









Metastatic Cervix Uterine Cancer and Therapeutics Updates: A Case Report and Literature Review

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Abstract

Metastatic cervical cancer presents new measures related to the association of biological therapies with conventional treatment that varies according to the presence of biomarkers. Based on a case report, we reviewed therapeutic modalities and updates on the use of concomitant immunobiological and oncological treatments to combat invasive cervical cancer. The use of pembrolizumab is a new option in patients with positive PD-L1 associated with metastatic cervical cancer, having demonstrated a favorable toxicity profile and improved survival. In this case report, we describe a 52-year-old woman diagnosed with metastatic cervical cancer who underwent to chemotherapy (CT) with paclitaxel and carboplatin, as well as immunotherapy with pembrolizumab for PD-L1 positive cervical neoplasm and metastasectomy of hepatic lesions. The patient remains under outpatient care with no signs of active disease.

Keywords

- ▶ uterine cervical neoplasms
- ▶ neoplasm metastasis
- ▶ immunotherapy
- ▶ neoplasm staging
- ▶ metastasectomy

Introduction

Cancer of the uterine cervix is the third most common gynecologic cancer diagnosis and cause of death among them. Human papillomavirus (HPV) is pivotal in the development of cervical neoplasm and is found in 99.7% of cervical cancers. The most prevalent types are squamous cell carcinoma (70%) and adenocarcinoma (25%).¹ A number of serum markers have been investigated for their utility in assessing prognosis, monitoring response to therapy, and detecting recurrence. The most common are squamous cell carcinoma (SCC) antigen, tissue polypeptide antigen, carcinoembryonic antigen (CEA), cancer antigen 125 (CA 125), and CYFRA 21-1.²

Cervical cancer spreads by direct, hematogenous, or lymphatic dissemination. The locations most affected by direct metastasis are the uterine body, parametrium, vagina, peritoneal cavity, or rectum. Rarely, there will be metastasis to

the ovaries. Hematogenous dissemination mainly affects the lungs and, secondarily, the liver and bones.³

The presentation of hematogenous metastatic disease is a poorer prognostic indicator and is associated with higher mortality rates compared to lymphatic dissemination.⁴ The management of cervical malignancy is directly related to the stage of the disease, the patient's clinical condition and factors associated to the tumor.⁵

Still, the tumor mutational burden (TBM) studies have found that it is a potential prognostic factor for worse survival in patients with cervical cancer treated with definitive radiotherapy, thereby providing a rationale for treatment of TBM-high cervical cancers with a combination of immune checkpoint inhibitors (ICIs) plus radiotherapy.⁶

Curative options for advanced stage disease are limited. Systemic therapy is the first line of treatment for cervical cancer with the indication of platinum-based chemotherapy associated with paclitaxel and bevacizumab. For patients

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with a positive PD-L1 biomarker, there is also the option of platinum-based chemotherapy combined with oncology immunotherapy with pembrolizumab, with or without bevacizumab, as it has a longer progression-free survival and overall survival.⁷

This paper aims to report a case of liver metastasis due to cervical cancer and clarify therapeutic updates regarding the combination of chemotherapy, immunotherapy, and associated surgery. Based on the KEYNOTE-826 trial, the use of pembrolizumab combined with chemotherapy, with or without bevacizumab, for patients with persistent, recurrent, or metastatic PD-L1 cervical cancer, was approved by the food and drug administration (FDA) and the Brazilian health regulatory agency (ANVISA).⁸ This case report was submitted to and approved by the Ethics Committee of the Universidade de Passo Fundo under submission number 6.911.615.

Case Report

A female patient, 52-years-old, with a history of radical hysterectomy for a high-grade squamous intraepithelial lesion in the cervix 10 years ago due to local recurrence of previous conizations. After 3-years of the procedure, the patient developed dyspareunia, with vaginal bleeding and lesion located in the vagina wall. A biopsy was performed, which revealed squamous cell carcinoma *in situ*, which was followed by brachytherapy.

After 5 years, the patient evolved with edema in the lower limbs and signs of unilateral ureteral obstruction, identifying retroperitoneal lymph node enlargement over the iliac vessels and ureter. The patient underwent double J-stent placement and chemotherapy (CT) with paclitaxel, carboplatin, and associated immunotherapy with pembrolizumab for PD-L1 positive cervical neoplasm. At 1-year after the emergence of the symptoms described, during oncological follow-up, despite being asymptomatic, the patient developed changes in tomography (→**Fig. 1**) and positron emission tomography computed tomography (PET-CT) (→**Fig. 2**), which evidenced the presence of liver lesions and increased uptake of liver lesions and also in portocaval lymph nodes, compatible with metastasis.

