Multimodal Therapy is a Better Choice for Patients with Brain Metastasis from Cervical Cancer

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Objective: To evaluate the prognostic factors and optimal management of cervical cancer patients with brain metastasis (BM).

Materials and Methods: We retrospectively reviewed the medical records of 7098 consecutive patients with cervical cancer from January 2000 to December 2019. Data for a total of 24 BM patients with cervical cancer were analyzed retrospectively in the present study.

Results: The incidence of BM from cervical cancer in our institution was 0.38%. The mean survival time was 7.2 months (median 6.2 months, 0.1–21.2 months). In the univariate analysis, the histopathology of neuroendocrine cancer, 2018 FIGO stage, Karnofsky performance status (KPS) at BM diagnosis, and treatment strategy were identified to be significant prognostic indicators for the survival of patients with BM from cervical cancer. In the multivariate analysis, KPS, chemotherapy, and radiotherapy were independent prognostic factors for survival. Recursive partition analysis (RPA) appeared to be a better prognostic tool than the other prognosis scoring classification systems.

Conclusion: When patients with BM from cervical cancer have good performance status and undergo comprehensive treatment, such as radiotherapy and chemotherapy, their survival time could be significantly prolonged. Patients with surgical indications may get better survival by postoperative radiotherapy and chemotherapy. Patients with BMs ≥3 may get better survival by whole-brain radiotherapy. But further studies are needed regarding the selection of surgical indications and radiotherapy modes. The prognosis scoring classification system for BM from cervical cancer needs to be improved.

Keywords: cervical cancer, brain metastasis, prognostic factors

Introduction

Cervical cancer is the most common cancer in women. The common metastatic sites are the lymph nodes, liver, lung, bone, etc. Brain metastasis (BM) is very rare. The incidence of BM from cervical cancer in the clinic is 0.4–2.3%.1–8 Most BM occurs approximately 1.5–2 years after the diagnosis of cervical cancer.4,5,9,10 The median survival time is 2–8 months,5,8,11–15 and there are no standard therapies. Additionally, RPA (recursive partition analysis) and GPA (Graded Prognostic Assessment) are currently the most commonly used prognosis scoring classification systems for BM. Uterine-GPA was also proposed based on prognostic factors for BM of uterine tumors.14 Many other prognosis scoring classification systems such as BS-BM (Basic Score for Brain Metastasis) and GGS (Golden Grading System) are mainly used in SRT.
This paper analyzed the prognostic factors and treatment mode of cervical cancer patients with BM and verified the above prognostic scoring classification system.

Materials and Methods
The data of 7098 consecutive patients with cervical cancer treated in Peking Union Medical College Hospital from January 2000 to December 2019 were analyzed retrospectively. Twenty-seven patients were diagnosed with BM from cervical cancer, and three patients were lost to follow-up. The 24 cases of BM from cervical cancer included in the study were diagnosed by clinical images or pathology.

The date and cause of death for all patients were recorded. The survival time of BM was calculated from the date of diagnosis of BM to the date of death from any cause. The clinical data included histopathology at the time of initial diagnosis; FIGO stage; control of primary cervical lesions; time interval from diagnosis of cervical cancer to a diagnosis of BM; age and KPS at BM diagnosis; volume, number and location of the BM; presence of meningeal metastasis; presence of extracranial metastasis; and therapeutic schedule after the diagnosis of BM including surgery, radiotherapy, and chemotherapy.

The median survival time after diagnosis of BM was calculated using Kaplan–Meier curve analysis. The Log rank test was used to compare differences in survival. The variables with p-value <0.1 in univariate analysis were included in Cox multivariate regression analysis. Differences in multivariate analysis were assumed to be statistically significant when p-value was <0.05. All statistical analyses were performed using IBM SPSS Statistics version 19.0.

Results

Patient Characteristics
The incidence of BM was 0.38%. The mean age at BM diagnosis was 48.9 years (median 47.5 years, 31.4–71.5 years), and KPS was 70 (20–100). The main symptoms were headache, dizziness, malignant vomiting, hypomnness, ataxia, diplopia, etc. The mean time interval between the diagnosis of cervical cancer to the identification of BM was 25.4 months (median 26.3 months, 0–57.4 months). All patients received surgery, radiotherapy or radiochemotherapy at the time of initial diagnosis of cervical cancer. After initial treatment, the primary tumor was controlled in 20 cases (83.3%).

