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REVIEW

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ABSTRACT

The lung is a distant metastatic site of gynecologic cancers. These metastases have clinical characteristics which can be solitary, multiple, solid, or manifest by pleural effusion. Diagnosing and managing lung metastasis is challenging because each type of gynecological cancer has different clinical characteristics. Some gynecologic cancers have tumor markers that can help diagnose lung metastasis; however, others do not have them. The options for managing lung metastasis in gynecologic cancer include; chemotherapy, surgery, or combination therapy. The clinical aspects of lung metastasis from cervical, endometrial, ovarian, vaginal, and vulvar cancers and gestational trophoblastic neoplasia were discussed in this article.

Keywords: cancer, gynecologic, lung, metastatic.
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INTRODUCTION

Gynecologic cancers consist of ovarian, tubal, uterine, cervical, and vaginal cancers and gestational trophoblastic neoplasia. In Indonesia, cervical, uterine, and ovarian cancers are the most common gynecological cancers. All these types of cancer may spread to the lungs with a different prevalence and behavior. There are two types of lung metastasis originating from gynecologic cancer (LMGC). The first is gynecologic cancer stage IV with lung metastasis, and the second is recurrence with lung metastasis. The clinical features of lung metastasis of each type of gynecologic cancer may vary from pleural effusion to multiple solid nodules. A history of gynecologic cancer, tumor markers, and histopathological type of the primary tumor are essential factors in diagnosing lung metastasis.[1]

However, confirming the diagnosis of lung metastasis from gynecological cancers is challenging. The cytological or histopathological examination may be performed on specimens from pleural effusion fluid or lung biopsy. The absence of cancer cells in pleural effusion does not exclude pleural or lung metastasis because it could be a false negative. Lung biopsy is not always possible, depending on the location of the nodule. Tumor markers may help diagnose lung cancer; however, not all gynecological cancers have specific tumor markers. The several management options for LMGC include chemotherapy, hormonal therapy, radiation, and surgery.[2-5] The main aim of LMGC treatment is palliative, although several publications have reported that some patients with lung metastasis survive until five years.[6-8] For gynecologic cancers that are highly sensitive to chemotherapy, such as gestational trophoblastic neoplasia, they are manageable by chemotherapy in most cases if there is metastasis to the lungs. Charing Cross Hospital in London reported 100% survival for gestational trophoblastic neoplasia with lung metastasis.[9] Resection of isolated lung metastasis may also improve survival in some gynecologic cancers.[10-12] The clinical aspects of lung metastasis from cervical, uterine, and ovarian cancers and gestational trophoblastic neoplasia are discussed here.

Lung Metastasis in Cervical Cancer

Cervical cancer is the most common gynecological cancer in Indonesia. High-risk human papillomavirus is a high-risk factor for cervical cancer. The most recent staging system for cervical cancer based on the International Federation of Gynecology and Obstetrics consists of stages IA-IA, IIA-IIB, IIIA-IIIB, and IVA-IVB. The definition of stage IVB is cervical cancer spread to distant organs outside the pelvis, including cervical cancer with lung metastasis.[13] A published study of 1347 patients newly diagnosed with cervical cancer showed that the incidence of lung metastasis was 37.9%, that of the lung and another distant site metastasis was 19%, and that of of the lung and two other distant site metastases was 7%.[14] Approximately 16%-30% of early-stage cervical cancers recur after the initial treatment and 50%–60% of those with distant metastasis.[15] However, another study reported that the incidence of lung metastasis in cervical cancer was 4.33%.[6] The main histologic types of cervical cancer are squamous cell cancer, adenocarcinoma, and adenosquamous, with some other less common histologic types, such as neuroendocrine tumor and sarcoma. A routine tumor marker check for cervical cancer is not recommended, although some tumor markers are still being studied.[16] The management of early-stage cervical cancer (IA-IIA) employs surgery followed by adjuvant radiation or chemoradiation if there is any indication; for locally advanced cervical cancer, the primary treatment is chemoradiation.[15] For metastatic cervical cancer due to both newly diagnosed and distant recurrence, the primary treatment is chemotherapy.

