

# Rapid Development of Brain Metastases in Poorly Differentiated Cervical Squamous Cell Carcinoma: A Rare Case Report

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**Background and Purpose:** Brain metastases from cervical cancer are exceedingly rare, with an incidence of 0.4% to 2.3%. Poorly differentiated histologic subtypes, particularly those with lymphovascular space invasion (LVSI) and parametrial involvement, may have a higher propensity for hematogenous spread. Current surveillance protocols do not routinely include brain imaging, potentially leading to delayed diagnosis in patients with early metastases. This case highlights an aggressive presentation of poorly differentiated squamous cell carcinoma (SCC) of the cervix with rapid brain metastases post-treatment, emphasizing the need for revised follow-up and therapeutic strategies.

**Case Presentation:** A 46-year-old woman presented with postcoital bleeding and was diagnosed with International Federation of Gynecology and Obstetrics (FIGO) stage IIA1 poorly differentiated non-keratinizing SCC of the cervix. She underwent radical hysterectomy with bilateral salpingo-oophorectomy and pelvic lymphadenectomy, followed by adjuvant chemoradiotherapy. Despite initial disease control, she developed progressive neurological symptoms five months post-treatment. Brain imaging revealed multiple intracranial metastases, confirmed histologically as metastatic SCC. She underwent craniotomy and tumor resection, followed by palliative care due to extensive systemic involvement, including lung metastases.

**Conclusion:** This case highlights the limitations of current surveillance and treatment paradigms in high-risk cervical cancer patients. Earlier imaging and innovative systemic therapies with improved blood-brain barrier penetration may enhance patient outcomes. Future research should focus on refining post-treatment follow-up protocols and integrating novel therapeutic approaches for metastatic cervical cancer.

**Keywords:** brain metastases, squamous cell carcinoma, cervix

## Introduction

Cervical cancer is the fourth most commonly diagnosed malignancy among women worldwide. In 2022, cervical cancer accounted for approximately 662,044 new diagnoses and 348,709 fatalities worldwide. More than 85% of these cases and 90% of the associated deaths occurred in women aged 40 years and above. Notably, the incidence and mortality rates in this older population were nearly ten times and twenty times greater than those observed in younger women diagnosed at an earlier age.<sup>1,2</sup>

Metastatic or recurrent cervical cancer carries a poor prognosis, with a median survival of less than two years. The most common metastatic sites include the lymph nodes, lungs, liver, and bones.<sup>3,4</sup> Brain metastases from cervical cancer are exceedingly rare, with an incidence ranging from 0.4% to 2.3%, increasing slightly to 2–8% in patients with extracranial metastases.<sup>5,6</sup> The risk of brain involvement is higher in poorly differentiated tumors, with lesions predominantly found in supratentorial regions due to vascular characteristics. Brain metastases are associated with poor survival outcomes, with a mean survival of only two to eight months despite multimodal treatment approaches that may include surgery, radiotherapy, and systemic therapy.<sup>7,8</sup>

Cervical cancer primarily spreads through direct extension, lymphatic dissemination, or hematogenous routes. Hematogenous spread to the brain occurs via the inferior vena cava, pulmonary circulation, and systemic arteries or through the paravertebral venous plexus.<sup>9,10</sup> While single-organ metastasis is more common, with the lungs being the predominant site, multi-organ involvement is rare, and isolated brain metastases are even less frequently reported.<sup>11</sup> Given its rarity, brain metastasis from cervical cancer remains poorly understood, and optimal surveillance and management strategies are yet to be clearly defined.

This case report illustrates a rare and highly aggressive course of poorly differentiated non-keratinizing squamous cell carcinoma (SCC) of the cervix, distant spread to organs such as the brain or scalp is exceptionally rare and poses significant diagnostic and therapeutic challenges. This case underscores the importance of aggressive post-treatment surveillance and highlights the limitations of current staging modalities in predicting systemic spread in high-risk patients. It advocates for a multimodal and individualized treatment approach including surgical resection of symptomatic metastases, cranial radiotherapy, and systemic chemotherapy while emphasizing the critical role of palliative care in advanced disease. Ultimately, this report contributes to the evolving understanding of atypical metastatic behavior in cervical cancer and reinforces the need for research into novel therapeutic strategies and refined follow-up protocols for patients with aggressive histological subtypes.

