DOI: 10.5137/1019-5149.JTN.13973-15.1
Received: 20.01.2015 / Accepted: 27.02.2015
Published Online: 11.07.2016

*Original Investigation*

# The Impact of the Stage and Tumor Size on Rare Brain Metastasis of Cervical Cancer

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## ABSTRACT

**AIM:** To investigate the clinical features, prognostic factors and survival times of cervical cancer patients with brain metastasis.

**MATERIAL and METHODS:** We retrospectively reviewed the medical records of 820 patients with cervical cancer. Data were analyzed using SPSS version 12.0 statistical software (SPSS, Chicago, IL, USA). Overall survival, time interval from diagnosis of cervical cancer to identification of brain metastasis, and median survival time after diagnosis of brain metastasis were calculated using Kaplan–Meier curve analysis. The log-rank test was used to compare differences in survival. Differences were assumed statistically significant when p-values were <0.05.

**RESULTS:** The incidence of brain metastases from cervical cancer in our institution was 1.82% (15/820) over a ten-year period. The median time interval from diagnosis of cervical cancer to detection of brain metastasis was 12.5 months (range: 2.9–91.9 months). Stage and tumor diameter were found to be significant relating to the interval from diagnosis of cervical cancer to detection of brain metastasis (p=0.001 for both).

**CONCLUSION:** This study provides much information about the prognosis of patients with brain metastases from cervical cancer and highlights the importance of initial stage and tumor diameter when determining the time interval until development of brain metastasis.

**KEYWORDS:** Cervical carcinoma, Brain metastasis, Prognosis

## INTRODUCTION

Uterine cervical cancer is the second most common malignancy in women worldwide (9,14,16). It spreads most often via local extension and through the lymphatics to the retroperitoneal lymph nodes. Distant organs are reached by hematogenous dissemination, which occurs infrequently, but especially influences the lungs, liver, bones, and extrapelvic lymph nodes (1,8). Despite the fact that metastatic brain tumors are said to constitute up to 50% of adult brain tumors, those arising from cervical cancer are a rare event, with an incidence rate between 0.4 to 1.2% among cervical cancer cases (3,4,7,13). Therefore, there are only case reports or small case series related to these rare metastases in the English medical literature (10–12,15-17). The median survival time from determination of brain metastasis from

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cervical cancer to death was reported to be 2.3 months in the cohort of the University of Minnesota Women's Health Center (13).

Because of the rarity of brain metastasis from cervical cancer, optimal treatment modality and prognosis are not fully known. When brain metastasis develops in patients with cervical cancer, it is indicator of a poor prognosis. If brain metastasis is detected late in the progression of the disease, the treatment modality is completely unsatisfactory. The aim of our study was to investigate the clinical features, prognostic factors, treatment modalities, and survival times of cervical cancer patients with brain metastasis.

## MATERIAL and METHODS

### Patient Selection and Data Collection

The medical records of 820 patients with cervix cancer at Radiation Oncology Clinic of Okmeydanı Training and Research Hospital between 1996 and 2006 were reviewed retrospectively. We identified fifteen patients with brain metastasis and assessed their survival, clinical progression, and the general characteristics of their case. Surgery reports, pathology reports, and clinical follow-up notes in the patient clinical charts were also reviewed. Patients with a secondary malignancy such as lung or breast cancer were excluded because brain metastasis may clinically originate from other malignancies at a higher rate. All patients with brain metastasis were examined in terms of prognostic factors, treatment modalities, and survival. Data reviewed and verified for each patient included: age; initial International Federation of Gynecology and Obstetrics (FIGO) stage; initial treatment; histopathologic findings; presence of other organ metastasis; diagnostic method and treatment of brain metastasis; recurrence date; date of metastasis; date of death or last follow-up appointment; and time intervals between the date of diagnosis of brain metastases and death or last follow-up.

### Staging

Patients were staged according to FIGO staging criteria. Initial clinical staging was determined by a pelvic examination from a radiation oncologist and a gynecologic oncologist. Imaging to detect the presence of a primary tumor and metastases included computed tomography (CT) and/or magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis. When symptoms of brain metastasis were suspected, patients were imaged with CT and/or MRI.

