Case Report

Breast metastasis from small cell neuroendocrine carcinoma of the cervix: a rare case report

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Background: Breast metastasis from small cell neuroendocrine carcinoma (SCNEC) of the cervix is an extremely rare condition with a poor prognosis. Metastatic SCNEC to the breast is difficult to differentiate from primary breast carcinoma on the basis of the clinical presentation alone.

Case Description: We report the case of a 23-year-old woman who was previously diagnosed with cervical cancer. She had undergone definitive concurrent chemoradiation treatment 1 year earlier and presented at this visit with left breast masses. Breast ultrasonography revealed two microlobulated hypoechoic masses with vascularity. Computed tomography revealed enlarged left supraclavicular lymph nodes, and multiple lung, skin, and peritoneal metastases. Core needle biopsies of the left breast masses indicated small cell tumors. Immunohistochemical staining revealed tumor cells diffusely positive for pan-cytokeratin (AE1/AE3), synaptophysin, chromogranin, paired-box gene 8, and p16. These were the same histological results as those for the previous cervical mass. Metastatic SCNEC from the cervix associated with human papillomavirus infection was diagnosed. We planned to initiate systemic chemotherapy; however, the patient's condition worsened rapidly, and chemotherapy was omitted. The patient died 2 months after the initiation of supportive care.

Conclusions: This case adds to the knowledge of an extremely rare presentation of breast metastases from an extramammary malignancy, cervical SCNEC. It is important to differentiate between primary breast cancer metastasis and metastasis to the breast from other cancers because of the different therapeutic options.

Keywords: Small cell carcinoma; neuroendocrine carcinoma; cervical cancer; breast metastasis; case report

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Introduction

Neuroendocrine tumors originate from neuroendocrine cells and can occur throughout the body. Most tumors arise in the gastroenteropancreatic region and lung and rarely from the cervix. Small cell neuroendocrine carcinoma (SCNEC) of the cervix is a rare variant of cervical cancer. SCNEC of the cervix is rare, representing less than 2% of all cases of cervical cancer, and is more aggressive compared with squamous cell carcinoma and adenocarcinoma subtypes. SCNEC is frequently locally advanced or associated with distant metastasis at diagnosis, and it exhibits a high recurrence rate (1). Common sites of metastasis are the liver (20.4%), lung (19.7%) and bone (13.4%). Forty-four-point-four percent of patients had multi-organ metastases. Metastatic SCNEC to the breast is extremely rare (2).

Whereas breast metastases from extramammary primary cancers commonly originate from lymphoma or leukemia,

breast metastases may also arise rarely from cervix (3). Therefore, this condition can be easily misdiagnosed. Metastases to the breast are difficult to distinguish from primary breast cancer because of similar radiological findings (4). Although primary breast cancers are more common, histopathological confirmation is necessary to differentiate metastatic extramammary cancer from metastatic primary breast cancer due to the different therapeutic options for the two conditions. The imaging and immunopathological correlations are crucial for distinguishing these conditions, especially in patients with a history of primary cancer in other organs, as in our patient.

Herein, we report a rare case of breast metastasis from cervical SCNEC in a patient who presented with suspicious breast masses and distant organ metastases with a history of previously treated cervical cancer. Owing to the aggressive condition, her health deteriorated rapidly after diagnosis, and she died shortly thereafter. We present this article in accordance with the CARE reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-2024-511/rc).

Case presentation

A 23-year-old woman presented with palpable left breast masses and left supraclavicular lymphadenopathy. She didn't have any underlying medical disease. She had one child and no family history of breast or ovarian cancer.

Highlight box

Key findings

- We report a rare case of breast metastasis from small cell neuroendocrine carcinoma (SCNEC) of the cervix.

What is known and what is new?

- Metastatic SCNEC to the breast is extremely rare and carries a poor prognosis, especially when the primary site is uncommon, such as the uterine cervix.
- There are only a few published case reports of breast metastasis from SCNEC of the cervix. The current report highlights the importance of accurate diagnosis and appropriate treatment.

What is the implication, and what should change now?

