

Local Therapies Can Improve Intracerebral Control in Patients with Cerebral Metastasis from Gynecological Cancers

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Abstract. *Background/Aim:* Patients with gynecological malignancies account for 2% of patients with cerebral metastases. Many patients receive whole-brain irradiation (WBI) alone. Local therapies (resection, stereotactic radiosurgery (SRS)) are becoming more popular. This study compared intracerebral control after local therapy to WBI alone in patients with gynecological malignancies. *Patients and Methods:* Of 56 patients, 45 received WBI alone, 6 SRS alone and 5 resection plus WBI. Treatment type, age, performance score, cancer site, number of cerebral lesions, metastases outside the brain, recursive partitioning analysis (RPA) class and period from gynecological cancer diagnosis to brain metastasis treatment were evaluated. *Results:* On univariate analyses, local therapy ($p=0.003$), single cerebral lesion ($p<0.001$) and RPA class 1/2 ($p=0.027$) were positively related to intracerebral control. On Cox regression analysis, local therapy ($p=0.013$) and RPA class 1/2 ($p=0.014$) were significant. *Conclusion:* Local therapies led to better intracerebral control than WBI alone and should be considered for brain metastasis from gynecological malignancies whenever reasonable.

Brain metastasis is a relatively common complication that cancer patients experience during the process of their disease (1). Patients with brain metastasis from gynecological

malignancies are less common. They account for approximately 2% of all cancer patients in whom cerebral metastases are diagnosed. The vast majority of these patients are treated with irradiation, mainly in the form of whole-brain irradiation (WBI) alone (1). However, local therapies, such as neurosurgical resection and stereotactic radiosurgery (SRS) have become more popular for several years, particularly for patients with a limited number of up to five brain lesions. One major goal of using a local therapy, particularly when administered without WBI, is to decrease treatment-related toxicity, mainly a decline in neuro-cognitive function, by delivering a lower radiation dose to major parts of the brain (2). Another important end-point is intracerebral control, which is defined as freedom from new and/or progressive treated cerebral lesions. A recurrence within the brain has been identified as one major cause of decreased neuro-cognitive function and must, therefore, be avoided as long as possible (3-5). Studies of patients with one to three brain metastases from many different cancer types suggested that SRS alone and resection followed by WBI were superior to WBI alone regarding intracerebral control (6-8). However, since cancer types respond differently to irradiation, it would be important to see whether this also applies to cancers that are considered not very radiosensitive. Therefore, this study was initiated, which evaluates intracerebral control rates after local therapy and compares them to intracerebral control rates after WBI alone, specifically in patients with cerebral metastases from a gynecological malignancy.

Patients and Methods

A cohort of 56 patients irradiated for metastases to the brain were included in this retrospective study. Of these, 45 patients received WBI alone, 6 patients SRS alone and 5 patients neurosurgical

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Table I. Variables included in the analyses of intracerebral control.

	Number of patients	Proportion of patients (%)
Type of treatment		
WBI alone	45	80
SRS alone	6	11
Surgery+WBI	5	9
Age		
≤62 years	28	50
≥63 years	28	50
ECOG score		
1-2	17	30
3-4	39	70
Cancer site		
Ovary	31	55
Uterus	14	25
Cervix	8	14
Vulva	3	5
Number of cerebral lesions		
1	17	30
≥2	39	70
Metastases outside the brain		
No	16	29
Yes	40	71
RPA class		
1	9	16
2	24	43
3	23	41
Period from diagnosis of gynecological cancer to treatment of brain metastasis		
≤24 months	27	48
≥25 months	29	52

WBI, Whole-brain irradiation; SRS, stereotactic radiosurgery; ECOG, Eastern Cooperative Oncology Group; RPA, recursive partitioning analysis.

resection supplemented by WBI. SRS and neurosurgical resection were defined as local therapies. The type of treatment plus seven other variables (Table I) were investigated for intracerebral control. Other variables included age (≤62 *versus* ≥63 years, median=62.5), performance score according to the Eastern Cooperative Oncology Group (ECOG) (1-2 *versus* 3-4), cancer site (ovary *versus* uterus *versus* cervix *versus* vulva), number of cerebral lesions (single *versus* multiple (≥2) lesions), metastases outside the brain (no *versus* yes), recursive partitioning analysis (RPA) class (1 *versus* 2 *versus* 3) and period from initial diagnosis of gynecological cancer to treatment of brain metastasis (≤24 *versus* ≥25 months, median=25).

RPA class 1 is defined as a Karnofsky performance score of 70 or more plus three other favorable prognostic factors, namely age less than 65 years, controlled primary tumor and no systemic metastases outside the brain (9). RPA class 2 patients have a Karnofsky performance score of 70 or more but less than all three other favorable factors. Patients belonging to RPA class 3 have a Karnofsky performance score of less than 70, regardless of the three other prognostic factors.