There are three routes through which cervical cancer spread via direct extension lymphatic vessels or hematogenous routes. The most common routes for lung metastasis are direct extension and the lymphatic vessels. In cervical cancer, hematogenous spread occurs in some unusual histologic types, such as neuroendocrine and adenosquamous tumors. Hematogenous spread is unusual compared to other routes. If it occurs, the most common target organ is the lung (36.3%), followed by the bone (16.3%).[4] Most lung metastasis occurs within two years after initial treatment (83.9%).[4] The routes of lung metastasis in cervical cancer could be hematogenous or lymphatic, although they occur via lymphatic vessels.[17] Twenty percent of patients with cervical cancer generally experience recurrences. In these patients with recurrent cervical cancer, distant metastasis is observed in 70% of patients with pulmonary metastasis.[1] Most recurrences occur within two years after the initial treatment.

A study involving 19,377 patients with cervical cancer showed that age, lymph node metastasis, poor differentiation, late-stage and non-squamous histologic type are predictors of developing lung metastasis.[6] Approximately 50% of all lung metastases in cervical cancer occurred in patients older than 60 years. In addition, patients with lung metastasis were older than those with other metastases.[14] Most patients with cervical cancer and lung metastasis did not have any symptoms related to lung function.[18] Based on these findings, lung metastasis detection is essential in older patients with cervical cancer, especially if the cervical cancer is at an advanced stage. However, in early-stage cervical cancer, routine chest radiography is not recommended and is unnecessary.[19]

Lung metastasis in cervical cancer may be detected using chest radiography with a sensitivity of 76.7%–79.3%, which is also the first imaging modality used to detect lung metastasis.[20] Computed tomography (CT) scan should be used if the findings from chest radiography are inconclusive. Multiple bilateral pulmonary nodules in patients with cervical cancer suggest lung metastasis from cervical cancer, although a single pulmonary nodule needs further investigation to exclude primary lung cancer. Moreover, benign pulmonary nodules, granuloma, infection, and intrapulmonary lymph node proliferation are excluded.[17] The most common clinical appearance of lung metastasis in cervical cancer is multiple pulmonary nodules. The other type of lung metastasis is solitary nodule or cavitary metastasis. Among other gynecologic cancers, cervical cancer presents a typical cavitary lung metastasis when spreading to the lung.[1] However, metastasis in cervical cancer may also affect mediastinal nodes, hilar lymph nodes, and pleura.[13] The primary predilection metastatic site in the lung is in the inferior lobe of the right lung.[4] Tumor markers in cervical cancer are not routinely used based on cervical cancer guidelines worldwide, and it is not checked for suspected lung metastasis in cervical cancer.

The management options for lung metastasis in cervical cancer are surgery and chemotherapy. Metastasectomy of lung metastasis without metastasis to other organs increases survival.[4,6] The conditions required for metastasectomy are no hilar and mediastinal metastasis, less than four nodules, 24 months disease-free after initial treatment, and a maximum tumor size of 3 cm.[4] The 5-year disease-free survival for patients after metastasectomy was 32.9%. The number of metastatic nodules, patients with two or fewer nodules had better survival than patients with three or four nodules.[21] For patients who did not undergo surgery, the primary treatment was chemotherapy. Patients who had never received chemotherapy in the initial treatment would respond better than those who had previously received chemotherapy. The choice of chemotherapy regimen is platinum-based chemotherapy. Chemotherapy can be performed using a single drug or combination therapy. Adding bevacizumab as an angiogenesis inhibitor during chemotherapy would have better survival than chemotherapy only (16.8 months vs. 13.3 months).[22] Generally, the median progression-free survival for cervical cancer with lung metastasis was 13 months with a 5-year survival rate of 7.5%.[4]

Lung Metastasis in Ovarian Cancer

Ovarian cancer management is challenging because most ovarian cancers are diagnosed at an advanced stage worldwide, thereby affecting the survival of patients.[23] Less than 20% of patients with advanced ovarian cancers would survive over ten years.[24] There are three main histologic types of ovarian cancer: epithelial ovarian cancer, which accounts for 90% of all ovarian cancers, germ cell ovarian cancer, and sex cord-stromal tumor.[25] Each histologic type has its clinical characteristics, and non-epithelial ovarian cancer is less invasive than epithelial ovarian cancer.[26] Most epithelial ovarian cancers occur at an older age, and less than 1% occurs at less than 30 years. Most germ cell ovarian cancers are diagnosed at a younger age.