## Case Presentation

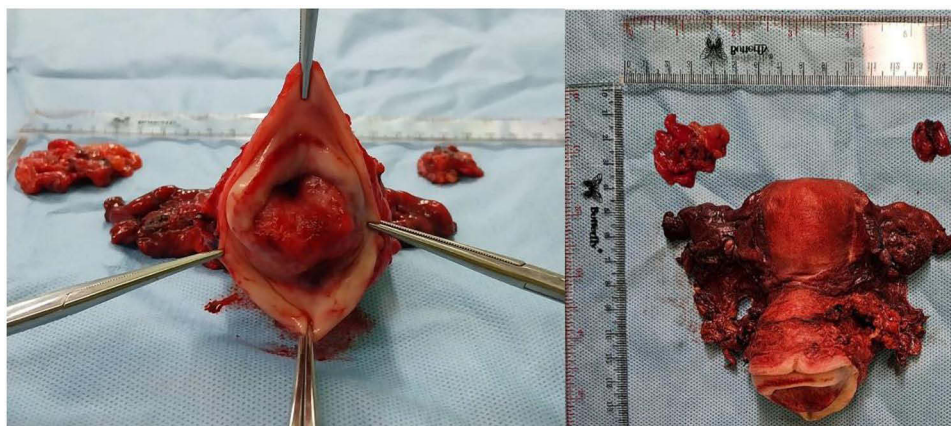
A 46-year-old woman, G2P1A1, was referred from Hermina Pasteur Hospital to Hasan Sadikin Hospital on May 29, 2024, due to persistent postcoital bleeding over the preceding two months. She reported no spontaneous vaginal bleeding, intermenstrual spotting, or pain during intercourse. Her menstrual cycles were regular, occurring every 28 days, lasting four days, with minimal bleeding requiring only one sanitary pad daily. She denied systemic symptoms, including weight loss, fatigue, or appetite changes, and reported no urinary or bowel disturbances. The patient's past medical history was un-remarkable, with no history of chronic illnesses such as hypertension, diabetes mellitus, or cardiovascular disease. She reported no family history of malignancy. Gynecologically, she experienced menarche at age 13, was married at 24, and used oral contraceptive pills for 13 years. She had no history of gynecologic surgeries.

On admission, the patient was hemodynamically stable. Her blood pressure was 136/84 mmHg, heart rate 84 beats per minute, respiratory rate 18 breaths per minute, and temperature 36.6°C. She weighed 61 kg with a height of 157 cm, resulting in a body mass index (BMI) of 24.75 kg/m<sup>2</sup>. Abdominal examination revealed no abnormalities. On speculum examination, a 3x3x3 cm exophytic mass was observed on the cervix, with no visible discharge or active bleeding. Bimanual examination confirmed the presence of a cervical mass without parametrial invasion and invasion into the proximal third of the vagina. Rectovaginal examination (RVT) showed soft, symmetrical fornices and a flat pouch of Douglas. Laboratory investigations were within normal limits, with hemo-globin at 14.2 g/dL, hematocrit at 40.5%, white blood cell count at 6,920/mm<sup>3</sup>, and platelets at 335,000/mm<sup>3</sup>. Liver and kidney function tests were normal, except for mildly elevated SGOT/SGPT levels at 46/73 U/L. A chest X-ray showed no evidence of pulmonary metastasis.

A cervical biopsy was performed on June 4, 2024, and revealed poorly differentiated non-keratinizing SCC. Further evaluation with pelvic magnetic resonance imaging (MRI) identified a 3x3x3 cm cervical mass with invasion into the proximal third of the vagina but no parametrial or distant metastases. On June 7, 2024, a chest X-ray was also performed, showing normal findings, which confirmed the absence of distant organ metastases. Based on clinical and imaging findings, the disease was staged as FIGO IIA1 cervical cancer. A multidisciplinary tumor board recommended radical surgery for definitive management.