Table II. Results of the univariate analyses of intracerebral control.

	At 3 months	At 6 months	At 12 months	<i>p</i>
Type of treatment				
WBI alone	76	50	30	
SRS alone	100	100	100	
Surgery + WBI	100	100	100	0.003
Age				
≤62 years	88	60	36	
≥63 years	74	61	61	0.65
ECOG score				
1-2	100	81	61	
3-4	72	52	52	0.09
Cancer site				
Ovary	86	63	50	
Uterus	70	61	41	
Cervix	73	44	44	
Vulva	100	100	100	0.33
Number of cerebral lesions				
1	100	90	90	
≥2	73	48	24	<0.001
Metastases outside the brain				
No	89	74	56	
Yes	78	55	55	0.07
RPA class				
1	100	78	47	
2	91	72	72	
3	61	41	n/a	0.027
Period from diagnosis of gynecological cancer to treatment of brain metastasis				
≤24 months	76	61	37	
≥25 months	86	62	62	0.30

WBI, Whole-brain irradiation; SRS, stereotactic radiosurgery; ECOG, Eastern Cooperative Oncology Group; RPA, recursive partitioning analysis; n/a, not available; bold, significant value.

Initially, all eight variables were analyzed in a univariate manner using Kaplan-Meier analyses. Comparisons of the corresponding curves were performed with the log-rank test. Significant (defined as $p<0.05$) variables were included in a Cox regression model.

Results

According to the univariate analyses, three variables showed a significantly positive association with better intracerebral control (Table II). These variables included administration of a local therapy ($p=0.003$), presence of only a single cerebral lesion ($p<0.001$) and RPA class 1 or 2 ($p=0.027$). According to the Cox regression model, administration of a local therapy (risk ratio= 2.02×10^{-5} , $p=0.013$) and RPA class 1 or 2 (risk ratio=2.36, $p=0.014$) were independent predictors of intracerebral control, whereas presence of a single cerebral lesion was no longer significant (risk ratio=1.28, $p=0.32$).

Discussion

Since patients with metastatic gynecological cancer generally experience poor prognoses, considerable efforts have been made to achieve improvement, including new systemic agents, novel surgical approaches and modern radiotherapy techniques (10-16). In case of brain metastases, most patients are treated with WBI alone (1). However, local therapies, namely surgical resection and stereotactic radiosurgery, have gained importance, particularly for patients with few lesions.

In 2004, a randomized trial of patients with one to three cerebral metastases has shown that WBI plus SRS resulted in significantly better survival than WBI alone in the subgroup of patients with a single lesion (8). Median survival times were 6.5 months and 4.9 months, respectively ($p=0.039$). However, this trial included patients with brain metastasis from many different cancer types. Moreover, intracerebral control, which is also an important end-point, was not investigated. Intracerebral control was investigated in a retrospective study of 186 patients with one to three brain lesions that compared SRS alone to WBI alone (6). According to multivariate analysis, SRS led to significantly better intracerebral control (risk ratio=1.33, $p=0.003$). In another retrospective study of 195 patients with a single cerebral lesion, WBI plus upfront resection was superior to WBI alone regarding intracerebral control (risk ratio=1.24, $p<0.001$) (7). However, the latter two studies included patients with brain metastasis from different cancer types as well. Because cancers vary considerably with respect to radio-sensitivity, it appears reasonable to evaluate the value of local therapies for brain metastasis treatment separately for different types of cancer or small groups of related cancer types. This study focused specifically on patients with cerebral metastases from gynecological malignancies and compared local therapies to WBI alone for intracerebral control. According to its results, SRS and neurosurgery plus WBI both resulted in excellent long-term intracerebral control rates of 100% at 12 months. These rates were significantly better than after WBI alone, which resulted in intracerebral control rates of only 50% at 6 months and 30% at 12 months, respectively. Thus, local therapies should be considered for these patients whenever reasonable. Surgical resection should be limited to a single lesion that is not located close to the brainstem or other critical structures (1). SRS is usually recommended only for patients with a limited number of up to five cerebral lesions with a maximum diameter of 3-4 cm (1, 12). If these criteria are met, patients with brain metastases from a gynecological malignancy can benefit from administration of a local therapy in terms of better intracerebral control. Intracerebral control is an important end-point, which is also very important for preserving the patient's neuro-cognitive function.

In summary, local therapies, namely neurosurgical resection and SRS, contributed to better intracerebral control when compared WBI alone. Thus, local therapies should be considered for the treatment of brain metastasis from gynecological malignancies whenever the criteria for their indication are met.

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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