### Follow-up

The patients were scheduled for follow-up appointments every three months after receiving initial cervical cancer treatments, then every six months over the next three years, and then once a year until disease recurrence, metastasis, or death. Patients received follow-up over a median of 22.2 months with a range of 4.6 months up to 98.2 months.

### Radiation Therapy (RT)

Radiotherapy was performed to the whole brain using 6 MV photon or cobalt 60 from right and left lateral fields. Doses of whole brain radiation therapy (WBRT) averaged 30 Gy at 10 fractions (Range: 10-30 Gy).

### Factors Analyzed

Six potential prognostic variables were chosen based on the previously published clinical trials. Each variable was divided into two categories: age (< 50 or ≥ 50); FIGO stage (≤ IIB or > IIB); pelvic lymph node (negative or positive); maximal tumor diameter (≤ 6 cm or > 6 cm); grade (Grade 2 or 3); and histology (Squamous cell carcinoma (SCC) or non-squamous cell carcinoma (NSCC)).

### Statistics

Data were analyzed using SPSS version 12.0 statistical software (SPSS, Chicago, IL, USA). Overall survival (OS), time interval from diagnosis of cervical cancer to identification of brain metastasis, and median survival time after diagnosis of brain metastasis were calculated using Kaplan–Meier curve analysis. The log-rank test was used to compare differences in survival. Differences were assumed to be statistically significant when p-values were $<0.05$.

## RESULTS

The incidence of brain metastases from cervical cancer in our institution was 1.82% (15/820) over a period of ten years. Patient properties are shown in Table I. The median age at time of initial diagnosis of cervical cancer was 50 years old (range: 32–77 years old). Concerning the initial FIGO stage, seven (46.7%) patients had stage IIB disease, two (13.3%) had stage IIA disease, two (13.3%) had stage IVA disease, and one (6.7%) each had stage IB1, IB2, IIIA and IVB disease. Eleven patients (73.3%) had SCC, three had adenocarcinoma (AC), and one had clear cell carcinoma. The pelvic lymph node (PLN) metastasis was positive in five patients (33.3%) and the paraaortic lymph node (PALN) metastasis was positive in only two patients at initial assessment. Ten patients (66.7%) had grade 3 diseases. Tumor diameter was ≥ 4 cm in twelve patients (80%). Five patients had surgery, undergoing either type I or II hysterectomy. Three patients received postoperative radiation therapy (post-op RT) and one patient was treated with post-op concurrent chemoradiation therapy (CCRT) for the initial disease. Forty percent of patients were treated with definitive RT and 26.6% of inoperable cases received CCRT, using weekly cisplatin 40 mg/m$^2$ as the chemotherapy agent for CCRT. There was local recurrence in 4 patients and lymph node metastasis in 80% of patients. Five patients had only brain metastasis, while others had lung, bone, spinal cord, or multi-organ metastases in addition to brain metastasis. Fourteen of the fifteen patients with brain metastases had multiple brain metastases. There was a solitary brain metastasis in only one patient and this patient was treated with whole brain irradiation due to refusal of metastasectomy. Treatment for brain metastasis was WBRT in 60% of patients using median doses of 30 Gy (range:10-30 Gy). When the performance status of patients with brain metastases was assessed according to the ECOG PS (Eastern Cooperative Oncology Group Performance Status) criteria, ECOG PS was 4 in eight patients, 3 in six patients and 2 in only one patients.