On July 3, 2024, the patient underwent a radical hysterectomy with bilateral salpingo-oophorectomy and pelvic lymphadenectomy. Intraoperative findings confirmed a localized cervical mass without parametrial or gross vaginal extension (Figure 1). Histopathological analysis reported a poorly differentiated non-keratinizing SCC with bilateral parametrial invasion and LVSI. Surgical margins were negative for malignancy, and no evidence of metastatic disease was found in the 14 pelvic lymph nodes sampled (4 from the right and 10 from the left). The pathological stage was determined to be pT2bN0Mx.

Following surgery, the patient underwent adjuvant concurrent chemoradiotherapy (CCRT), which was completed in October 2024. The treatment regimen consisted of 25 fractions of external beam radiotherapy combined with cisplatin-



**Figure 1** Intraoperative Findings of Radical Hysterectomy. Surgical exploration revealed a confined cervical mass with no evident parametrial invasion or gross extension into the vagina.

based chemotherapy. Post-treatment assessment demonstrated no evidence of residual disease at the primary cervical site. During the course of therapy, a metastatic workup was conducted to evaluate the potential spread of cervical cancer. On September 20, 2024, a thoracoabdominal computed tomography (CT) scan was performed. The abdominal scan revealed hepatomegaly with multiple cystic lesions located in liver segments II, IVa, and VII. Skeletal imaging showed signs of vertebral spondylosis at Th8, Th10, and Th11, as well as a sclerotic lesion in the C6 vertebral body, which was suggestive of either a benign bone island or metastatic involvement. Additionally, multiple pulmonary nodules were identified, raising high suspicion for metastatic dissemination (Figure 2).

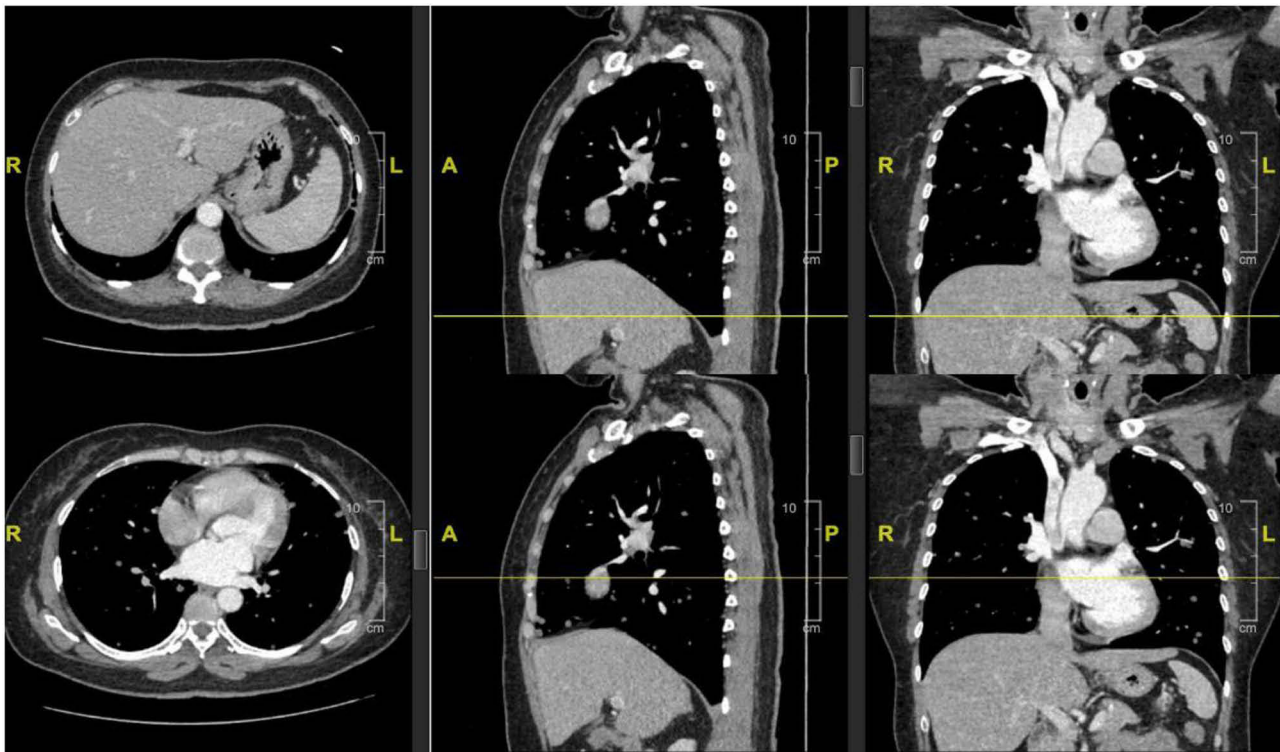
In October 2024, patient presented with a progressively enlarging mass in the occipital scalp region, measuring approximately 5×3 cm (Figure 3). The patient was noted to be drowsy and difficult to awaken, prompting urgent evaluation at the Neurology Emergency Unit. Physical examination revealed stable vital signs and no signs of meningeal irritation. Neurologically, the patient had a Glasgow Coma Scale (GCS) score of 15, no cranial nerve deficits, and preserved motor and sensory function. Fundoscopic examination of the right eye revealed papilledema, raising concern for increased intra-cranial pressure.

