs that take up to four weeks (*e.g.* 10×3 Gy and 20×2 Gy) (11, 12). When aiming to select for the optimal WBI program for an individual patient, many factors should be considered, including the patient's social situation, distance to the Radiation Oncology Department, personal treatment preferences, and the patient's remaining lifespan. A prognostic score to estimate the survival prognosis of patients irradiated for cerebral metastases from head-and-neck cancer is already available (13). Previous studies suggested that patients with a very limited prognosis are better candidates for a less time-consuming shorter WBI program, whereas those with a very favorable survival prognosis can benefit from longer programs with lower doses per fraction, in terms of better survival and fewer neurocognitive deficits (11, 14-16). However, the appropriate regimen for patients with an intermediate survival prognosis is often unclear. For these patients, another aspect becomes more important, namely the ability of WBI to provide long-term intracerebral control, *i.e.* freedom from new and progression of treated cerebral metastases. The biologically-

Correspondence to: Dirk Rades, MD, Department of Radiation Oncology, University of Lübeck, Lübeck, Ratzeburger Allee 160, 23562 Lübeck, Germany. Tel: +49 45150045401, Fax: +49 45150045404, e-mail: Rades.Dirk@gmx.net

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effective dose, which can be given as equivalent dose in 2-Gy-fractions (EQD2), of a WBI program depends on both total dose and dose per fraction (17). In general, longer WBI programs are associated with higher EQD2. For example, the EQD2 of 5×4 Gy, 10×3 Gy and 20×2 Gy are 23.3 Gy, 32.5 Gy and 40.0 Gy, respectively. In radiation oncology, a higher EQD2 generally means a greater efficacy with respect to tumor cell kill and local (intracerebral) control, which has been described for the treatment of primary head-and-neck cancer and for cerebral metastases from other solid tumors (18-23). However, a higher EQD2 often also means a higher risk of radiation-related toxicities. Prior to radiotherapy, it would be advantageous to identify those patients with cerebral metastases from head-and-neck cancer and an intermediate survival prognosis who may benefit from WBI with a higher EQD2 with respect to long-term intracerebral control. The present study aimed to provide a prognostic tool to do so by predicting the risk of developing recurrent or new cerebral metastases following WBI in patients with cerebral metastases from head-and-neck cancer.

Patients and Methods

Twenty-three patients who had received WBI alone (n=19), WBI with upfront resection or WBI with boost with upfront resection for cerebral metastases from head-and-neck cancer between 1995 and 2015 were included in this retrospective study. Dose-fractionation of WBI regimens included 5×4 Gy in 1 week (n=4), 10×3 Gy in 2 weeks (n=11) and longer-course regimens with doses >30 Gy given over 3-4 weeks (n=8). Seven pre-treatment characteristics were evaluated with respect to intracerebral control. Intracerebral control was defined as lack of progression of treated lesions and freedom from new cerebral metastases. These characteristics included age (≤64 *vs.* ≥65 years, median age: 65 years), gender, Eastern Cooperative Oncology Group (ECOG) performance score (0-1 *vs.* 2-3, median performance score: 2), site of origin of head-and-neck cancer (nasopharynx *vs.* oropharynx *vs.* larynx *vs.* other sites), number of cerebral lesions (1-2 *vs.* ≥3, median: 3 lesions), extra-cerebral metastases (no *vs.* yes) and time between diagnosis of head-and-neck cancer and treatment of cerebral metastases (≤24 *vs.* >24 months, median time: 24 months). Distributions of the characteristics are shown in Table I. For statistical analyses, the Kaplan–Meier method and log-rank test were used (24). Those characteristics that showed significance ($p<0.05$) or a trend ($p<0.07$) with respect to intracerebral control were used to design the prognostic tool. For each of these characteristics, a separate score was created by dividing the 6-month intracerebral control rate (as a percentage) by 10. The prognostic score for each patient was then obtained by summing the scores for each characteristic.

Table I. *Distribution of patient characteristics.*

	Number of patients (%)
Age at the time of treament	
≤64 Years	11 (48)
≥65 Years	12 (52)
Gender	
Female	5 (22)
Male	18 (78)
ECOG performance score	
0-1	11 (48)
2-3	12 (52)
Site of primary tumor	
Nasopharynx	2 (9)
Oropharynx	5 (22)
Larynx	8 (35)
Other	8 (35)
Number of cerebral lesions	
1-2	10 (43)
≥3	13 (57)
Extracerebral metastases	
No	11 (48)
Yes	12 (52)
Time between cancer diagnosis and treatment of cerebral metastases	
≤24 Months	12 (52)
>24 Months	11 (48)

WBI: Whole-brain irradiation, ECOG: Eastern Cooperative Oncology Group.