At the time of initial diagnosis of cervical cancer and BM diagnosis, the clinicopathological features of the patients are shown in Table 1. The average volume of BMs was 27.6 cm³ (median 18.7 cm³, 0.2–81.5 cm³). Twenty patients (83.3%) had extracranial metastasis, most of occurred in the lung, liver, bone, lymph node, or soft tissue. All treatment characteristics of the patients are shown in Table 2.

In addition, 24 patients were evaluated by the prognosis scoring classification systems for BM. The results are shown in Table 3.

| Table 1 | The Clinicopathological Features of 24 Patients |
|-----------------|-----------------|-----------------|-----------------|
| **Variables**   | **All Patients** |
| Age at BM diagnosis (years) | ≤65 | 22 (91.7) | >65 | 2 (8.3) |
| KPS at BM diagnosis | ≥70 | 16 (66.7) | <70 | 8 (33.3) |
| 2018 FIGO stage | IB1 | 4 (16.7) | IIB | 3 (12.5) |
| | IIIA1 | 7 (29.2) | IIIA2 | 5 (20.8) |
| | IVB | 5 (20.8) |
| Pathology | Squamous carcinoma | 14 (58.3) | Adenocarcinoma | 1 (4.2) |
| | Adenosquamous carcinoma | 1 (4.2) | Neuroendocrine carcinoma | 8 (33.3) |
| Number of BMs | 1 | 8 (33.3) | 2 | 2 (8.3) |
| | 3 | 3 (12.5) | 4 | 2 (8.3) |
| | 5 | 2 (8.3) | >10 | 2 (8.3) |
| | Unknown | 5 (20.8) |
| Meningeal metastasis | Yes | 2 (8.3) | No | 22 (91.7) |
| Location of BM | Above the tentorium | 11 (45.8) | Below the tentorium | 2 (8.3) |
| | Both above and below the tentorium | 6 (25) | Unknown locations | 5 (20.8) |
| Extracranial metastasis | Yes | 20 (83.3) | No | 4 (16.7) |
| Control of primary cervical lesions | Yes | 20 (83.3) | No | 4 (16.7) |

**Abbreviations:** BM, brain metastasis; KPS, Karnofsky performance status.
Table 2 Treatment Characteristics of 24 Patients

| Variables          | All Patients (%) |
|--------------------|------------------|
| Therapeutic schedule |                  |
| RT alone           | 1 (4.2)          |
| S followed by RT   | 1 (4.2)          |
| CT alone           | 3 (12.5)         |
| RT and CT          | 10 (41.7)        |
| S followed by RT and CT | 3 (12.5)  |
| Palliative care    | 6 (25)           |
| RT status          |                  |
| WBRT ± SIB         | 9 (37.5)         |
| SRT                | 6 (25)           |

Abbreviations: BM, brain metastasis; S, surgery; RT, radiotherapy; CT, chemotherapy; SIB, simultaneous integrated boost; SRT, stereotactic radiotherapy; WBRT, whole-brain radiotherapy.

Survival Analysis

The mean survival time of all 24 cervical cancer patients with BM after diagnosis was 7.2 months (median 6.2 months, 0.1–21.2 months). The survival curve is shown in Figure 1. Among them, 18 patients (75%) died of cervical cancer due to systemic progression, and 6 patients (25%) died of BM. Among the 15 patients who delivered radiotherapy, 11 patients (73.3%) had controlled intracranial lesions, and 4 patients (26.7%) experienced progression.

In the univariate analysis, the histopathology of neuroendocrine cancer, FIGO stage, KPS at BM diagnosis, and treatment strategy (surgery, radiotherapy or chemotherapy) were identified to have prognostic significance regarding the survival of patients with BM from cervical cancer (P < 0.05). The age at BM diagnosis and extracranial metastasis were close to statistical significance, as shown in Table 4.