- The early detection and precise diagnosis of breast metastasis from SCNEC of the cervix was made using imaging and immunopathological correlations, is associated with clinical challenges where the effective treatment strategies differ greatly from that for primary breast cancer.

She had been diagnosed with stage IIB cervical cancer 1 year earlier and was treated as squamous cell carcinoma of cervix. There was a result of cervical biopsy specimen from a rural hospital. So, she didn't undergo trachelectomy or hysterectomy. But she was treated with laparoscopic ovarian transposition with bilateral salpingectomy, followed by definitive concurrent chemoradiation. No tumor recurrence was identified during surveillance. On physical examination at the current visit, two left breast masses were identified that measured approximately 2 centimeters (cm) and 3 cm, respectively, with a 4 cm left supraclavicular lymph node. There was no axillary lymphadenopathy. The patient underwent breast ultrasonography, which revealed 2 and 3.5 cm microlobulated hypoechoic masses with vascularity in the left upper outer quadrant (*Figure 1A*,*1B*). Mammography was not possible because the patient had difficulty standing owing to a poor performance status. Computed tomography (CT) revealed two left breast masses, enlarged left supraclavicular lymph node, multiple lung and mediastinal lymph node metastases, and peritoneal and subcutaneous metastases in the right back but a normal uterus and ovaries (*Figure 1C-1F*). Core needle biopsies of both left breast masses and the left supraclavicular lymph node were performed and revealed small cell tumors with papillary features on microscopic examination. These tumor cells were positive for pan-cytokeratin (AE1/AE3), synaptophysin, chromogranin, paired-box gene 8 (PAX8), and p16 (*Figure 2*) and negative for cytokeratin (CK)5/6, gross cystic disease fluid protein-15, estrogen receptor, and progesterone receptor. We retrospectively reviewed the tissue blocks and performed immunostains of the cervical mass, which showed pure small cell carcinoma without any squamous or adenocarcinoma component and positive for synaptophysin, chromogranin, AE1/AE3, PAX8, p16. There were the same histomorphological and immunohistochemical results as those of the breast masses. These findings were consistent with metastatic SCNEC originating from the cervix associated with human papillomavirus (HPV) infection. But this patient was not tested for HPV strain.

The patient's condition worsened rapidly shortly after the diagnosis, with a poor performance status; therefore, palliative systemic chemotherapy with etoposide and cisplatin was omitted. We discussed the prognosis with the patient, and she refused more treatment. Followed the patient closely with symptom control and psychosocial support. She died 2 months after supportive care was initiated.