**Table I:** Patients Characteristics

| Variables | | Number (n) | Percentage (%) |
|---|---|---|---|
| Age (years) | Average | 50 | |
| | Range | 32-77 | |
| FIGO stage | IB1 | 1 | 6.7 |
| | IB2 | 1 | 6.7 |
| | IIA | 2 | 13.3 |
| | IIB | 7 | 46.7 |
| | IIIA | 1 | 6.7 |
| | IVA | 2 | 13.3 |
| | IVB | 1 | 6.7 |
| Tumor histology | Squamous cell carcinoma | 11 | 73.3 |
| | Adenocarcinoma | 3 | 20 |
| | Clear cell carcinoma | 1 | 6.7 |
| PLN | Negative | 10 | 66.7 |
| | Positive | 5 | 33.3 |
| Paraaortic nodal metastasis | Negative | 13 | 86.7 |
| | Positive | 2 | 13.3 |
| Grade | 2 | 5 | 33.3 |
| | 3 | 10 | 66.7 |
| Greatest tumor diameter | <4 cm | 3 | 20 |
| | 4-6 cm | 7 | 46.7 |
| | >6 cm | 5 | 33.3 |
| Initial surgery | Inoperable | 10 | 66.7 |
| | Operated | 5 | 33.3 |
| Initial treatment | Definitive RT | 6 | 40.0 |
| | CCRT | 4 | 26.6 |
| | Post-op RT | 3 | 20 |
| | Post-op CCRT | 1 | 6.7 |
| | Only operated | 1 | 6.7 |
| Local recurrence | Negative | 11 | 73.3 |
| | Positive | 4 | 26.7 |
| LN metastasis | Negative | 3 | 20 |
| | Positive | 12 | 80 |
| Side of distant metastasis | Only brain | 5 | 33.3 |
| | Brain and lung | 5 | 33.3 |
| | Brain and bone | 2 | 13.3 |
| | Brain and spinal cord | 1 | 6.7 |
| | Brain and multiple organs | 2 | 13.3 |
| Treatment of brain metastasis | WBRT | 9 | 60.0 |
| | Supportive care | 6 | 40.0 |
| WBRT dose (cGy) | Average | 3000 | |
| | Range | 1000-3000 | |

***PLN:*** *Pelvic lymph node,* ***LN:*** *Lymph node,* ***RT:*** *Radiation therapy,* ***CCRT:*** *Concurrent chemo-radiation therapy,* ***WBRT:*** *Whole brain radiation therapy.*

Six patients did not receive RT or chemotherapy except for symptomatic treatment for brain metastases due to their poor performance. The median time interval from cervical cancer diagnosis to detection of brain metastasis was 12.5 months (range: 2.9–91.9 months). Median survival time from identification of brain metastasis to death was 4.1 months (range: 0.3–22.6 months). Median overall survival of fifteen cases with brain metastasis from cervical cancer was 22.2 months (range: 4.6–98.2 months).

Tables II, III, and IV show the results of the univariate analysis. Among the variables in the univariate analysis, age groups and PLN metastasis were identified to have prognostic significance on survival after identification of brain metastasis (p=0.04 and p=0.01, respectively) (Table II). Six variables were analyzed for OS and interval from diagnosis of cervical cancer to identification of brain metastasis. Stage and tumor diameter were found to be significant regarding the interval from diagnosis of cervical cancer to detection of brain metastasis (p=0.001 for both) (Table III). Stage and tumor diameter were also significant for overall survival in our univariate analysis (p=0.001 for both) (Table IV).

## ■ DISCUSSION

Brain metastasis is the most common intracranial tumor in adults, frequently occurring in patients with lung cancer, breast cancer and melanoma. However, it is a rare development in uterine cervical cancer, with an incidence rate of only 0.4% to 1.2% (3,4,7,16). Recently, brain metastasis has been seen more frequently. This increase may be due to improved diagnostic methods (such as MRI) for brain metastasis and better OS rate coming from more efficient treatment options. We found the incidence of brain metastasis from cervical carcinoma in our institution was 1.82 % (15/820).

