# Synchronous multiple primary cancers involving cervical cancer and follicular lymphoma: A case report

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**Abstract.** Multiple primary cancers refers to the occurrence of two or more histologically distinct tumor types, either simultaneously or sequentially. The present report describes a rare case of a 46-year-old female patient simultaneously diagnosed with cervical cancer and low-grade follicular lymphoma (FL). The patient presented with vaginal bleeding and a subsequent cervical biopsy confirmed cervical squamous cell carcinoma. Imaging examinations indicated suspicious para-aortic lymph node metastasis, leading to a laparoscopic radical hysterectomy with lymph node dissection. Postoperative histopathological examination revealed cervical squamous cell carcinoma. However, para-aortic lymph node metastasis was not observed and instead, primary FL was detected. The current case underscores the importance of surgical intervention in cases where cervical cancer presents with isolated para-aortic lymph node enlargement, as it is essential for distinguishing between lymph node metastasis and the presence of a second primary tumor.

## Introduction

The incidence of multiple primary cancers (MPC) is rising in the general population (1) and accounts for 2-17% of all cancer cases (2,3). The pathogenesis of MPC is complex and multifactorial. The pathogenesis involves genetic susceptibility, environmental exposures, lifestyle factors, immune system abnormalities and treatment-related side effects (4). Due to the rarity and complexity of MPC, available data and literature are limited, leading to a lack of unified guidelines and consensus on its diagnosis and treatment. Accurate histopathological classification and staging of MPC are crucial, as they provide the foundation for individualized treatment strategies tailored to each tumor type (5). This approach helps address the challenges posed by MPC and improves treatment outcomes and quality of life of patients.

Cervical cancer is one of the most prevalent malignancies of the female reproductive system, and the incidence of synchronous double primary malignancies in patients with cervical cancer is relatively low (6). According to the literature, cervical cancer may coexist with various other cancer types, including endometrial, ovarian, breast, colorectal and lung cancer (6-8). However, the simultaneous occurrence of primary lymphoma in patients with cervical cancer is exceedingly rare. The present report aims to highlight a rare case involving a 46-year-old female patient diagnosed with dual primary malignancies: Cervical cancer and FL. The specific objective of this case report is to address the diagnostic challenges and clinical significance encountered when evaluating cervical cancer patients with isolated para-aortic lymph node enlargement. Through this case, we seek to emphasize the importance of surgical intervention, which is crucial for differentiating between lymph node metastasis and the presence of a second primary tumor, thereby impacting treatment decisions and patient outcomes.

## Case report

In September 2023, a 46-year-old female patient presented to Xiangyang First People's Hospital (Xiangyang, China), with a chief complaint of vaginal bleeding lasting 28 days. The female patient had previously experienced regular menstrual cycles but reported changes over the past 6 months, with cycles starting 7-15 days earlier than usual. However, there were no marked changes in the duration or volume of menstrual flow; thus, it did not raise any concern. Over the past month, the patient

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*Abbreviations:* MPC, multiple primary cancers; FL, follicular lymphoma; HPV, human papillomavirus; NCCN, National Comprehensive Cancer Network

*Key words:* MPC, cervical cancer, FL, isolated para-aortic lymph node enlargement

experienced continuous vaginal bleeding, which resembled menstrual flow. The gynecological examination, including a bimanual examination, revealed an enlarged cervix with erosive changes (3.0x2.0 $cm^2$) and active bleeding upon contact. The uterus was retroverted and irregularly shaped (7.0x6.0x6.0 $cm^3$), with no abnormalities in the surrounding area. A cervical biopsy and endocervical curettage were subsequently performed under colposcopic guidance. Cervical curettage samples were fixed in 4% formalin at room temperature for 12 h, embedded in paraffin at 60˚C for 15 min, sectioned to a thickness of 4 $\mu$m, stained with hematoxylin and eosin for 5 min at room temperature, and then observed under a light microscope, confirming the diagnosis of squamous cell carcinoma (Fig. S1). Laboratory tests showed that the tumor marker CA-125 was elevated at 112.5 IU/ml (normal range: 0-35 IU/ml), and the squamous cell carcinoma antigen (SCC) was 5.27 ng/ml (normal range: 0-1.5 ng/ml), both exceeding the normal range. Real-time fluorescence quantitative PCR for human papillomavirus (HPV) nucleic acid typing indicated a positive result for the high-risk subtype HPV 16. Pelvic enhanced magnetic resonance imaging revealed a slightly hyperintense lesion in the cervix, which was ~2.1x2.4x2.3 $cm^3$ in size, with poorly defined boundaries (Fig. 1A and B). The lesion involved the anterior and posterior fornices but exhibited no infiltration into the parametrium, raising a high suspicion of cervical cancer. Whole-body positron emission tomography-computed tomography (PET-CT) revealed an occupying lesion in the cervical region (Fig. 1C) and a soft tissue density lesion between the infrarenal abdominal aorta and the inferior vena cava, with increased abnormal metabolism, which suggested a malignant cervical tumor with metastatic lymph nodes (Fig. 1D).