Table 4 Univariate Analysis of Cervical Cancer Patients with BM

| Variables                      | Mean Survival Time (Months) | P-value | \( \chi^2 \) |
|--------------------------------|-----------------------------|---------|-------------|
| Age at BM diagnosis (years)    | ≥65                         | 7.6     | 0.056       |
| KPS at BM diagnosis            | ≥70                         | 8.8     | 0.024       |
| Histopathology (neuroendocrine cancer) | Yes | 10.5 | 0.018       |
| 2018 FIGO stage                | IIB                         | 14.2    | 0.014       |
| Extracranial metastasis        | Yes                         | 8.0     | 0.054       |
| Treatment status               | Yes                         | 9.0     | 0            |
| Local treatment status (surgery and RT) | Yes | 9.6 | 0.001       |
| Chemotherapy                   | Yes                         | 9.2     | 0            |

Abbreviations: BM, brain metastasis; RT, radiotherapy.
Table 5  Multivariate Analysis of Cervical Cancer Patients with BM

| Variables          | B     | SE    | Wald | df | P-value | Exp(B) | 95% CI for Exp(B) |
|--------------------|-------|-------|------|----|---------|--------|-------------------|
|                    | Lower | Upper |
| KPS at BM diagnosis| −0.037| 0.999 |
| RT                 | 1.302 | 0.044 |
| CT                 | 1.184 | 0.367 |

Abbreviations: BM, brain metastasis; KPS, Karnofsky performance status; RT, radiotherapy; CT, chemotherapy.

Table 6  Mean Survival Time by Different Therapeutic Schedules in 24 Patients

| Therapeutic Schedule | All Patients (%) | Mean Survival Time (Months) | P-value for Treatment Group | P-value for All Patients |
|----------------------|------------------|-----------------------------|-----------------------------|--------------------------|
| S followed by SRT and CT | 1 (42) | 9.3 | 0.577 |
| S followed by WBRT and CT | 2 (83) | 16.1 | 0 |
| S followed by WBRT | 1 (42) | 6.3 |  |
| SRT alone | 1 (42) | 9.0 |  |
| SRT and CT | 4 (167) | 6.5 |  |
| WBRT and CT | 2 (83) | 9.6 |  |
| WBRT with SIB and CT | 4 (167) | 10.5 |  |
| CT alone | 3 (125) | 6.2 |  |
| Palliative care | 6 (25) | 1.8 |  |

Abbreviations: S, surgery; RT, radiotherapy; CT, chemotherapy; SIB, simultaneous integrated boost; SRT, stereotactic radiotherapy; WBRT, whole-brain radiotherapy.

The above variables with P < 0.1 in univariate analysis were included in Cox multivariate regression analysis. In the multivariate analysis, KPS, chemotherapy, and radiotherapy were identified as independent prognostic factors for survival, as shown in Table 5. The mean survival times by the different therapeutic schedules are shown in Table 6.

Because the treatment options need to consider the patient’s systemic lesions, the number of BM and pathological types, we conducted stratified analysis on the number of BM, whether extracranial metastases and neuroendocrine carcinoma in the following analysis.

In the stratified analysis on the number of BMs, all patients with BMs>3 underwent WBRT. In BMs≤3 group, the proportion of patients undergoing local treatment (SRT ±surgery) was significantly higher than that of patients undergoing WBRT (50% vs 25%, P= 0.011, $\chi^2= 9$). The mean survival times of the different therapeutic schedules for patients with BMs>3 and ≤3 are shown in Table 7.

Among the eight patients with neuroendocrine carcinoma, five patients had BMs ≤3, two patients had BMs >3, and the BMs of one patient was unknown. All patients received chemotherapy. Of the six patients who underwent radiotherapy, four underwent WBRT and two underwent SRT.

Among the 20 patients with extracranial metastasis, 17 received aggressive treatment including surgery, radiotherapy or chemotherapy, and 3 only received palliative care; of the 4 patients without extracranial metastasis, only 1 received treatment, and the remaining 3 received palliative care. Tables 7 and 8 respectively show the mean survival times by different therapeutic schedules and by the treatment group and palliative care group for the patients with neuroendocrine carcinoma and extracranial metastasis.

During the verification for the prognostic scoring classification systems of BM, only in the RPA, the comparison of grade II and grade III showed significant differences (P=0.014, $\chi^2= 6.077$). In the other prognostic scoring classification systems, such as GPA, uterine-GPA, BS-BM, and GGS, the P-values were 0.584, 0.518, 0.893, and 0.234, respectively.