The largest lesion was located between segments VI and VII, measuring 7.8 cm, and another lesion was also identified in segment VII, measuring 4.7 cm. Right hepatectomy (→**Fig. 3**) was performed followed by retroperitoneal lymphadenectomy. In pathology, the presence of metastasis from squamous cell carcinoma, due to cervical cancer, was identified in the liver, paracaval, and common bile duct lymph node samples. The patient remains in outpatient care with no signs of active disease.

Discussion

Although rare at initial diagnosis, metastatic disease will develop in 15 to 61% of women with cervical cancer. In most cases, metastatic cervical cancer is not curable. However, for some patients who present with recurrent disease in the pelvis or with limited distant metastatic disease, surgical treatment is curative. Considering the probability of developing metastasis,

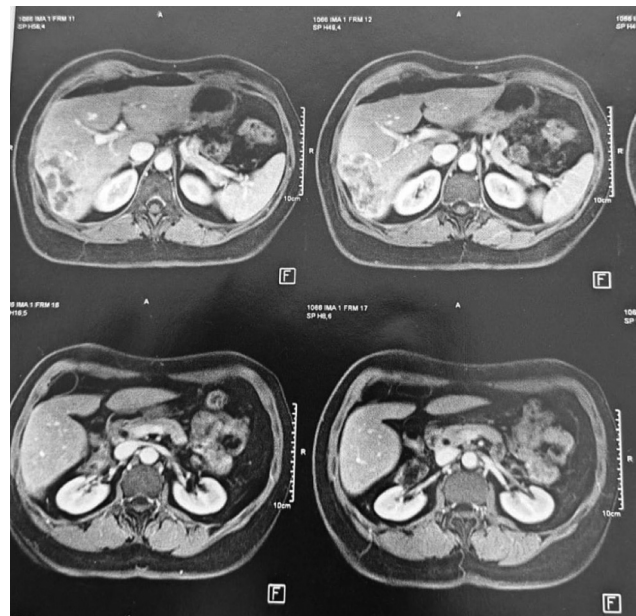


Fig. 1 The computed tomography scan with the presence of liver lesions in segments VI and VII.

it is shown that liver metastasis is one of the most common types of cervical cancer, occurring in around 33% of cases.⁹

Patients with metastatic cervical cancer usually have no symptoms or nonspecific complaints, such as fatigue, nausea, or weight loss. However, they may present symptoms related to the site of metastasis. For diagnosis, the PET scan is suggested to evaluate local and distant disease. Those who present with isolated metastatic findings on imaging studies should undergo a biopsy to prove metastatic disease.^{10,11}

For women with recurrent, metastatic, or advanced cervical cancer, treatment consisting of a combination of cisplatin, an angiogenesis inhibitor bevacizumab and an immune checkpoint inhibitor is recommended. In the first-line setting, a combination of cisplatin and paclitaxel is suggested. Due to the toxicity seen with combination chemotherapy, carboplatin is a reasonable alternative to cisplatin. Chemotherapy combined with bevacizumab has been shown to provide a significant improvement in overall survival compared to chemotherapy alone.¹²

For patients with metastatic or recurrent cervical cancer who are not amenable to localized curative therapies, the addition of atezolizumab or pembrolizumab is recommended. For women who have progressed after first-line treatment and for patients who are not candidates for combination chemotherapy, single-agent therapy is indicated. The single most active agents are carboplatin, paclitaxel, topotecan, and tisotumab.¹³

In spite of atezolizumab plus bevacizumab and chemotherapy for metastatic, persistent, or recurrent cervical cancer resulting in an increase in progression-free survival and overall survival, according to the BEATcc trial, it has not yet been approved by regulatory agencies.¹⁴

Patients in FIGO 2014 stage III-IVA of cervical cancer, who have not undergone curative surgery, radiation, or chemotherapy, were evaluated in the KEYNOTE-A18 study