Given the relatively localized nature of the primary cervical lesion and the isolated retroperitoneal lymph node metastasis indicated by PET-CT, thorough discussions with the patient and her family were performed regarding treatment options. Two primary approaches were considered: First, surgery could be performed to determine tumor staging through postoperative pathology, though this option involves significant risks, including bleeding. Should the retroperitoneal lymph nodes be confirmed to be metastatic post-surgery, concurrent radiotherapy and chemotherapy would follow. Alternatively, if surgery was not pursued, concurrent radiotherapy and chemotherapy were advised for the patient's condition. After careful consideration, the patient strongly favored surgical intervention, culminating in a laparoscopic total hysterectomy, high-level ligation of the ovarian vessels, bilateral salpingo-oophorectomy, pelvic lymphadenectomy and para-aortic lymph node excision. Cervical and lymphoid tissues were subjected to H&E staining and immunohistochemical staining, observed using an Olympus BX53 optical microscope. The H&E staining method followed the protocol for cervical smear samples detailed above. For immunohistochemical staining, tumor tissues were embedded in paraffin and sectioned into 4-$\mu$m slices. These sections underwent deparaffinization and rehydration. Heat-induced antigen retrieval was performed using 10 mM citrate buffer (pH 6.0). Endogenous peroxidase activity was blocked by incubating with 3% $H_2O_2$ for 10 min. Sections were permeabilized with 0.1% Triton X-100. To prevent non-specific binding, sections were incubated for 25 min at room temperature in PBS-T (QuickBlock™ Blocking Buffer; Beyotime Institute of Biotechnology) containing 10% goat serum. The following primary antibodies were then applied and incubated overnight at 4˚C: For cervical tissue, cytokeratin 5/6 (CK5/6; cat. no. PA6040; dilution, 1:100), P40 (cat. no. PA7069; dilution, 1:200), P16 (cat. no. PA6909; dilution, 1:50); for lymphoid tissue, CD20 (cat. no. PA6149; dilution, 1:200), paired box 5 (PAX-5; cat. no. PA6688; dilution, 1:50), CD10 (cat. no. PA6911; dilution, 1:100) and Bcl-2 (cat. no. PA7109; dilution, 1:200). Bcl-6 (cat. no. ab272859; dilution, 1:100) was supplied by Abcam. After washing, HRP-conjugated secondary antibodies were added at a dilution of 1:50 (cat. no. A0216; Beyotime Institute of Biotechnology) and incubated for 20 min at room temperature. DAB (DAB Horseradish Peroxidase Color Development Kit; cat. no. P0203; Beyotime Institute of Biotechnology) was then applied for color development in the dark for 30 sec to 5 min. The staining reaction was monitored under a microscope and terminated with distilled water. Finally, sections were counterstained with hematoxylin for 30 sec at room temperature. Images were acquired using an optical microscope. Immunostained sections were imaged with a Leica DM4000B fluorescence microscope (Leica Microsystems GmbH).