**Table II:** Univariate Analysis of Survival Time After Diagnosis of Brain Metastasis by Categorical Variable

| Variable | Log-rank test value | Degrees of freedom | p value |
|---|---|---|---|
| Age groups | 4.02 | 1 | 0.04 |
| Stage groups | 2.92 | 1 | 0.08 |
| Pelvic lymph node | 5.78 | 1 | 0.01 |
| Grade | 0.07 | 1 | 0.78 |
| Histology | 0.01 | 1 | 0.90 |
| Maximal tumor diameter | 3.52 | 2 | 0.17 |

**Table III:** Univariate Analysis of Time Interval from Diagnosis of Cervical Cancer to Identification of Brain Metastasis by Categorical Variable

| Variable | Log-rank test value | Degrees of freedom | p value |
|---|---|---|---|
| Age groups | 0.009 | 1 | 0.92 |
| Stage groups | 15.5 | 1 | 0.001 |
| Pelvic lymph node | 1.38 | 1 | 0.23 |
| Grade | 2.13 | 1 | 0.14 |
| Histology | 0.21 | 1 | 0.64 |
| Maximal tumor diameter | 15.6 | 2 | 0.001 |

**Table IV:** Univariate Analysis of Overall Survival by Categorical Variable

| Variable | Log-rank test value | Degrees of freedom | p value |
|---|---|---|---|
| Age groups | 0.24 | 1 | 0.62 |
| Stage groups | 13.4 | 1 | 0.001 |
| Pelvic lymph node | 2.9 | 1 | 0.08 |
| Grade | 1.5 | 1 | 0.21 |
| Histology | 0.01 | 1 | 0.92 |
| Maximal tumor diameter | 13.9 | 2 | 0.001 |

Once brain metastases have developed, the prognosis of a patient with cervical cancer is poor, with a low survival rate after detection of the metastasis. In a study by Chura et al. (3), the median survival time from diagnosis of brain metastasis of uterine cervical cancer to death was reported to be 2.3 months (range: 0.3– 7.9 months). Hwang et al. (6) reported that the median survival time after diagnosis of the brain metastasis was 5.9 months (range: 0.7–19 months). In our series, the median survival time from diagnosis of brain metastasis to death was 4.1 months (range: 0.3– 22.6 months).

In a previous study, the median interval from the diagnosis of the primary cancer to the appearance of brain metastases was twelve months in five patients (10), while Cormio et al. (5) reported that it was eighteen months. In addition, Chung et al. (2) reported a median interval of 38 months (range: 8.7–127.2 months) and Ikeda et al. (7) reported 28.4 months (range: 6.1-61.8 months). Our report is comparable to previous studies, finding a median interval from diagnosis of the primary cancer to brain metastasis of 12.5 months (range: 2.9– 91.9 months).

Brain metastasis may occur in any histologic type of uterine cervical cancer, but the most common subtype is squamous cell carcinoma (2, 6). Ikeda et al. report (7) that five of their eight cases had an SCC histology. In our series, eleven patients (73.3%) had SCC and four patients had non-SCC histology (three adenocarcinoma and one clear cell carcinoma). However, in our study, histology was not a significant variable in the univariate analysis of time interval from diagnosis of cervical cancer to identification of brain metastasis or survival time after diagnosis (p>0.05).

In the study by Hwang et al. (6), most of the cases were at an advanced stage, as the initial stage in six of eleven patients was higher than stage IIB and in two cases, the stage was unknown. Ikeda et al. (7) reported that the initial stage was IIB in four of eight patients with brain metastasis from uterine cervical cancer. In a series of twelve cases from Chura et al. (3), nine patients were stage IIB or below, while three patients were higher than stage IIB. In our study, four cases had an initial stage higher than IIB and eleven patients were stage IIB or below. We found that overall survival was better and time interval from diagnosis of cervical cancer to identification of brain was longer in stages IIB and below compared to those with more advanced stages (p=0.001 for both) (Figure 1).

Although the previous studies presented sizes of brain metastases, the diameter of primary tumor was reported only in few case reports. Setoodeh et al. (15) evaluated two cases with brain metastasis that had large cervical masses (12 cm and 10 cm). In our study, maximal diameter of the primary tumor was a significant variable in the univariate analysis of time interval from diagnosis of cervical cancer to identification of brain metastasis and OS (p=0.001 for both). We showed that when the diameter of primary tumor in cervix was more than 6 cm, the brain metastases developed more quickly (Figure 2).