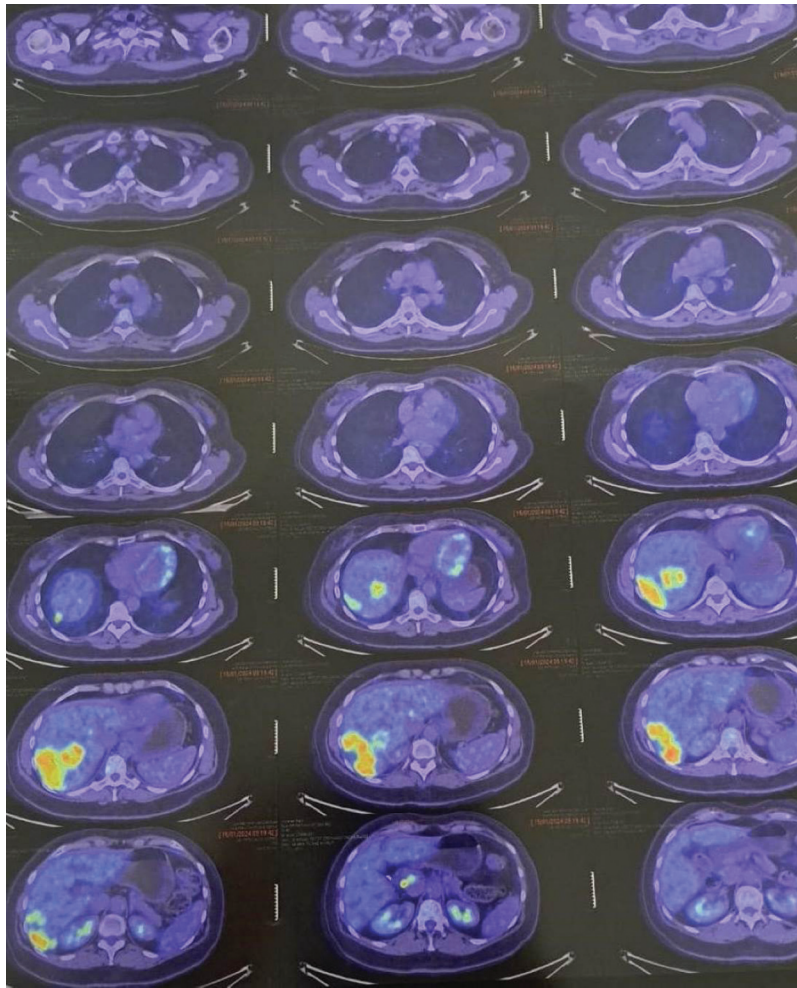


Fig. 2 The positron emission tomography-computed tomography scan with the presence of hyperuptake of liver lesions in segments VI and VII.

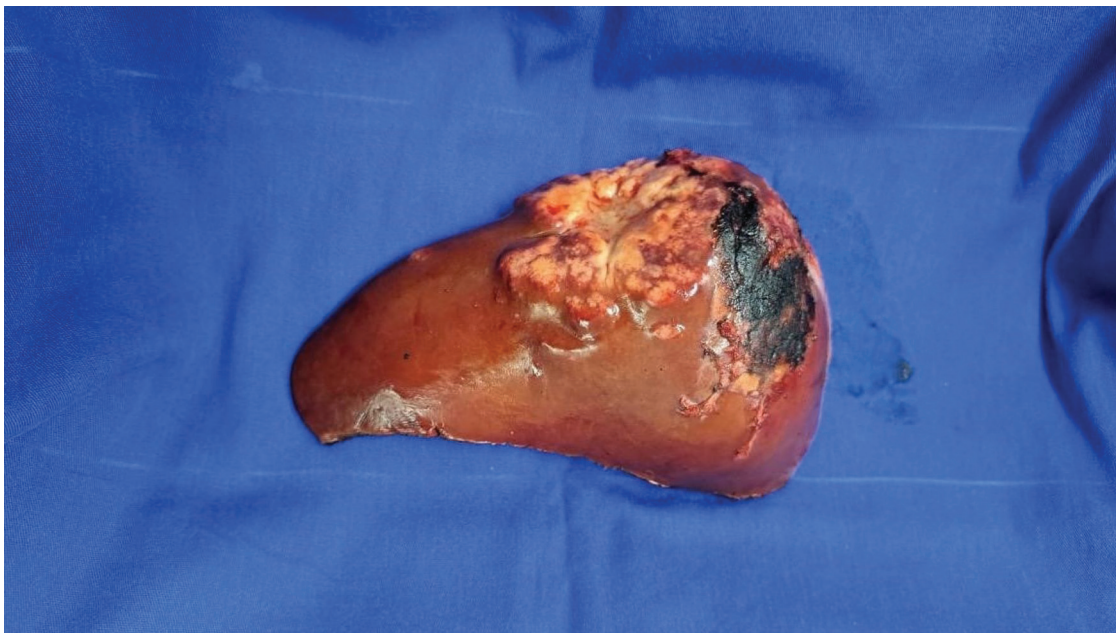


Fig. 3 Metastatic hepatic lesions due to malignant neoplasm of the uterine cervix. Liver sample resulting from right hepatectomy for metastatic lesions originating from malignant neoplasm of the uterine cervix.

regarding the combination of therapies containing cisplatin with pembrolizumab. The multicenter, randomized, double-blind, placebo-controlled trial with 596 patients showed improved outcomes when radiochemotherapy was combined with immunotherapy. For patients with PD-L1 positive status, pembrolizumab is the biological agent of choice, whereas atezolizumab, bevacizumab and chemotherapy with cisplatin can be used regardless of PD-L1 status.^{15,16} And more recently, tisotumab was incorporated, which is a tissue factor-directed antibody and microtubule inhibitor drug conjugate, an option for second- or third-line therapy.¹⁷