Based on the experimental methods described above, postoperative pathological examination utilizing H&E staining revealed prominent nuclear enlargement and irregular cellular morphology, along with an elevated nuclear-to-cytoplasmic ratio, as well as varying degrees of destruction in glandular and squamous epithelial structures (9). Additionally, immunohistochemical analysis demonstrated positive expression of CK5/6, P40 and P16, confirming a diagnosis of invasive squamous cell carcinoma (Fig. 2A-D). Postoperative immunohistochemical analysis showed that the tumor had infiltrated more than two-thirds of the cervical fibromuscular layer, with tumor emboli present in blood vessels but no evidence of neural invasion. The stromal tissue was involved. No cancer infiltration was observed in the bilateral parametrium, adnexa or vaginal margins, and there was no lymph node metastasis in the pelvic or para-aortic lymph nodes. Notably, the retroperitoneal lymph nodes exhibited lymphoid follicle hyperplasia, with some follicles irregularly fused and losing polarity under microscopic examination (Fig. 3A). Immunohistochemical analysis demonstrated positivity for CD20, PAX-5, CD10, Bcl-6 and Bcl-2 (Fig. 3B-F), with a Ki-67 index of 20%. Based on the morphological and histopathological findings (10), a final diagnosis of para-aortic FL, grade 1-2, was made. The FL International Prognostic Index-2 scoring system for prognostic evaluation was utilized (11,12), which includes the following factors: Age, whether the hemoglobin level is <120 g/l, the normality of β2-microglobulin, the presence of bone marrow involvement and whether the largest lymph node diameter exceeds 6 cm. According to these scoring criteria, the hemoglobin level was 93 g/l, which is below 120 g/l, resulting in a score of 1. The final prognosis was classified as intermediate risk. During clinical assessment, genetic testing and fluorescence *in situ* hybridization analysis were recommended. However, due to financial considerations, the patient opted not to proceed with these additional tests. The final diagnosis was therefore double primary tumors: i) Cervical squamous cell carcinoma, stage IB2 (according to the 2018 FIGO staging) (13); and ii) FL, grade 1-2, stage I.

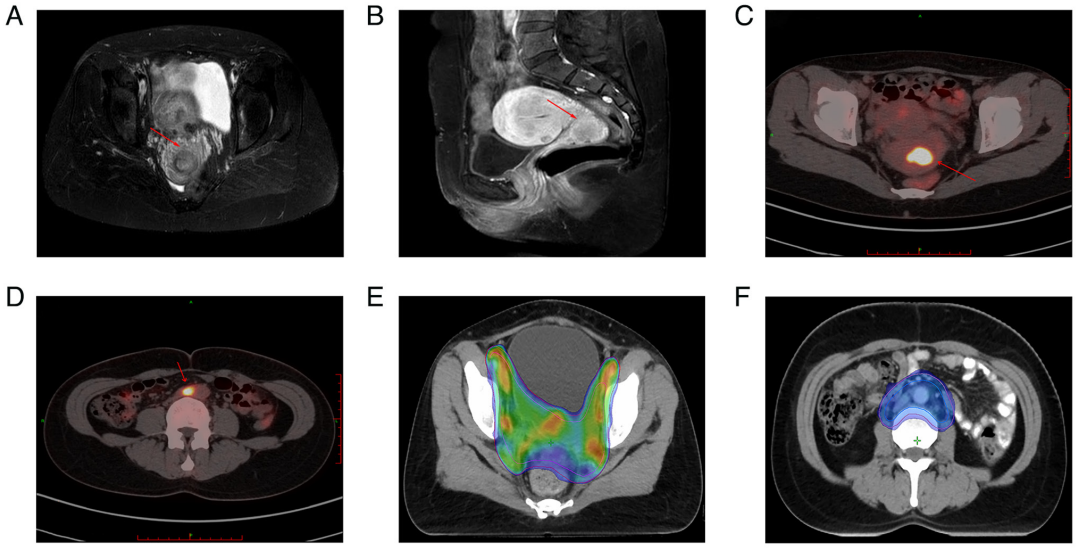


Figure 1. Radiological examination findings. Magnetic resonance imaging findings of the cervical mass: (A) Coronal view and (B) sagittal view. Positron emission tomography-computed tomography revealed abnormal metabolic activity in the (C) cervix and (D) para-aortic lymph nodes. Images illustrating (E) the range of the radiation therapy target area for the retroperitoneal lymph node drainage area and (F) the planning target volume for the residual vaginal stump and lymph node drainage area. Please note the following clarification: In panels A, B and C, the arrows indicate the location of the cervical mass, while in panel D, the arrows point to the para-aortic lymph nodes.