On October 29, 2024, an incisional biopsy of the occipital mass was performed. Histopathological analysis, reported on November 4, 2024, revealed brownish, elastic tissue comprising four fragments of skin-covered, hair-bearing material. Microscopic examination showed stratified squamous epithelium with normal nuclear morphology and underlying fibrous collagenous stroma infiltrated by lymphocytes. Sheets of round to oval and spindle-shaped cells demonstrated hyperplastic growth with pleomorphic, hyperchromatic nuclei and frequent mitotic figures. These findings were consistent with metastatic non-keratinizing SCC in the occipital region.

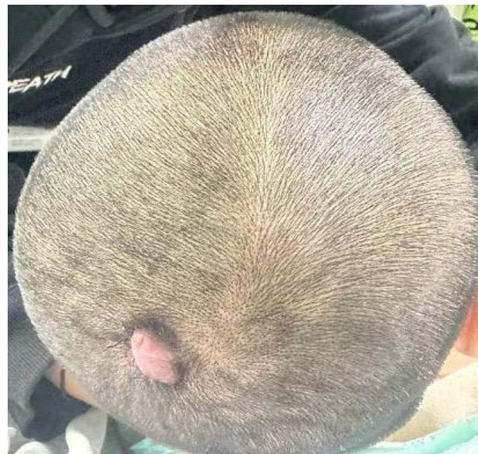
On November 6, 2024, the patient experienced a sudden decline in consciousness. Contrast-enhanced head CT scan revealed multiple inhomogeneous, non-calcified solid masses within the right frontoparietal and left frontal lobes, accompanied by perifocal edema and subfalcine herniation, suggestive of intracranial metastases (Figure 4). These masses caused narrowing of the surrounding cortical sulci and gyri, as well as compression of the right lateral ventricle. Perifocal edema was present, leading to subfalcine herniation towards the left. Post-contrast imaging showed homogeneous enhancement, supporting the diagnosis of intracranial metastases. Additionally, the sulci, gyri, and Sylvian fissure were compressed, along with the ventricles, while the cisterns remained unaffected. The lesions enhanced heterogeneously after contrast administration, further indicating the presence of metastatic involvement.

MRI of the brain with contrast, performed on November 12, 2024, confirmed the presence of multiple mixed-intensity lesions in the right frontoparietal and left parietal regions, with inhomogeneous enhancement and surrounding edema, supporting the diagnosis of metastatic brain lesions.