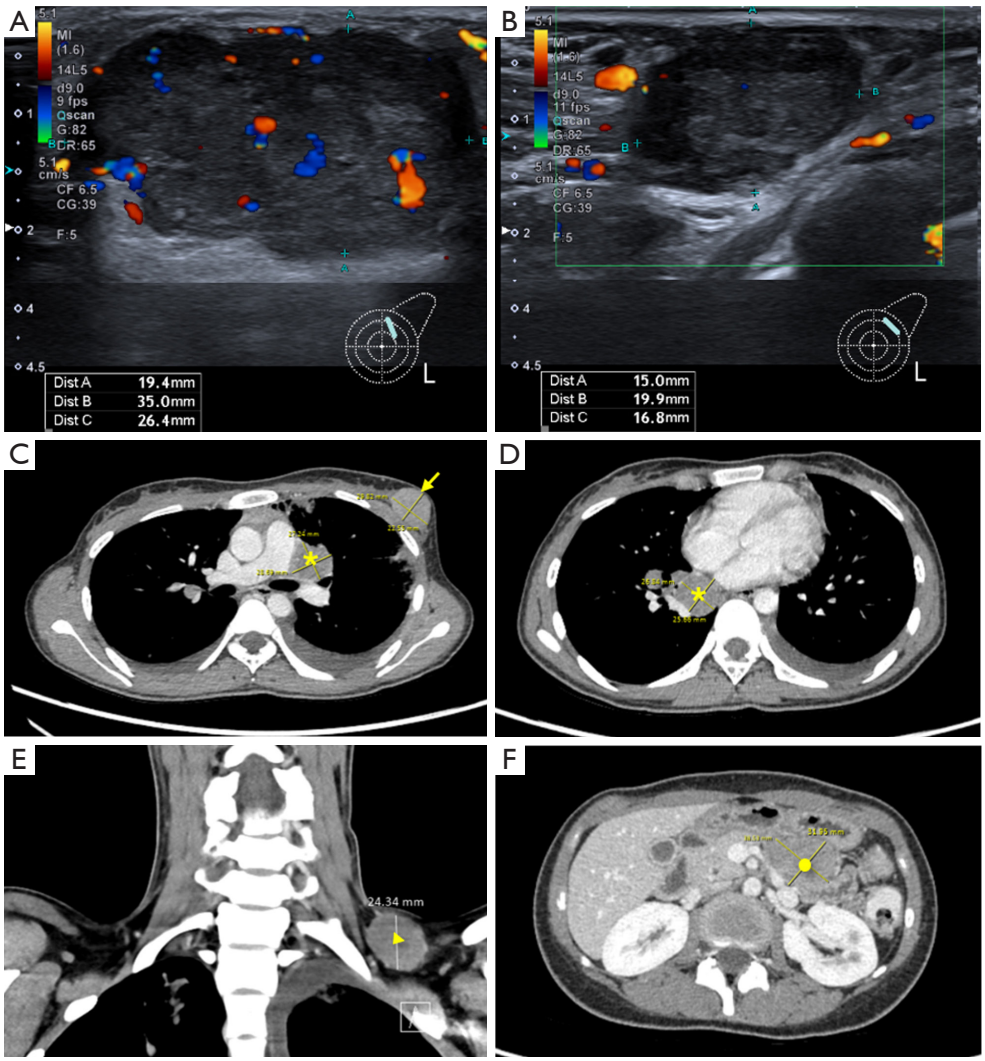

Figure 1 Imaging results of breast ultrasonography (A,B) and chest and abdominal CT (C-F). (A,B) Breast ultrasonographic images showing two left breast masses: a 1.7-cm irregular hypoechoic mass with vascularity at 2 o'clock and a 2.6-cm microlobulated and partially indistinct hypoechoic mass with vascularity at 1 o'clock. No axillary lymphadenopathy is present. (C-E) Chest CT showing bilateral pulmonary metastases [asterisk in (C) and (D)], with several enlarged mediastinal lymph nodes. The arrow in (C) indicates a 3-cm left breast mass, and the arrowhead in (E) indicates a 2.6-cm left supraclavicular lymph node. (F) Abdominal CT showing several peritoneal metastases (circle) in the anterior abdomen, perihepatic region, and pelvic cavity, with a maximum diameter of 3.9 cm. No uterine cervical mass was identified. CT, computed tomography; Dist, distance; mm, millimeters.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient's authorized attorney (her brother) for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

We have reported an unusual case of breast metastases from an extramammary malignancy. This condition has a reported incidence of 0.3–2.7% (4). SCNEC originating from the cervix as the primary site is rare; therefore, there