Chung et al. (2) reported that in their study, there were six patients under age fifty, and they had a lower survival rate after treatment of brain metastasis. Both age and pelvic lymph node metastasis were significant variables for survival time after diagnosis of brain metastasis in our study (p<0.05 for both). We found that when age was < 50 or PLN metastasis was positive, survival time after diagnosis of brain metastasis was reduced.

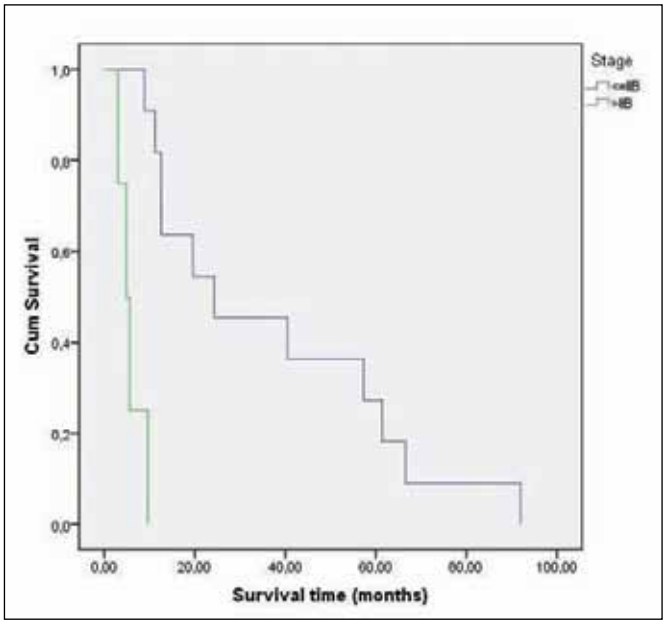


**Figure 1:** Time interval from diagnosis of cervical cancer to identification of brain metastasis according to the stage groups (p=0.001).

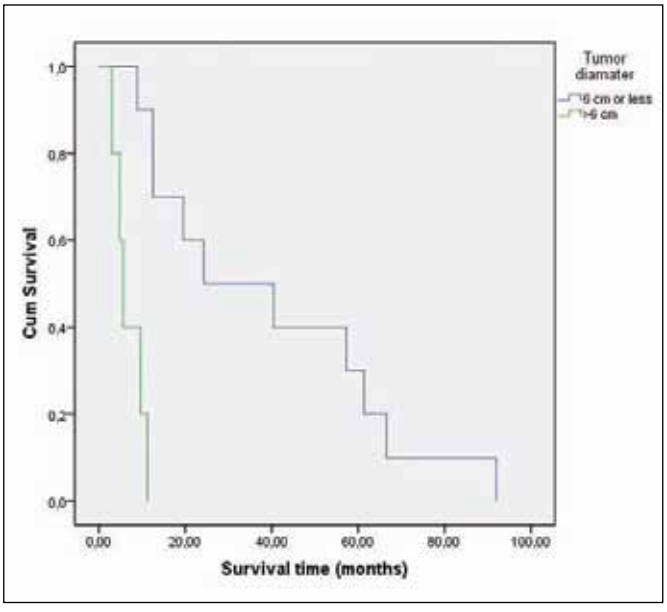


**Figure 2:** Time interval from diagnosis of cervical cancer to identification of brain metastasis according to the tumor diameter (p=0.001).

There were some limitations to our study. First, it is a retrospective study. Second, according to the literature,

although we had a reasonable number of patients with brain metastasis from cervical cancer, they were not enough to analyze. The analysis we performed was designed to give a better idea about prognostic factors with the log-rank test. Finally, because there are insufficient publications in English literature related to this subject, our findings could not be compared to them effectively.

## CONCLUSION

It is premature to draw statistical conclusions from this retrospective study. However, it provides much needed information about the prognosis of patients with brain metastases from cervical cancer. Our analysis indicates that initial stage and tumor diameter are important in determining the time interval until development of brain metastasis.