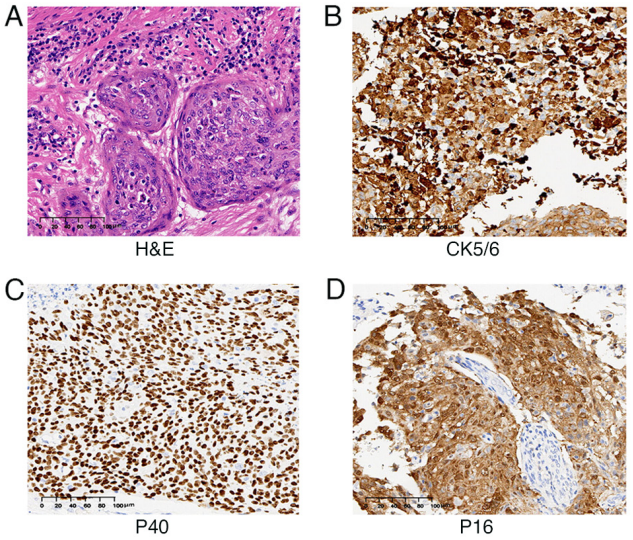


Figure 2. Histopathological findings of the cervical mass. (A) H&E staining revealed squamous cell carcinoma in the cervix. Immunohistochemical examination indicated malignant cells immunoreactive for (B) CK5/6, (C) P40 and (D) P16 (scale bar, 100 $\mu$m). CK5/6, cytokeratin 5/6 antibodies; P40, subunit β of interleukin 12; P16, cyclin-dependent kinase inhibitor 2A.

According to the National Comprehensive Cancer Network (NCCN) B-cell Lymphoma Guidelines (2023.6 Edition) (14), for patients with stage I and grade1-2FL, adjuvant radiotherapy can be administered following surgical treatment to enhance local control rates and reduce the risk of recurrence. The patient received adjuvant radiotherapy 1 month after surgery. Intensity-modulated radiation therapy was delivered to the retroperitoneal lymph node drainage area, with a planned total dose of 30.6 Gy administered in 17 fractions, each delivering a dose of 1.8 Gy. Radiation treatment was conducted from Monday to Friday, with weekends off, targeting planning volume 1 (Fig. 1E). According to the NCCN Cervical Cancer Guidelines (2020 Version 1) (15), if a patient has undergone radical surgical resection and the pathological results indicate the presence of vascular cancer emboli and risk factors such as an invasive depth greater than 2/3 of the fibromuscular layer, pelvic external beam radiation therapy may be considered. For the residual vaginal and lymph node drainage areas, the prescribed dose was 46.8 Gy delivered in 28 fractions to the planning target volume 2 (Fig. 1F). Following the respective disease-specific guidelines, no additional treatment is required at this stage, with the focus primarily on regular follow-up. As of January 2025, the patient returns to the hospital every 3 months for abdominal MRIs, chest CT scans and tumor marker tests, during which no tumor progression has been observed, and the patient is recovering well.

## Discussion

MPC refers to the simultaneous or sequential occurrence of two or more distinct types of cancers in the same individual. The concept of MPC was first described in 1921 (16). Warren and Gates (17) established three criteria for diagnosing MPC: Each tumor must have distinct histological characteristics, each tumor must exhibit well-defined malignant features and the possibility that one tumor is a metastatic lesion from another must be excluded. The simultaneous occurrence of cervical squamous cell carcinoma and FL as MPC is extremely rare. To the best of our knowledge, the present report was the first to describe a case of MPC involving both cervical squamous cell carcinoma and low-grade FL.