A craniotomy with tumor resection was performed on November 14, 2024. Intraoperatively, a yellowish-white, moderately vascularized tumor was identified in the frontoparietal region. The mass had well-defined borders, bled easily,



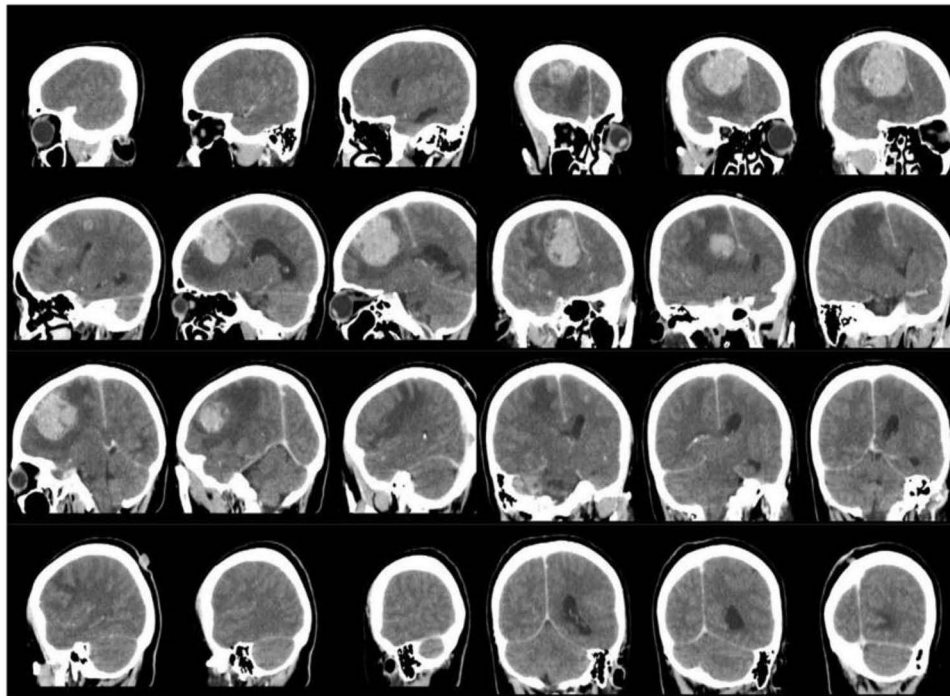
**Figure 2** Thoracic CT scan showed enlarged lymph nodes in the paraortic region, approximately 1.13 cm in diameter. Multiple nodules were randomly distributed throughout both lung lobes, ranging in size from approximately 0.19 to 1.06 cm, consistent with metastatic processes. Minimal fibrosis was noted in the medial segment of the right middle lobe, likely due to chronic inflammatory processes.  
**Abbreviations:** R, right; L, left; A, anterior; P, posterior.



**Figure 3** On physical examination, a 5 x 3cm mass was found in the occipital region.

and was fully excised. Histopathological examination of the resected 54.4 grams specimen revealed a tumor composed of densely packed round to spindle-shaped cells with pleomorphic, hyperchromatic nuclei and high mitotic activity. The stroma was infiltrated with lymphocytes, and areas of hemorrhage and extensive necrosis were noted. No keratin pearl formation was observed. The findings were consistent with metastatic non-keratinizing SCC of the frontoparietal lobe.

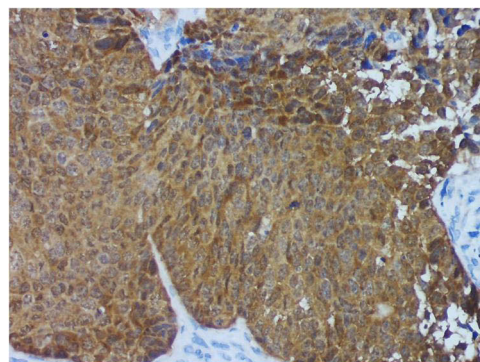
On December 11, 2024, the patient was referred back to the surgical oncology department for further management, including mass excision and external beam radio-therapy (EBRT). Immunohistochemical (IHC) analysis for p16 was initiated to assess possible HPV-related etiology and the p16 immunohistochemical analysis of the tumour mass yielded