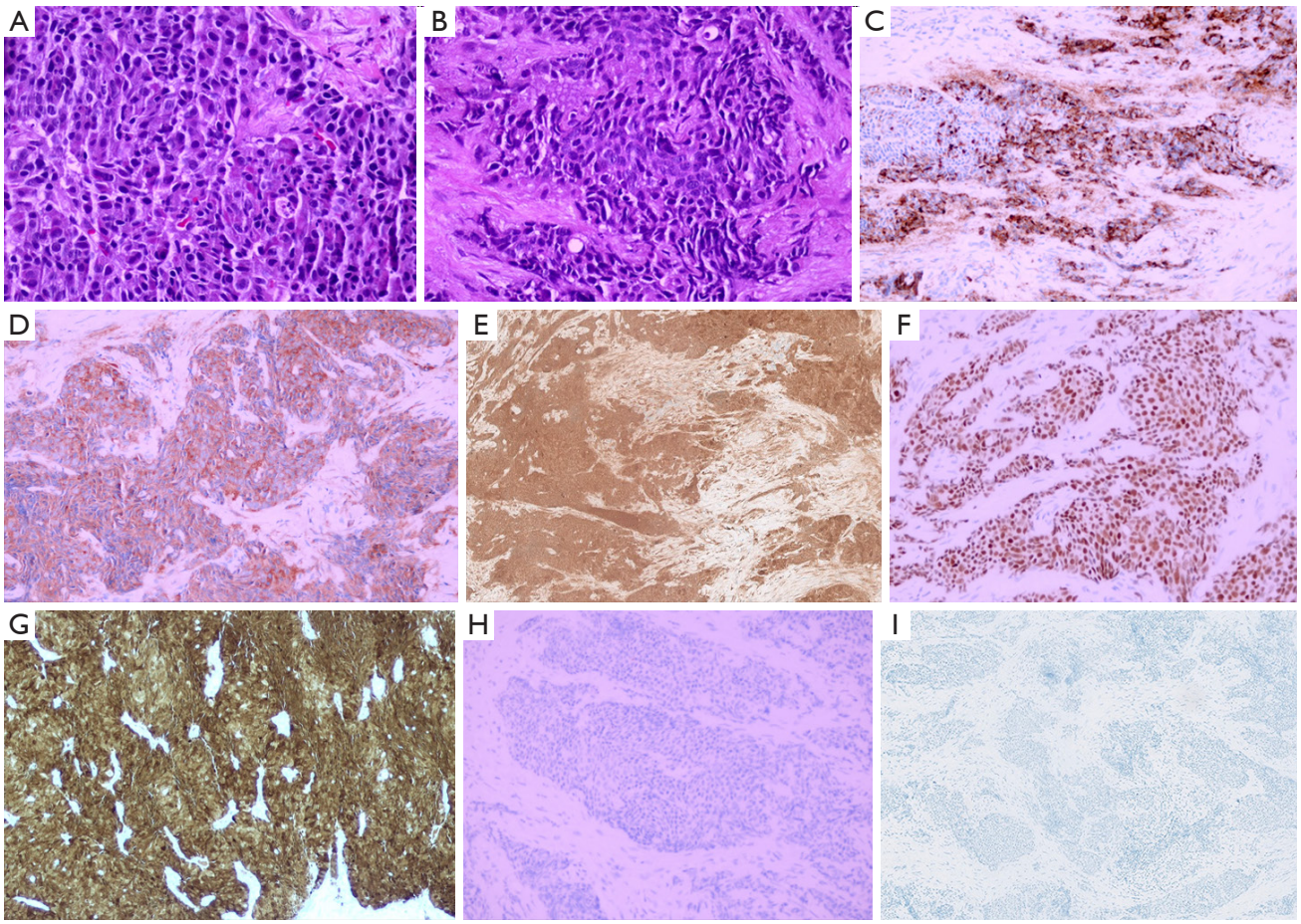

Figure 2 Micrographs: (A) high power view (200× magnification) on H&E stain of left breast mass; (B) high power view (200× magnification) of cervical mass on H&E stain; (C-I) low power view (40× magnification) of left breast mass on immunostains (same results as the cervical mass): chromogranin, synaptophysin, pan-cytokeratin (AE1/AE3), PAX8, p16, CK5/6, respectively. On H&E staining, the tumor cells in the left breast mass (A) exhibited similar histology to that of the previous cervical mass (B). The images show high cellularity of neoplastic cells arranged in a nest pattern. Dedicated fibrovascular cores are present among the tumor cells. These cells have small, round nuclei, nuclear molding, and scant cytoplasm, with a high mitotic rate. Staining for neuroendocrine markers, including chromogranin (C) and synaptophysin (D), is positive. Immunostaining for the epithelial marker AE1/AE3 (E), and PAX8 (F) are positive, while staining for markers that indicate squamous cell carcinoma, such as CK5/6 (H) and p63 (I), are negative. These findings suggest small cell neuroendocrine carcinoma originating from the cervix. Staining for p16 (G), an indirect marker of human papillomavirus-related tumors, shows block-type staining among the tumor cells. H&E, hematoxylin and eosin; PAX8, paired-box gene 8; CK5/6, cytokeratin 5/6.

are only a few case reports of cases of metastatic SCNEC from cervix to breast (5-8) (*Table 1*). Clinical history, imaging findings, and histological confirmation can aid in obtaining the correct diagnosis.