The pathogenesis of MPC is not fully understood; however, it is considered to involve complex, multifactorial processes, including genetic predisposition, immune deficiencies, immune evasion by cancer cells, accumulation of gene mutations and abnormal gene expression, as well as exposure to radiation therapy, chemotherapy and certain medications (18,19). Cervical cancer, a common tumor type

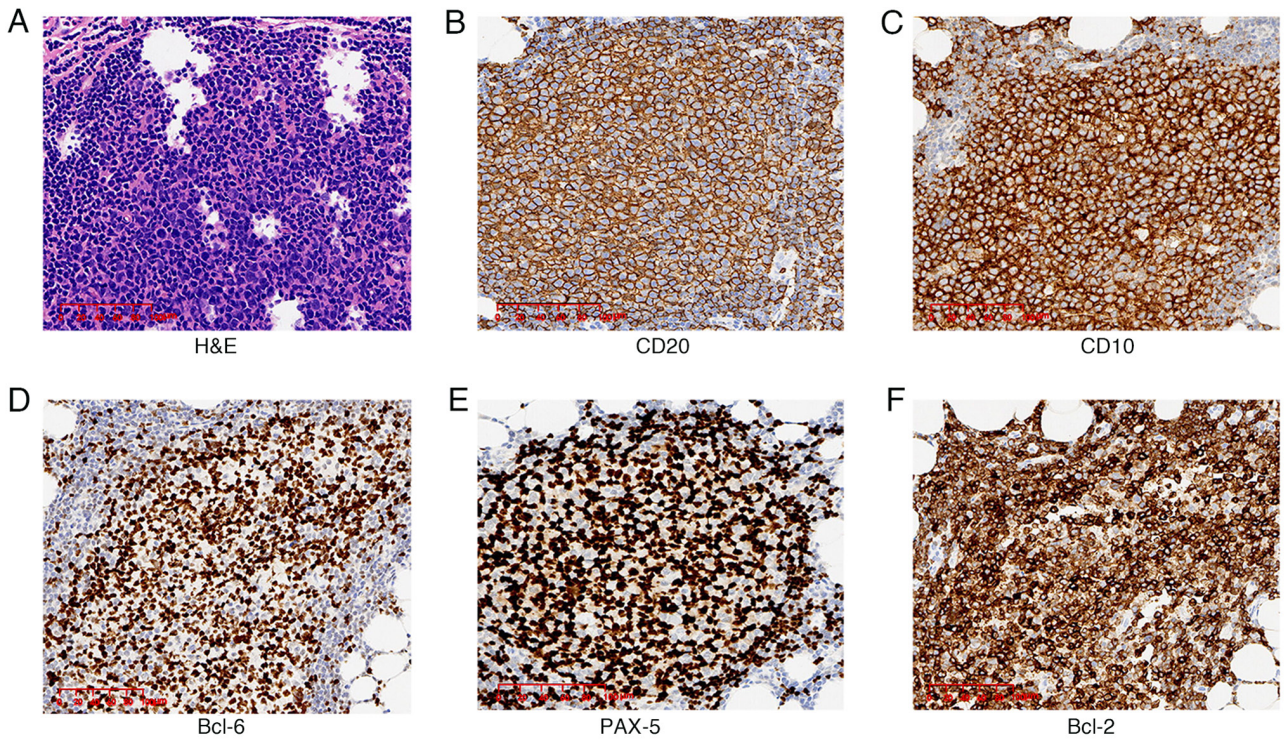


Figure 3. Pathological features of Hodgkin lymphoma components. (A) H&E staining revealed the presence of heterogeneous follicles within the lymph node, accompanied by a prominent perifollicular zone rich in lymphocytes, forming well-defined germinal centers. Tumor cells exhibited positive immunohistochemistry staining for (B) CD20, (C) CD10, (D) Bcl-6, (E) PAX-5 and (F) Bcl-2 (scale bar, 100 $\mu$m). PAX-5, paired box 5.