Epithelial ovarian cancer is a tumor marker commonly used for diagnosis and monitoring treatment. Cancer antigen 25 or carbohydrate antigen 25 (Ca125) is a tumor marker for epithelial ovarian cancer. Its sensitivity in early-stage ovarian cancer is low, with only 50% of early-stage epithelial ovarian cancer having elevated Ca125.[24] Inflammation of the peritoneum in the pelvis and abdomen endometriosis and pelvic inflammatory disease also elevates the Ca125 levels. In addition, some other non-cancer conditions that will elevate Ca125 levels are fibroid, ovarian hyperstimulation syndrome, and peritoneal carcinomatosis.[24,27] Not all ovarian cancers produce Ca125, and it can only be used during follow-up to detect recurrence of epithelial ovarian cancer if the initial level before treatment was elevated. Tumor markers for germ cell ovarian cancer are alpha-fetoprotein for endodermal sinus tumor, lactate dehydrogenase for dysgerminoma, and beta-human chorionic gonadotropin (HCG) for ovarian choriocarcinoma.[28] The basic level of the tumor markers should be evaluated before they can be used for the follow-up to detect recurrences.

Tumor presence in the thorax was observed in 169 patients (44.5%) with ovarian cancer, 73% of them had pleural effusion containing malignant cells, 12.3% had pulmonary parenchymal metastasis, and 1% had lymphangitic/

nodal metastasis.[29] Pleural effusions are thought to be caused by invasion from the peritoneum transdiaphragmatic.[1] Positive fluid cytology is required to confirm that pleural effusion is a metastasis from ovarian cancer, although the false-negative rate was 30%.[30] Another study of 33.418 patients with epithelial ovarian cancer showed that 6.7% of the patients had lung metastasis at the epithelial ovarian cancer diagnosis.[31] This study also revealed that lymph node metastasis, higher stage, elevated Ca125 level, and tumor grade was associated with a higher risk of lung metastasis. Confirming the diagnosis of lung metastasis using histopathological examination is challenging. Video-assisted thoracoscopic surgery was performed to increase the malignant cell detection rate in pleural fluid. Diagnosis of pulmonary parenchymal metastasis cytologically can be achieved by fine-needle aspiration biopsy or core biopsy. The diagnostic accuracy of CT-guided pulmonary core biopsy was significantly better if the size of the nodule was >15 mm (96.8%) than if the size was less than 15 mm (83.7%).[32] The most common complication of this procedure was pulmonary hemorrhage and pneumothorax, and tumor markers were beneficial in predicting if the lung metastasis originated from ovarian cancer.

The liver was the most common site of distant metastasis of ovarian cancer, followed by distant lymph nodes, lung, bone, and brain. However, the most insufficient overall survival was ovarian cancer with lung metastasis.[33] The primary treatment for patients with an initial diagnosis of ovarian cancer with lung metastasis or recurrent ovarian cancer with lung metastasis is chemotherapy. Chemotherapy regimens are based on the histopathological type of ovarian cancer. The standard first-line chemotherapy regimen for epithelial ovarian cancer is carboplatin and paclitaxel every three weeks with bevacizumab or carboplatin every three weeks and weekly paclitaxel and bevacizumab.[34] For recurrent ovarian cancer, the chemotherapy regimen for platinum-sensitive ovarian cancer is similar to that of first-line chemotherapy. For platinum-resistant ovarian cancer, the chemotherapy regimen is non-platinum-based chemotherapy. The treatment of ovarian cancer with lung metastasis is palliative.

Lung Metastasis in Endometrial Cancer

Uterine cancers consist of endometrial cancer and sarcoma, and only less than 10% of all uterine cancer are sarcoma, most of which are endometrial cancers.[35] Different from ovarian cancer, 80% of patients with endometrial cancer are detected at early stages.[35] There are two types of endometrial cancers: endometrioid (80%), estrogen-dependent, and non-endometrioid, which is non-estrogen-dependent (20%).[36] The non-endometrioid type has a poorer prognosis than the endometrioid type, with 37% of patients having extrauterine metastasis. The 5-year overall survival rate of endometrial cancer is more than 90%, as most of them are detected early.[36] When compared to other gynecologic cancers, endometrial cancers have the highest rate of lung metastasis with an incidence of 20%–25%.[37] Another study of 73.328 patients with endometrial cancer showed that the lung is the most common metastatic site (1.8%), followed by distant lymph node (1.6%), liver (0.9%), bone (0.65%), and brain (0.18%).[38] This study also showed that patients with endometrial cancer and lung metastasis had a median survival of 15 months, with the best overall survival than other metastatic sites. The most frequent type of lung metastasis of endometrial cancer were multiple bilateral nodules, although it is also possible to see a solitary nodule that looks like primary lung cancer. The rare lung manifestations were lymphangitis carcinomatosis and endobronchial tumor.[37] Pleural involvement such as effusions and thickening were uncommon.[37,39] A study involving 90 patients with endometrial cancer and lung metastasis showed the most common manifestations of lung metastasis were multiple pulmonary nodules (72%), followed by solitary pulmonary nodules (18%), mass lesion (11%) and pleural effusion was only found in 6.7% of the patients.[40]