Discussion
Cervical cancer is the most common cancer in women. The common metastatic sites are the lymph nodes, liver,
Table 7 Mean Survival Time by Different Therapeutic Schedules in the Stratified Analysis on the Number of BMs, Whether Extracranial Metastases and Neuroendocrine Carcinoma

| Stratified Variable | Mean Survival Time (Months) | P-value | χ² |
|---------------------|-----------------------------|---------|-----|
| Number of BMs       |                             |         |     |
| BMs ≤3              | S Followed by SRT and CT: 9.3 | 10.9    | /   |
|                    | S Followed by WBRT and CT: 9.0 | /       | 6.5 |
|                    | SRT Alone: 6.5              | /       | 11.8|
|                    | WBRT and CT: 7.4            | /       | 7.8 |
|                    | WBRT with SIB and CT: 7.8   | /       | /   |
| BMs >3              | /                           | 2.12    | 6.3 |
|                    | SRT Alone: 7.4              | /       | 12.8|
|                    | WBRT: 7.8                   | /       | /   |
|                    | WBRT with SIB: 7.8          | /       | /   |
| Neuroendocrine cancer | S Followed by SRT and CT: 9.3 | 2.12    | /   |
| Extracranial metastasis | S Followed by WBRT and CT: 9.0 | /       | 6.3 |
|                      | SRT Alone: 6.5              | /       | 11.8|
|                      | WBRT and CT: 7.4            | /       | 7.8 |
|                      | WBRT with SIB and CT: 7.8   | /       | /   |
| Palliative Care     | 1.8                         | 1.5     | 0.001|

Clinical Characteristics

Prognostic Factors

It has been reported that the prognosis of cervical cancer patients with BM is affected by many factors, such as histopathology, stage, control of primary cervical lesions, time interval from diagnosis of cervical cancer to the diagnosis of BM, number of BM and tumor size. Prognostic factors related to survival in many pieces of literature. The most common histopathology of cervical cancer is squamous cell carcinoma. Although cervical adenocarcinoma is rare, the risk of BM is as high as 20%. The clinical manifestations of BM are nervous system symptoms such as headache, dizziness, ataxia, muscle weakness, etc. The clinical survival time of BM ranges from 2 to 8 months. The clinical survival time of BM is 1.1-2 years after the diagnosis of cervical cancer. 

It has been reported that the mean age of BM from cervical cancer is 45-50 years old. The mean survival time interval after diagnosis of cervical cancer is approximately 1-2 years. The incidence of BM from cervical cancer is 0.4-2.3%.

Table 8 Mean Survival Time (Months) by Treatment Group and Palliative Care Group for the Patients with Neuroendocrine Carcinoma and Extracranial Metastases

| Treatment Group | Palliative Care Group |
|-----------------|----------------------|
| Yes (Metastasis)| No (Metastasis)      |
| Extracranial   | Cancer               |
| 11.9            | 11.9                 |
| 17.2            | 21.9                 |
| 0.065           | 0.065                |
| 0.333           | 0.333                |

Palliative Care Group for the Patients with Neuroendocrine Carcinoma and Extracranial Metastases
extracranial metastasis, treatment factors (radiotherapy, chemotherapy, surgery, etc.) are prognostic factors related to the BM of cervical cancer. Additionally, molecular biology studies have shown that some of the molecular characteristics in tissue samples are also related to survival. In our univariate analysis, histopathology of neuroendocrine cancer, the early stage of the 2018 FIGO stage, age <65 years and KPS ≥70 at BM diagnosis, extracranial metastasis, and aggressive treatment had statistical significance. In the multivariate analysis, only higher KPS, radiotherapy, and chemotherapy provided significant benefits. These results are consistent with the above literature.

In further stratified analysis on whether neuroendocrine carcinoma and extracranial metastasis group, the survival time of palliative care was 0.9 months vs. 1.9 months (P = 0.583) and 1.5 months vs. 2.0 months (P = 0.486), respectively. After aggressive treatment, the survival time of the two groups was similar and was even higher than that of the control group (11.9 vs. 7.2 months, P = 0.026; 9.1 vs. 7.4 months, P = 0.670). Therefore, for patients with a high KPS score, aggressive treatment can significantly improve survival, and similar conclusions have been obtained in other studies.