in MPC, has been extensively studied to investigate its underlying mechanisms (20,21). The coexistence of endometrial and cervical cancers is not uncommon, possibly due to their occurrence in adjacent sites within the reproductive system (6,22). The simultaneous presence of cervical cancer and breast or ovarian cancer may involve shared driver gene mutations, such as those in BRCA1 and BRCA2 (23,24). The coexistence of colorectal and cervical cancers may be attributed to shared embryonic origins and underlying genetic factors (25). HPV infection can induce cell proliferation and mutation, and can potentially promote cancer development through mechanisms such as interference with cell cycle control, inhibition of apoptosis and activation of proliferation signaling pathways (26). HPV types 16 and 18 are particularly known for their oncogenic potential, leading to the transformation of cervical epithelial cells and the subsequent development of cervical intraepithelial neoplasia and invasive cervical cancer (27). It is estimated that >99% of cervical cancers are associated with HPV infection (28). Lymphoma occurrence is also closely related to viral infections, with Epstein-Barr virus infection being common in Hodgkin lymphoma, natural killer/T-cell lymphoma and diffuse large B-cell lymphoma (29). Previous literature has suggested a possible association between HPV infection and certain types of lymphoma, notably detecting HPV DNA positivity in cases of Hodgkin lymphoma and some diffuse large B-cell lymphomas (30,31). Animal studies have demonstrated that immune system alterations resulting from HPV infection may affect lymphocyte function, thereby increasing susceptibility to lymphoma development, particularly in immunocompromised individuals such as those with HIV/acquired immunodeficiency syndrome (32,33). This suggests that HPV may serve a role in the pathogenesis of lymphoma. The female patient in the present case study also had an HPV infection, specifically a high-risk subtype. While the potential relationship between HPV and lymphoma has not been fully elucidated, the role of HPV infection in the development of cervical cancer and FL warrants further investigation.

In the absence of a definitive diagnosis of MPC, the primary challenge in managing the patient was deciding whether to perform surgery first or to proceed with concurrent chemoradiotherapy. According to the revised International Federation of Gynaecology and Obstetrics 2018 staging criteria for cervical cancer, the presence of lymph node metastasis in the para-aortic region is a crucial factor for treatment decision-making and prognosis in patients with cervical cancer (34). According to the NCCN Cervical Cancer Guidelines (2020 Version 1) (15), if the para-aortic lymph nodes were deemed metastatic, the patient would be classified as having stage III C2 invasive cervical squamous cell carcinoma, thus necessitating concurrent chemoradiotherapy as the primary treatment modality. Conversely, in the absence of para-aortic lymph node metastasis, the patient would be diagnosed with stage IB2 disease, making surgical resection the main therapeutic approach. Clinicians face challenges in determining whether para-aortic lymph node enlargement is due to metastasis or represents a primary lesion.

Kostov *et al* (35) introduced a three-tier lymph node staging system for cervical cancer: Tier one includes the para-uterine, obturator, internal iliac and external iliac lymph nodes; tier two encompasses the common iliac and presacral lymph nodes; and tier three consists of the para-aortic lymph nodes. Most tumor lymph node metastases typically progress