Patients with recurrent endometrial cancer and lung metastasis had better survival if recurrence occurred two years after the initial therapy than those who had recurrency before two years after initial therapy (31 months vs. 10 months, P=0.01).[41] Patients with bilateral lung metastasis also had poorer survival than those with unilateral lung metastasis. Surgical excision was an option for isolated, solitary lung metastasis of endometrial cancer. Since it is difficult to determine the difference between primary and secondary lung cancers on chest imaging, a lung biopsy was performed before.[42] Reported a 100% 5-year survival rate for patients with solitary lung metastasis who underwent wedge resection followed by adjuvant hormonal therapy. In addition, it is suggested that wedge resection for small solitary lung metastasis with a size less than 3 cm and lobectomy for tumors larger than 3 cm be performed because of the possibility of microscopic satellite lesions.[2] Another management of lung metastasis of endometrial cancer is hormonal therapy with progesterone. It has been reported that patients with lung metastasis who received progesterone therapy can be stable and free of disease for up to 10 years.[43] Patients with advanced endometrial cancer, including those with lung metastasis and histologic type of endometrioid, may receive hormonal therapy with progesterone. The histologic grade of endometrial cancer influenced the response rate of hormonal therapy. Grade 2 had a response rate of 37%, 23% for grade 2, and 9% for grade 3.[44] Estrogen and progesterone receptor (ER/PR receptor) status was determined before hormonal therapy treatment; tumors with ER/PR receptor would have better survival than tumors without ER/PR receptor.[45] The ER/PR receptor status could be different in primary and metastatic tumors; thus, it is advisable to check the hormone receptor status in the metastatic tumor, which may lose the expression of the hormone receptor.[46] For extensive pulmonary metastasis, chemotherapy is the best option, and a study showed that patients who received chemotherapy had better overall survival than those who received radiotherapy.[43]

Lung Metastasis in Gestational Trophoblastic Diseases

A gestational trophoblastic disease is a group of diseases originating from trophoblast cells, which form the outer layer

of the blastocyst and become a large part of the placenta. The gestational trophoblastic disease consists of five types: hydatidiform mole (HM), choriocarcinoma, invasive mole, epithelioid trophoblastic tumor, and placental site trophoblastic tumor. The last four types are categorized as gestational trophoblastic neoplasia (GTN).[47] Hydatidiform mole is a benign tumor and a continuation of abortion (30%) or normal pregnancy (20%).[48] For complete hydatidiform mole, the incidence is estimated to be 1-3 per 1000 pregnancies and for partial hydatidiform mole, it is estimated to be 3 per 1000 pregnancies.[49] Approximately 9 of 20% of HM may develop into GTN.[48] To diagnose trophoblast-related disorders, such as pregnancy and gestational trophoblastic disease (GTD), laboratory tests for serum HCG are the most responsive and specific.[50,51] An increase in human chorionic gonadotropin (HCG) levels above the reference range in a treated GTD case indicates the possibility of a local or distant metastatic recurrence.

The most common metastatic site of GTD is the lung which shows up as pulmonary nodules on chest radiography and/or lung CT.[52] The pulmonary lesion was asymptomatic in many patients.[53,54] Approximately 30% of GTN patients have metastases at the time of diagnosis, the most frequent of which are to the lungs (80%).[10] Even in normal pregnancies, a lung nodule can be observed by radiography or CT during or after molar pregnancy evacuation.[55] A chest radiography can be used to detect lung metastases and count the number of metastases to calculate the risk score of GTN, lung CT could also be performed.[51] Initial diagnostic procedure for GTN, including chest radiography. If chest radiography is negative, a chest CT scan can be used to detect micrometastases in 40% of patients with negative chest radiography.[56] Regarding diagnosing lung metastases, a CT scan is more sensitive than a chest radiograph. Multiple, oval, soft tissue density lesions up to 3 cm in size are seen as parenchymal lung metastases. The lesions may be solitary, miliary, and exhibit cavitation on rare occasions.[57] However, if the chest radiograph is without particularities, there is no need for a chest CT because pulmonary micrometastases do not affect the patient's outcome.[1,58] Lung micrometastasis from CT scan do not correlate with the level of beta HCG.[58] Sometimes, tissue biopsy is necessary to confirm the lung metastasis of GTN. It was reported that non-small cell lung cancer also secreted beta HCG.[59]