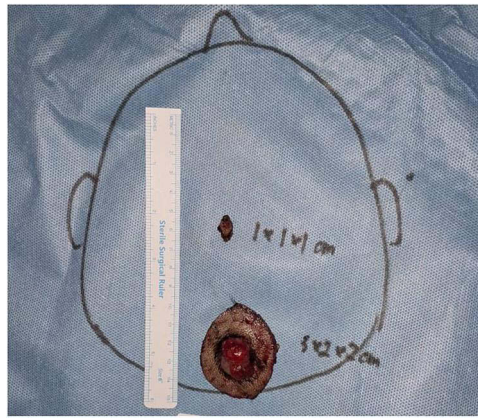
**Figure 4** The CT scan revealed multiple solid, inhomogeneous masses, without calcification, located in the right frontoparietal and left frontal lobes.

positive results (Figure 5). On December 13, 2024, a second surgical excision was performed, yielding a  $1 \times 1 \times 1$  cm parietal mass and a  $3 \times 2 \times 2$  cm occipital mass (Figure 6). Full-thickness skin grafting (FTSG) was used to cover the resulting defects. Histopathological examination confirmed metastatic non-keratinizing SCC in both parietal and occipital regions.

Following the procedure, EBRT was continued for the cranial tumor, and systemic chemotherapy was planned to address the pulmonary metastatic lesions. By the time of discharge, the patient's neurological status had improved significantly, though mild left-sided weakness persisted. She was diagnosed with FIGO stage IVB cervical cancer with confirmed brain and lung metastases. Despite extensive metastatic disease, she was referred for palliative care, with a focus on symptom management and maintaining quality of life. Prognosis remains poor given the aggressive nature of the disease and the extent of systemic involvement. The patient and her family were counseled extensively on her condition, treatment limitations, and the importance of palliative support.



**Figure 5** Immunohistochemical staining showing strong and diffuse nuclear and cytoplasmic p16 positivity in tumor cells (magnification  $\times 400$ ).



**Figure 6** Intraoperative findings revealed a 3×2 × 2 cm mass in the occipital scalp region and a 1 × 1×1 cm mass in the parietal scalp region.

## Discussion

Brain metastases from cervical cancer are rare, with an estimated clinical incidence ranging from 0.4% to 2.3%, while autopsy studies report a higher prevalence of 3–10%.<sup>5</sup> The rarity of brain involvement may be attributed to the hematogenous spread pattern, which more commonly affects the lungs, liver, and bones.<sup>12,13</sup> However, in aggressive histologic subtypes, such as poorly differentiated non-keratinizing SCC, early dissemination to the brain may occur, distinguishing it from secondary brain involvement from other malignancies like lung or breast cancer. The neoplastic cells from the vaginal tract spread through the haematogenous route via the inferior vena cava, pulmonary artery, pulmonary veins, left atrium, left ventricle, and aorta to the brain. An alternate route exists from the pelvic veins to the paravertebral venous plexus, subsequently entering the venous sinuses of the brain, and finally reaching the brain parenchyma.<sup>9</sup> The presence of LVSI and bilateral parametrial involvement further increases the risk of distant metastases by facilitating hematogenous and lymphatic spread.<sup>14,15</sup> The identification of these high-risk pathological features underscores the necessity for a more tailored surveillance approach, as traditional follow-up strategies may not adequately capture early metastatic spread. Given the potential impact of early intervention on clinical outcomes, further studies should explore predictive biomarkers that can identify patients at elevated risk for brain metastases.

Despite standard treatment with radical hysterectomy and adjuvant chemoradiotherapy, the patient developed early brain metastases, raising concerns about the adequacy of current systemic therapy in preventing distant spread. Routine brain imaging is not recommended in post-treatment surveillance due to the low incidence of brain metastases in cervical cancer. However, symptoms such as headache and nausea may be misinterpreted as treatment-related side effects, leading to delayed diagnosis.<sup>9,16</sup> Given the rapid onset of neurological symptoms in this case, earlier imaging might have facilitated timely intervention and improved clinical outcomes. This underscores the need for modified surveillance protocols, particularly in patients with high-risk pathological features.<sup>16,17</sup> In addition to early imaging, liquid biopsy and circulating tumor DNA (ctDNA) analysis may offer non-invasive tools for detecting early metastatic spread, which could transform monitoring strategies for high-risk patients.