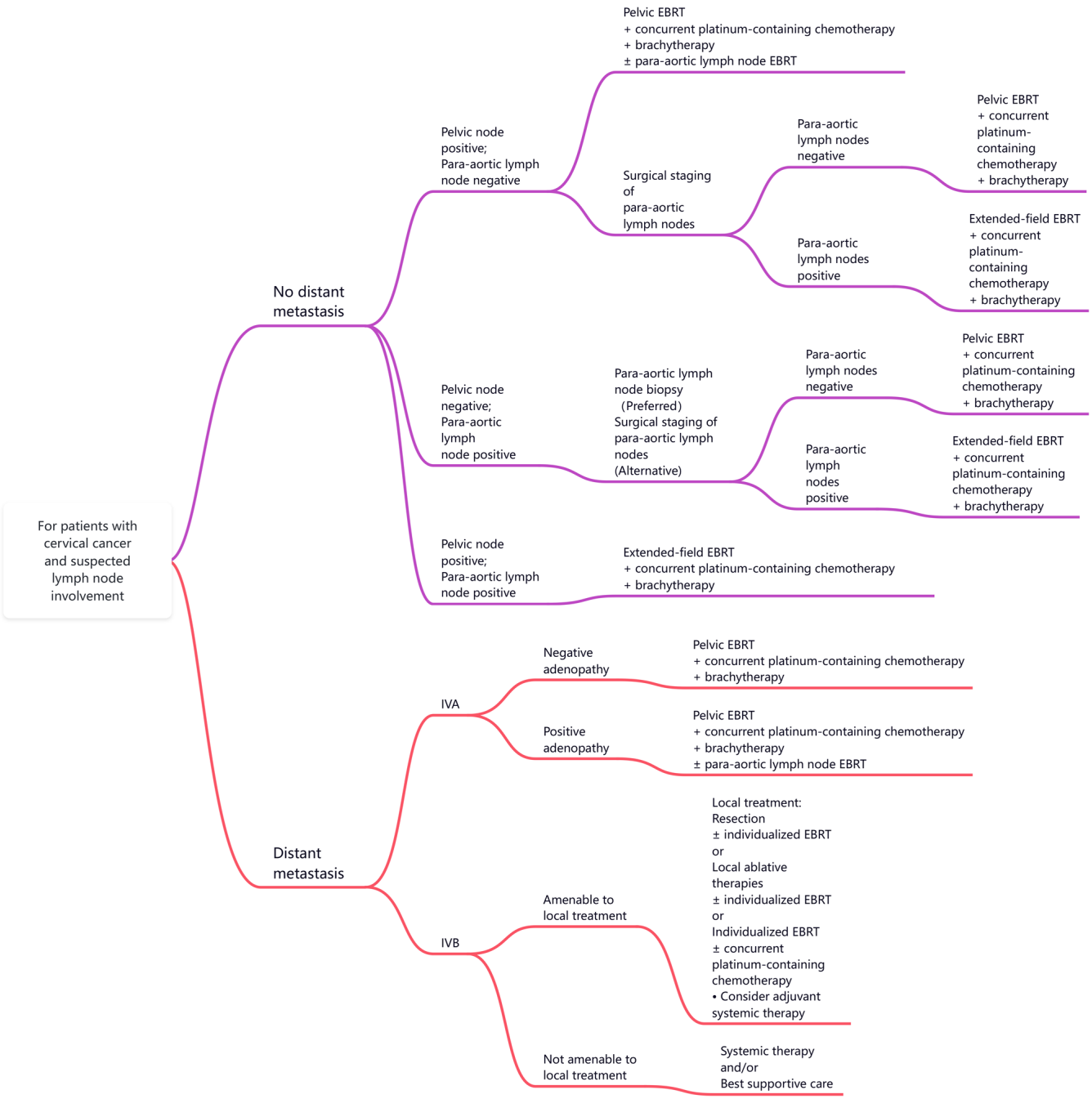


Figure 4. Flowchart for the diagnosis and management of cervical cancer with suspected lymph node metastasis. EBRT, external beam radiation therapy.

sequentially from tier one to tier two, and then to tier three. Depending on the tumor type, approximately 5 to 10% of cases may exhibit cross-tier metastasis (36,37). This pattern suggests that patients with para-aortic lymph node metastasis often have concurrent involvement of pelvic lymph nodes (38,39). However, in the present case, the PET-CT indicated only possible para-aortic lymph node metastasis, with no evidence of metastasis in the pelvic lymph nodes. This represents a rare occurrence of lymph nodes crossing tiers based solely on imaging diagnosis. Several studies have reported the relatively low sensitivity and negative predictive value of PET-CT in diagnosing para-aortic lymph node metastasis, highlighting the potential for false-positive or false-negative results (40,41).

Given the inherent limitations of imaging examinations, such as the possibility of false negatives or positives, there is a risk of administering either inadequate or excessive treatment to patients. Therefore, in the context of precision medicine, surgical staging offers a favorable approach by providing accurate lymph node pathology results. Considering the lack of reproductive needs of the patient and the localization of the cervical lesion confirmed by imaging, laparoscopic total hysterectomy and para-aortic lymph node excision were performed. Postoperative pathology confirmed the diagnosis of MPC. Both tumors were in the early stages, which makes surgery the most critical treatment method. However, upon further consideration, if the authors had proceeded with concurrent chemoradiotherapy based on a diagnosis of

stage IIIC cervical cancer, the patient would not only have been misdiagnosed but also potentially overtreated and the opportunity for surgery would be missed. Therefore, when patients with cervical cancer present with a skip pattern or unusual lymph node enlargement suspected of metastasis, surgery or biopsy is essential. According to the recommendations of the NCCN cervical cancer guidelines and the authors' experience (15), a diagnostic and management flowchart for patients with suspected lymph node metastasis in cervical cancer was developed (Fig. 4).