GTN is divided into two categories based on prognosis: low and high risks. Categorization can be determined using the World Health Organization (WHO) scoring system of 2000. A score ≤ 6 is categorized as low risk, while a score > 6 is categorized as high risk.[51] Low-risk GTN is treated with single-agent chemotherapy, such as methotrexate, and combination chemotherapy is used for high-risk GTN. Combination chemotherapy with etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine is the most widely used treatment for high-risk GTN.

The incidence of lung metastasis in low-risk GTN is reported to be 6.3%, with overall survival of 100%, and lung metastasis does not affect cure rates and overall survival.[60] However, the clinical implication of lung metastasis in low-risk GTN is the tendency to recur, and patients with lung metastasis have a higher risk of recurrence.[9,61,62] Lung metastasis is more common in high-risk GTN, and 69.2% of stage IV GTN stage had lung metastasis.[8] For patients with high-risk GTN, the average cure rate is between 90% and 100%.[63] Chemotherapy is the treatment of choice for metastatic GTN. For solitary pulmonary nodules, excision of the nodule decreased treatment time, the need for aggressive multi-drug combination regimens, and chemotherapy resistance.[53,64] Generally, GTD is a chemosensitive disease with a good prognosis even with lung metastasis.

Lung Metastasis in Vulvar Cancer

Vulvar cancer is the fourth most prevalent gynecologic cancer after uterine, ovarian, and cervical cancers.[65] The most common histological type is squamous cell carcinoma, accounting for 90% of all vulvar cancers.[66] Vulvar cancer that has spread to other parts of the body is a rare disease, and there is little information on metastatic patterns and the associated prognosis or therapeutic approaches. One of the most significant studies reported that 5.1% of vulvar cancer had distant metastasis, among which the lung was the most common metastatic site.[67] Other studies reported that the incidence of lung metastasis of vulvar cancer was very low (1.9%).[68] For a recurrent case, only 15% of recurrent vulvar cancer had distant metastasis.[69] Vulvar cancer metastasize to the lung hematogenously. There was no pulmonary metastasis in any of the patients with early-stage disease and tumor size of less than 40 mm; therefore, chest imaging was not necessary for patients with early-stage and small vulvar cancer.[68] There is no standard treatment for lung metastasis of vulvar cancer as the incidence is rare. Chemotherapy is the primary treatment for vulvar cancers with distant metastasis.

Lung Metastasis of Vaginal Cancer

Primary vaginal cancer is uncommon, accounting for only 1%–2% of all female genital tract malignancies.[70] Primary vaginal cancer is diagnosed when there is no previous history of cancer of the cervix or vulva or when there has been no cervical squamous cell carcinoma or vulvar carcinoma throughout the previous five years.[71] Since vaginal cancers are metastatic from other primary locations, diagnosing a primary vaginal cancer is uncommon. Although vaginal cancer can be secondary cancer from lung cancer that metastasizes to the vagina.[72] Vaginal cancer metastasizes to the lung hematogenously, and lung metastasis represents the late stage. A manifestation of lung metastasis is multiple pulmonary nodules.[73] The treatment of vaginal cancer with lung metastasis involves a combination of radiation and chemotherapy. A case report showed that concurrent chemoradiation with 5-fluorouracil and cisplatin is effective for vaginal cancer with lung metastasis, and the patient was disease-free at the 40-month follow-up.

CONCLUSION

Lung metastasis is a common problem in gynecologic cancer. Each lung metastases from each type of gynecological cancer have specific clinical characteristics. The diagnostic procedure and the treatment of lung metastasis of gynecologic cancer are challenging. Treatment of pulmonary metastases varies depending on the

general clinical condition and the type of pulmonary metastases that occur. The main goal of the therapy is to preserve the quality of life of the patient. By understanding the clinical aspect of lung metastasis of gynecologic cancer, we can provide the best treatment for the patients.

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The author contributed to all processes publishing this review.

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PAGE 7

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