Results

Better intracerebral control was significantly associated with oropharyngeal and laryngeal cancer ($p=0.014$). In addition, absence of extra-cerebral metastases ($p=0.069$) and longer time (*i.e.* >24 months) between diagnosis of head-and-neck cancer and treatment of cerebral metastases ($p=0.053$) showed trends for better intracerebral control (Table II). These three characteristics were used to design the prognostic tool to estimate the 6-month probability of intracerebral control, as described in the Patients and Methods section (Table III). The prognostic scores for individual patients ranged between 3 and 24 points and were 3, 7, 10, 11, 13, 14, 15, 17, 18, 20, 22 or 24 points, respectively. Based on these scores, three prognostic groups were formed, namely 3-11 points, 13-18 points and 20-24 points. The 6-month intracerebral control rates were 0% (median control of 4 months), 50% (median control of 9.5 months) and 100% (median control not reached), respectively ($p=0.003$).

Discussion

The primary treatment of locally advanced head-and-neck cancer can be improved due to modern radiotherapeutic approaches and combination with chemotherapy and immunotherapy (25-27). Therefore, more patients live longer, which generally translates into an increased risk of experiencing metastatic disease correlating with a patient's lifespan. Patients presenting with cerebral metastases of head-and-neck cancer are still rare and account for only about 1% of patients with metastatic disease affecting the brain (1).

Table II. *Intracerebral control rates 6 months following whole-brain irradiation.*

	Intracerebral control at 6 months (%)	*p*-Value
Age at time of treament		
≤64 Years	53	
≥65 Years	48	0.676
Gender		
Female	56	
Male	51	0.796
ECOG performance score		
0-1	69	
2-3	26	0.093
Site of primary tumor		
Nasopharynx	0	
Oropharynx	100	
Larynx	80	
Other	0	**0.014**
Number of cerebral lesions		
1-2	45	
≥3	67	0.878
Extracerebral metastases		
No	74	
Yes	0	0.069
Time between cancer diagnosis and treatment of cerebral metastases		
≤24 months	29	
>24 months	67	0.053

WBI: Whole-brain irradiation, ECOG: Eastern Cooperative Oncology Group. Significant *p*-values are shown in bold type.

Table III. *Points assigned for the characteristics included in the prognostic tool derived by dividing the percentage 6-month intracerebral control rate by 10.*

Characteristic	Intracerebral control at 6 months (%)	Points
Site of primary tumor		
Nasopharynx	0	0
Oropharynx	100	10
Larynx	80	8
Other	0	0
Extra-cerebral metastases		
No	74	7
Yes	0	0
Time between cancer diagnosis and treatment of cerebral metastases		
≤24 Months	29	3
>24 Months	67	7

The prognoses of these patients require improvement that may be achieved with individualized treatment approaches. For patients assigned to receiving WBI for their cerebral metastases, individualization would include the selection of the appropriate dose-fractionation schedule. In a previous study, an instrument was presented that can help predict the survival times of individual patients with cerebral metastases from head-and-neck cancer (13). That scoring instrument was based on performance status, and number of cerebral lesions and extracranial metastases, and included three prognostic groups with 6-month survival rates of 0% (0-1 point), 50% (2 points) and 100% (3 points). In a larger retrospective study of 442 patients with cerebral metastases from different solid tumors and mainly poor survival prognoses, 5×4Gy in 1 week was not inferior to 10×3 Gy in 2 weeks regarding intracerebral control (p=0.07), survival (p=0.29) and acute toxicity; 5×4 Gy was recommended particularly for patients with a poor survival prognosis (11). This would apply to the 0-1 point group by the survival score previously created for patients with cerebral metastases form head-and-neck cancer (13). On the other hand, patients with a very favorable survival prognosis were reported to benefit from longer-course WBI programs with lower doses per fraction in terms of improved intracerebral control and survival with fewer neurocognitive deficits (14-16). Therefore, patients of the group with 3 points by the previously created survival score would appear to be good candidates for a longer-course WBI program (13). However, for patients of the intermediate group (2 points) by that survival score, the optimal WBI program is more difficult to select. To make an appropriate treatment decision, additional information would be required including the risk of an intracerebral failure.

Therefore, in the present study, an additional prognostic tool was developed that allows estimation of the intracerebral control rates at 6 months following WBI. Based on three pre-treatment characteristics, namely site of origin of head-and-neck cancer, extracerebral metastases and time between diagnosis of head-and-neck cancer and treatment of cerebral metastases, three groups were identified with significantly different 6-month intracerebral control probabilities. These rates were 0% for 3-11 points, 50% for 13-18 points and 100% for 20-24 points, respectively. Because a higher dose of WBI can be expected to result in more efficient tumor-cell kill, patients of the group with 3-11 points and the 13-18 points with an intermediate survival prognosis may benefit from longer-course WBI programs with a higher EQD2 in order to achieve a better 6-month intracerebral control. In conclusion, a new tool was created that can help predict the intracerebral control probability 6 months following WBI and can, therefore, contribute to the personalization of the treatment for patients with cerebral metastases from head-and-neck cancer.

Conflicts of Interest

On behalf of all Authors, the corresponding Author states that there is no conflict of interest related to this study.

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