## REFERENCES

1. Carlson V, Delclos L, Fletcher GH: Distant metastases in squamous-cell carcinoma of the uterine cervix. Radiology 88: 961–966, 1967
2. Chung SB, Jo KI, Seol HJ, Nam DH, Lee JI: Radiosurgery to palliate symptoms in brain metastases from uterine cervix cancer. Acta Neurochir (Wien) 155: 399–405, 2013
3. Chura JC, Shukla K, Argenta PA: Brain metastasis from cervical carcinoma. Int J Gynecol Cancer Off J Int Gynecol Cancer Soc 17: 141–146, 2007
4. Cordeiro JG, Prevedello DM-S, Ditzel LF da S, Pereira CU, Araújo JC: Cerebral metastasis of cervical uterine cancer: Report of three cases. Arq Neuropsiquiatr 64: 300–302, 2006
5. Cormio G, Pellegrino A, Landoni F, Regallo M, Zanetta G, Colombo A, Mangioni C: Brain metastases from cervical carcinoma. Tumori 82: 394–396, 1996
6. Hwang JH, Yoo HJ, Lim MC, Seo SS, Kang S, Kim JY, Park SY: Brain metastasis in patients with uterine cervical cancer. J Obstet Gynaecol Res 39: 287–291, 2013
7. Ikeda S, Yamada T, Katsumata N, Hida K, Tanemura K, Tsunematu R, Ohmi K, Sonoda T, Ikeda H, Nomura K: Cerebral metastasis in patients with uterine cervical cancer. Jpn J Clin Oncol 28: 27–29, 1998
8. Janni W, Hepp F, Strobl B, Rack B, Rjosk D, Kentenich C, Schindlbeck C, Hantschmann P, Pantel K, Sommer H, Braun S: Patterns of disease recurrence influenced by hematogenous tumor cell dissemination in patients with cervical carcinoma of the uterus. Cancer 97: 405–411, 2003
9. Maheshwari GK, Baboo HA, Ashwathkumar R, Dave KS, Wadhwa MK: Scalp metastasis from squamous cell carcinoma of the cervix. Int J Gynecol Cancer Off J Int Gynecol Cancer Soc 11: 244-246, 2001
10. Mahmoud-Ahmed AS, Suh JH, Barnett GH, Webster KD, Kennedy AW: Tumor distribution and survival in six patients with brain metastases from cervical carcinoma. Gynecol Oncol 81: 196–200, 2001
11. Omari-Alaoui HE, Gaye PM, Kebdani T, El Ghazi E, Benjaafar N, Mansouri A, Errihani H, Kettani F, El Ouahabi A, El Gueddari BK: Cerebellous metastases in patients with uterine cervical cancer. Two cases reports and review of the literature. Cancer/ Radiothérapie 7: 317–320, 2003
12. Piura E, Piura B: Brain metastases from cervical carcinoma: Overview of pertinent literature. Eur J Gynaecol Oncol 33: 567–573, 2012
13. Robinson JB, Morris M: Cervical carcinoma metastatic to the brain. Gynecol Oncol 66: 324–326, 1997
14. Scarinci IC, Garcia FAR, Kobetz E, Partridge EE, Brandt HM, Bell MC, Dignan M, Ma GX, Daye JL, Castle PE: Cervical cancer prevention: New tools and old barriers. Cancer 116: 2531–2542, 2010
15. Setoodeh R, Hakam A, Shan Y: Cerebral metastasis of cervical cancer, report of two cases and review of the literature. Int J Clin Exp Pathol 5: 710–714, 2012
16. Takagi H, Miura S, Matsunami K, Ikeda T, Imai A: Cervical cancer metastasis to the scalp: Case report and literature review. Eur J Gynaecol Oncol 31: 217–218, 2010
17. Yuan G, Wu L, Huang M, Yao H: Analysis of 25 cases of brain metastasis from gynecological cancers. Zhonghua Fu Chan Ke Za Zhi 47: 191–195, 2012