Breast cancer is the most frequently diagnosed cancer in women, on a global basis (9). Most metastases to the breast originate from the contralateral breast (10). The most common extramammary primary cancers with breast metastasis are lymphoma, leukemia, and melanoma (3). Most metastases to the breast spread via hematogenous routes, and metastatic lesions are likely to be multiple or bilateral, which differs from primary breast cancers. The typical imaging manifestations are round, circumscribed, hypoechoic masses with internal vascularity and without architectural distortion, suspicious calcifications, and axillary lymphadenopathy, which can mimic benign tumors. Other less common findings are microlobulated masses or masses with indistinct margins, making it difficult to distinguish

Table 1 Summary of the findings in four previous similar case reports

Reference	Age (years), sex	Immunohistochemistry staining			First treatment	Time to recurrence after first treatment	Metastatic organ in recurrence setting	Imaging findings of breast metastasis					Treatment in recurrence setting
		AE1/AE3	Synaptophysin	Chromogranin				Method	Shape	Location, size	Axillary lymphadenopathy	Calcification	
Hsieh *et al.* 2012 (6)	46, Female	NR	+	NR	Alternative herbal therapy	4 months	Breast, adrenal gland	FDG PET/CT	NR	NR	NR	NR	NR
Yadav *et al.* 2015 (7)	42, Female	NR	+	+	CCRT	After completion CCRT	Breast, bone, liver	FDG PET/CT	NR	NR	NR	NR	Palliative radiation therapy to spine and liver
Kwak *et al.* 2018 (8)	51, Female	NR	+	+	Radical hysterectomy with BSO and adjuvant RT	3 months	Breast, bone	MMG, ultrasound	Well-defined, round, lobulated	Right upper outer, 3 cm and 2 cm	No	No	Simple mastectomy without axillary lymph node dissection then chemotherapy
Sapiai *et al.* 2022 (5)	58, Female	+	+	–	CCRT with brachytherapy	3 months	Breast, lung	MMG, ultrasound	Well defined lobulate, hypoechoic, with vascularity	Left mid inner, 1.5 cm	No	No	Brachytherapy for cervix and chemotherapy

BSO, bilateral salpingo-oophorectomy; CCRT, concurrent chemoradiation; FDG PET/CT, fluorodeoxyglucose-positron emission tomography/computerized tomography; MMG, mammogram; NR, non-reported; RT, radiation therapy.

breast metastases from primary breast cancer (3).

Our patient presented with breast masses and multiple organ metastases. Imaging revealed two microlobulated hypoechoic left breast masses with vascularity but without axillary lymphadenopathy. Mammography was not possible because the patient had difficulty standing owing to a poor performance status. Metastatic primary breast cancer was a differential diagnosis. However, the patient had been diagnosed with cervical cancer and underwent definitive concurrent chemoradiation 1 year earlier. Therefore, recurrent cervical cancer with breast metastasis was also a differential diagnosis. Notably, imaging could not identify the type of primary tumor because the findings from breast ultrasonography indicated a low suspicion of breast cancer, and there were no uterine or cervical masses on CT. Therefore, an accurate diagnosis was made using histology and immunohistochemistry.

Metastatic cancer to the breasts can histologically resemble primary breast cancer; therefore, immunohistochemistry should be performed. In our case, tumor cells in both the cervical and breast tissues exhibited similar histology characterized by small round cell tumors with papillary features and a high mitotic rate. Immunohistochemical staining was positive for AE1/AE3 (epithelial marker), and synaptophysin and chromogranin (neuroendocrine markers), and negative for p63 and CK5/6 (squamous cell carcinoma markers). Therefore, neuroendocrine carcinoma was the final diagnosis. The next step was to identify the primary cancer. There was also positive staining for PAX8 and negative staining for the breast markers, gross cystic disease fluid protein-15, estrogen receptor, and progesterone receptor. Notably, staining for the indirect marker of HPV-related tumors, p16, was positive. The overall findings and the correlation with the clinical manifestations and imaging findings indicated a diagnosis of metastatic SCNEC from the cervix to the breast associated with HPV infection.