**Therapeutic Schedule**

At present, the treatment options of BM from cervical cancer mainly include surgery, WBRT, SRS (stereotactic surgery), SRT, or chemotherapy. For patients with high KPS scores, surgery or SRS combined with WBRT and sequential chemotherapy has been proven to increase survival time in many pieces of literature. Some authors strongly suggest that surgery followed by radiotherapy is an effective treatment for patients with solitary BM that prolongs survival. The result of our study shows that surgery followed by SRT and chemotherapy may be better than the combination of SRT and chemotherapy; surgery followed by WBRT and chemotherapy may be better than surgery followed by SRT and chemotherapy; surgery followed by WBRT and chemotherapy may be better than surgery followed by WBRT; WBRT with SIB and chemotherapy may be better than WBRT and chemotherapy. Although there was no significant difference in the above data (P=0.577), there was a numerical advantage in terms of survival time. It is suggested that only the combination of local treatment such as radiotherapy or surgery and chemotherapy may improve the survival time, which is better than that with any single treatment.

In our study, the proportion of patients undergoing local treatment (SRT+surgery) was significantly higher than that of patients undergoing WBRT (50% vs. 25%, P=0.011) for the patients with BMs<3. On the other hand, all patients with BMs>3 underwent WBRT. In the previous literature, for patients with surgical indications, surgery followed by radiotherapy and chemotherapy can improve survival time. At present, of the radiation interventions, it was believed that WBRT will benefit survival. This also supports our treatment options. Moreover, of our data, the higher the total dose of radiation was, the greater the potential survival benefit maybe. Additionally, it has been reported that SRS combined with WBRT can alleviate the neurological symptoms caused by BM.

**Prognosis Scoring Classiﬁcation System of Cervical Cancer with BM**

At present, there are many prognostic scoring classiﬁcation systems in the clinic, and RPA and GPA are the most commonly used. Because of the differences in the biological characteristics of BM of a different histology, a disease-speciﬁc GPA (disease-speciﬁc GPA) has been proposed. The abovementioned prognosis scoring classiﬁcation systems of BM are mainly based on cases with WBRT. Additionally, the BS-BM and GGS are based on SRT or combined with WBRT. In 2012, the disease-speciﬁc GPA can also be used as a prognostic scoring classiﬁcation system for BM based on SRT. Japanese scholars put forward the uterine-GPA for uterine cancer (endometrial cancer and cervical cancer) in 2017.

In this study, RPA, GPA, uterine-GPA, BS-BM, and GGS were used to predict prognosis. They did not show signiﬁcant statistical signiﬁcance except for RPA because our results were more consistent with those predictive factors in RPA. These results were consistent with the previous literature. Most of the data in these prognosis scoring classiﬁcation systems were from lung cancer and other common cancers, so it may not be suitable for patients with BM from cervical cancer. Hayashi et al proposed that the ﬁnal prognostic factors in uterine-GPA are completely different from those in this study. Therefore, the prognosis scoring classiﬁcation system of BM from cervical cancer needs further study with a larger sample for improvement.

Because of the low incidence of BM from cervical cancer, the data in this study were from the same center, which could introduce center bias. However, compared
with the data in similar literature from a single cancer treatment center, the number of cases in this study is the largest. The results of this study may provide important evidence for the treatment of cervical cancer patients with BM.

In conclusion, when patients with BM from cervical cancer have good performance status and undergo comprehensive treatment, such as radiotherapy and chemotherapy, their survival time could be significantly prolonged. Patients with surgical indications may get better survival by postoperative radiotherapy and chemotherapy. Patients with BMs ≥3 may get better survival by WBRT. But further studies are needed regarding the selection of surgical indications and radiotherapy modes. The prognosis scoring classification system for BM from cervical cancer needs to be improved.

**Ethics and Consent Statement**
This study was conducted in accordance with the Declaration of Helsinki. This study was approved by the Ethics Review Committee of Peking Union Medical College Hospital, Chinese Academy of Medical Sciences [Protocol number S-K1298]. Informed consent was obtained from each patient or his/her guardian prior to initiating the treatment.

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**Disclosure**
All the authors declare that they have no conflicts of interest.

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