It is important to highlight that the liver is one of the most affected organs by metastasis, and the efficacy of resecting hepatic metastasis from colorectal origin has been established. However, there is limited data on the treatment of noncolorectal metastasis, such as the case described with a primary lesion originating in the cervix. In the past, the presence of hepatic metastasis was considered a criterion of incurability for gynecological neoplasms. Nevertheless, recent studies suggest that hepatectomy combined with lymphadenectomy for metastasis from noncolorectal primary tumors improves prognosis, especially in cases of primary tumors from the urogenital tract and gynecological origins. Therefore, surgical treatment has been implemented for hepatic metastasis from noncolorectal tumors, provided there is control of the primary lesion, as described in this case. Finally, metastasectomy, when applied to selected cases, along with treatment of the primary tumor, prolongs disease-free survival, as observed in the described case.^{18,19}

Regarding surgical approaches for treating hepatic metastasis, some studies provide relevant data. In a comparative study between hepatectomies performed for metastasis of colorectal and non-colorectal non-neuroendocrine origin, the authors found similarities in surgical specifics such as type of hepatectomy and surgical duration, as well as in survival rates, with a 50% survival rate at 3 years and 20% at 5 years.²⁰

Additionally, Costa et al.²⁰ demonstrated that patients with colorectal origin metastasis had more hepatic recurrences, whereas those without colorectal or neuroendocrine origins had higher rates of multiple and systemic recurrences in comparison. The authors also emphasize the relevance of hepatectomies as surgical treatment for metastatic cases, representing a technique that ensures a good degree of success and significant survival when compared to chemotherapy alone. Multivariate analysis by the authors also identified two important prognostic factors for patients with hepatic metastasis: lymph node involvement and number of lesions.

In another case report, Pais-Costa and Lupinacci¹⁸ demonstrated hepatectomy performed on a 45-year-old patient with metastatic cervical carcinoma, previously treated for the primary cancer with extended radical hysterectomy with lymphadenectomy. Similar to the present report, the patient presented with hepatic metastasis in segments VI and VII, undergoing right hepatectomy, with histopathological analysis confirming squamous cell carcinoma. The authors highlight the potential for improved prognosis with hepatectomies performed in cases of hepatic metastasis with gynecological origin in patients without other comorbidities. The authors

also note the rarity of hepatic metastasis from cervical carcinoma, citing a study from 1998 which reported this condition in only 1.2% of cervical cancer patients over a 6-year period.¹⁸

Furthermore, a retrospective analysis by Bacalbasa et al.²¹ followed 15 patients who underwent hepatectomy due to hepatic metastasis from cervical carcinoma, with the majority diagnosed with metachronous liver lesions. After their analysis, the authors considered factors associated with better prognosis for those with metachronous lesions: lower tumor differentiation grade, overall health status, and absence of extrahepatic lesions. They also demonstrated that both major and minor hepatectomies did not differ significantly in terms of outcomes, concluding that surgical resection of hepatic metastasis can be highly beneficial, safe, and potentially providing a better prognosis, especially in cases without extrahepatic involvement.²¹

Conclusion

In this case, we described a patient who underwent hepatic resection for disseminated cervical cancer treated almost a decade ago. Staging this case as T2aN2pM1 according to the 2018 FIGO classification categorizes it as stage IVB metastatic cervical cancer, and the expected prognosis is a 0 to 15% survival rate at 5 years.²² The indicated treatment was surgical resection and continuation of chemotherapy combined with biological therapy using pembrolizumab, a drug recommended for PD-L1 positive cases. Recent trials also showed improved prognosis in patients with disseminated cervical cancer, regardless of PD-L1 status, when Atezolizumab was combined with chemotherapy with Cisplatin plus bevacizumab, or tisotumab, which was recently incorporated into the treatment team for cervical cancer, increasing options and consequently survival.^{14,17}

Author's Contribution

LGRRP: data collection, conceptualization, study design, data analysis, final approval of manuscript, writing – original draft, provision of study materials or patient. LMC: data collection, conceptualization, study design, data analysis, final approval of manuscript, writing – original draft, provision of study materials or patient. MG: data collection, conceptualization, study design, data analysis, final approval of manuscript, writing – original draft, provision of study materials or patient. EALS: data collection, conceptualization, study design, data analysis, final approval of manuscript, writing – original draft, provision of study materials or patient. JSR: data collection, conceptualization, study design, data analysis, final approval of manuscript, writing – original draft, provision of study materials or patient. LRN: data collection, conceptualization, study, data analysis, final approval of manuscript, writing – original draft, provision of study materials or patient. RSC: data collection, conceptualization, study design, data analysis, final approval of manuscript, writing – original draft, provision of study materials or patient. PRR: data collection,

conceptualization, study design, data analysis, final approval of manuscript, writing – original draft, provision of study materials or patient.

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Conflict of Interests

The authors have no conflict of interests to declare.

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