Emerging therapies, including immune checkpoint inhibitors like pembrolizumab and anti-angiogenic agents such as bevacizumab, have shown efficacy in recurrent or metastatic cervical cancer, with the KEYNOTE-826 trial demonstrating improved overall survival when pembrolizumab is added to chemotherapy.<sup>18,19</sup> Fetcko et al noted the absence of a standardized treatment for brain metastases from cervical cancer but emphasized that a multimodal approach including SRS, WBRT, surgery, and chemotherapy provides the best outcomes, with treatment guided by performance status rather than age.<sup>20</sup> Ghergu et al supported individualized treatment, highlighting that craniotomy is preferred for larger symptomatic lesions, while SRS is more suitable for smaller or inaccessible tumors.<sup>21</sup> Further research is needed to determine whether such therapies can prevent or delay brain metastases in high-risk patients. While these agents have shown promise in systemic disease control, their penetration across the blood-brain barrier remains a critical challenge, necessitating investigations into novel drug delivery mechanisms or combination therapies that enhance central nervous

system penetration. Additionally, clinical trials assessing the role of prophylactic cranial irradiation in selected high-risk populations could provide further insights into preventive strategies for brain metastases.

The management of brain metastases requires a multimodal approach, incorporating surgery, radiation therapy, and corticosteroids to alleviate symptoms and improve neurological function. Surgical resection is considered for patients with limited brain metastases, especially those causing significant neurological deficits. Corticosteroids, such as dexamethasone, are used to reduce peritumoral edema and intracranial pressure, providing symptomatic relief.<sup>22,23</sup> Despite these interventions, prognosis remains poor, with a median survival of 3–4 months among treated patients.<sup>24</sup> Palliative care remains essential in managing symptoms and ensuring quality of life in patients with metastatic disease.<sup>25</sup> The integration of stereotactic radiosurgery (SRS) into treatment algorithms has demonstrated potential in improving local control while minimizing neurocognitive side effects associated with whole-brain radiotherapy. Given the limited survival benefit with existing treatments, novel approaches, including tumor-treating fields and targeted radionuclide therapy, warrant further exploration in the management of brain metastases from cervical cancer.

This case highlights the aggressive nature of poorly differentiated SCC of the cervix and the challenges in predicting distant metastases. Future research should focus on individualized surveillance strategies and the integration of novel systemic therapies to improve outcomes in high-risk patients. Additionally, collaborative efforts to establish multi-institutional registries for rare metastatic presentations could enhance understanding of disease patterns and refine management protocols.

## Conclusion

Poorly differentiated cervix SCC with early brain metastases is rare and aggressive, challenging conventional surveillance and therapy paradigms. Despite the undergoing radical hysterectomy and adjuvant chemoradiotherapy, the patient developed rapid neurological deterioration, emphasizing the limitations of standard systemic therapy in preventing hematogenous spread to the brain. Clinicians should be aware of neurological symptoms and keep the potential for metastasis from cervical cancer. The presence of high-risk pathological features, including lymphovascular space invasion and bilateral parametrial involvement, suggests a potential need for revised follow-up protocols in patients with aggressive histologic subtypes. Given the poor prognosis associated with brain metastases, earlier imaging and innovative systemic therapies with improved blood-brain barrier penetration may be necessary to enhance patient outcomes.

## Ethical Approval

Informed written consent was obtained from the patient for publication of this case report included publication of the images. Ethical approval was applicable from the Institutional Review Board (IRB) of Hasan Sadikin Hospital and institutional approval was required to publish the case details.

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## Disclosure

The authors report no conflicts of interest in this work.

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