The treatment and prognosis differ between primary breast cancer with breast metastasis and breast metastasis from cervical SCNEC. Cervical SCNEC is a biologically aggressive uterine malignancy, the cause of which is generally HPV infection (1). Metastatic cervical SCNEC has a very poor prognosis, with a 5-year survival rate in advanced stages of 0% (1). In comparison, the 5-year survival rate for metastatic breast cancer is approximately 30% (11).

Owing to its rarity, there is no standard treatment for metastatic cervical SCNEC. Systemic chemotherapy with etoposide and cisplatin should be considered as initial treatment, followed by palliative radiotherapy in the pelvic area (12). In contrast, for metastatic breast cancer, systemic drug therapies can include hormone therapy, chemotherapy, targeted drugs, and immunotherapy, depending on the subtype. However, although the surgical management of both diseases is the same, surgery for metastatic cervical SCNEC should be considered only for palliative proposes to alleviate symptoms. For these reasons, an accurate diagnosis is necessary for treatment planning. The poor performance status in our patient meant that systemic treatment was not an option. Therefore, supportive care was initiated, and she died 2 months later.

Conclusions

Metastatic SCNEC to the breast is extremely rare and carries a poor prognosis, especially when the primary site is uncommon, such as the uterine cervix. However, early detection of the disease is important because this condition is associated with clinical challenges where the management differs greatly from that for primary breast cancer. Therefore, multiple diagnostic modalities are often essential to determine the therapeutic strategies and prognosis for a specific patient.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-2024-511/rc

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related

to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(ss) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient's authorized attorney (her brother) for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

References

1. Chao A, Wu RC, Lin CY, et al. Small cell neuroendocrine carcinoma of the cervix: From molecular basis to therapeutic advances. Biomed J 2023;46:100633.
2. Li Q, Yu J, Yi H, et al. Distant organ metastasis patterns and prognosis of neuroendocrine cervical carcinoma: a population-based retrospective study. Front Endocrinol (Lausanne) 2022;13:924414.
3. Li J, Wahab R, Brown AL, et al. Extramammary Metastases to the Breast. Radiographics 2023;43:e230036.
4. Lee SK, Kim WW, Kim SH, et al. Characteristics of metastasis in the breast from extramammary malignancies. J Surg Oncol 2010;101:137-40.
5. Sapiai NA, Abdul Muthalib F, Mat Idris NA, et al. A rare case of metastatic small cell carcinoma of breast from mixed types of cervical carcinoma. Radiol Case Rep 2022;17:2673-6.
6. Hsieh TC, Wu YC, Sun SS, et al. Rare breast and adrenal gland metastases from small-cell neuroendocrine carcinoma of uterine cervix. Clin Nucl Med 2012;37:280-3.
7. Yadav D, Yadav S, Chisti MM. A Rare Case of Metastasis of Small Cell Carcinoma of Cervix to Breast. World J Oncol 2015;6:301-3.
8. Kwak BS. Metastatic Small Cell Carcinoma of the Breast from Cancer of the Uterine Cervix: A Case Report. Case Rep Oncol 2018;11:38-42.
9. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2024;74:229-63.
10. Sangha Brar J, Lo L, Wong J. Metastases to the breast: great radiological mimicker of primary breast carcinoma and a forgotten entity. A case series of three patients and a review of the literature. BJR Case Rep 2017;3:20160137.
11. Maajani K, Jalali A, Alipour S, et al. The Global and Regional Survival Rate of Women With Breast Cancer: A Systematic Review and Meta-analysis. Clin Breast Cancer 2019;19:165-77.
12. Zhang Q, Xiong Y, Ye J, et al. Influence of clinicopathological characteristics and comprehensive treatment models on the prognosis of small cell carcinoma of the cervix: A systematic review and meta-analysis. PLoS One 2018;13:e0192784.

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