Another controversial issue is whether adjuvant radiotherapy is necessary after surgery. According to the NCCN guidelines for cervical cancer, surgery is the preferred treatment option for patients with stages up to IIB, while concurrent chemoradiotherapy is recommended for those beyond stage IIB (42). In the present case, the patient had stage IB2 cervical squamous cell carcinoma. Although the para-aortic lymph nodes were negative, the tumor had invaded more than two-thirds of the cervical fibromuscular layer and blood vessels. According to the criteria of Sedlis *et al* (43), the patient exhibited intermediate-risk factors. Therefore, postoperative radiotherapy to the cervical stump and pelvic lymphatic drainage areas was administered to reduce the risk of relapse (44). For early-stage FL, even when the primary lesion is resected, our preference would be to administer field radiation therapy (14).

It is worth considering whether cervical cancer and FL occurred simultaneously or sequentially in the present case. Previous studies suggest that in patients with MPC, FL often appears subsequently and frequently follows cancer treatment, especially after chemotherapy or radiotherapy (45,46). For example, FL has been documented in patients who received immunotherapy for lung cancer and in individuals with a history of breast cancer who underwent radiation therapy (47,48). To date, research specifically addressing secondary lymphomas arising from cervical cancer is lacking. This further emphasizes the importance of early cancer screening, raising our concern.

Managing MPC requires the collaborative efforts of a multidisciplinary team, including surgeons, oncologists, radiologists and pathologists (49). Effective cancer treatment must consider key factors such as tumor stage, anatomical location and the physical condition of the patient. In the present case, despite the initial stage III diagnosis based on imaging, surgical intervention was carefully performed, which ultimately confirmed the presence of low-grade FL adjacent to the abdominal aorta. The present case underscores the importance of lymph node biopsy for suspected abdominal aortic lymph node metastasis and emphasizes that MPC treatment should be individualized.

A study revealed that the prognosis of patients with MPC is generally poorer compared with that of patients with a solitary primary tumor (50). The prognosis of these patients is influenced by various factors, including tumor stage, biological characteristics, treatment response and overall physical condition (51). Given the limited data and the rarity of cases involving concurrent cervical cancer and FL, evaluating the prognosis of these patients presents challenges. Therefore, there is an urgent need to gather more similar cases, establish standardized treatment protocols and conduct comprehensive prognostic assessments.

A limitation of the present study is the absence of genetic testing of the patient due to financial constraints. Research indicates that MPC may share common driver genes, such as KRAS or BRCA mutations identified in concurrent cases of breast and ovarian cancer, suggesting a shared pathway in oncogenesis (52,53). This underscores the imperative role of genetic testing in elucidating the underlying mechanisms of these malignancies and providing critical insights into potential diagnostic markers and therapeutic targets. This limitation may affect the comprehensiveness of the present findings and the potential for personalized treatment strategies. Future studies should prioritize genetic testing to deepen the understanding of the relationship between synchronous tumors and improve patient management.

In conclusion, this report presents a unique case of concurrent cervical cancer and low-grade FL. This case provides new clinical insights and serves as a reference in the literature on MPC. The mechanisms underlying the simultaneous occurrence of these two conditions remain unclear, which highlights the need for further research to understand their etiology and develop effective therapeutic strategies.

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**Availability of data and materials**

The data generated in the present study may be requested from the corresponding author.

**Authors' contributions**

DZ and YD conceptualized the present study. SL, HL, YD and HY curated the data, acquired and managed the patients and provided the radiology images. DZ, HY and SL contributed to the study design and analyzed and interpreted the data. SL and HY confirm the authenticity of all the raw data. All authors helped to write the manuscript. All authors read and approved the final manuscript.

**Ethics approval and consent to participate**

The present study was approved (approval no. XYYY20240074) by the Ethics and Scientific Committee of Hubei University of Medicine (Xiangyang, China). Written informed consent was obtained from the individual for participation in the study, including the publication of any potentially identifiable images or data included in this article.

## Patient consent for publication

Written informed consent was obtained from the patient for the publication of any potentially identifiable images or data included in the present study.

## Competing interests

The authors declare that they have no competing interests.

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