

## Thoracic manifestations of common nonpulmonary malignancies of women

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The thorax is a frequent site of metastasis from numerous nonpulmonary cancers. Intrathoracic metastatic disease may manifest in a variety of forms, including solitary or multiple pulmonary nodules, endobronchial tumor, lymphangitic carcinomatosis, or a pleural effusion. Different tumor types may have a predilection for metastasis to particular organs and for particular patterns of metastasis within an organ.

Although many common forms of cancer, such as lung cancer and colon cancer, are “equal opportunity” malignancies for men and women, other cancers are “sex-specific” or “sex-associated” and occur exclusively or predominantly in men or women. This article reviews and discusses the clinical and biologic aspects of intrathoracic metastases that result from common, gender-specific malignancies of women: cancers of the breast, ovary, cervix, and uterus.

### Biology of metastasis

The ability of cancer cells to metastasize largely is responsible for the fatal course of many cancers. Tumors that do not have the ability to metastasize may grow, but remain confined and are often resectable, and thus, curable, although local invasion may cause a fatal course. The metastatic process is complex and our understanding of the molecular biology of cancer cell proliferation and metastasis is expanding rapidly. Although we discuss the basic mechanisms of metastasis, a detailed discussion of these processes is beyond the scope of this article [1].

For a cancer cell to metastasize, it needs to possess a “metastatic phenotype”—a collection of traits that allows it to extend beyond its initial compartment, gain access to local lymphatics and capillaries, travel in the blood stream to a distant organ, cross the endothelial barrier, and implant successfully in a new compartment [2]. These steps are depicted in Fig. 1. To accomplish this, most malignant tumors that frequently metastasize have acquired specific properties—examples include unlimited growth potential and the ability to evade the immune system. Many of the molecular markers represent one or more steps in this paradigm. For example, vascular endothelial growth factor (VEGF) is a marker of angiogenesis, a process whereby tumors are able to generate their own blood supply.

Normal cells require extrinsic growth factor to become active, whereas cancer cells are able to produce their own growth factors. This enables the latter to increase receptor density in response to their surrounding environment and perpetuates their growth [3–5]. Although normal cells also are under the control of inhibitory growth factors, metastatic cells are able to overcome this limitation. Moreover, normal cells have a life span that includes programmed cell death (apoptosis). Cancer cells use a variety of mechanisms to combat apoptosis [1]. One of the most celebrated examples of an antiapoptotic mechanism is the mutation of the p53 tumor suppressor gene, which has been found in more than 50% of cancers [6]. After cancer cells have acquired this ability to grow and to be immortal, they have to be able to migrate and to provide their own blood supply. Tumor angiogenesis is important for supplying nutrients to a growing tumor and to serve as an entry point for metastatic cells into the blood stream [7].

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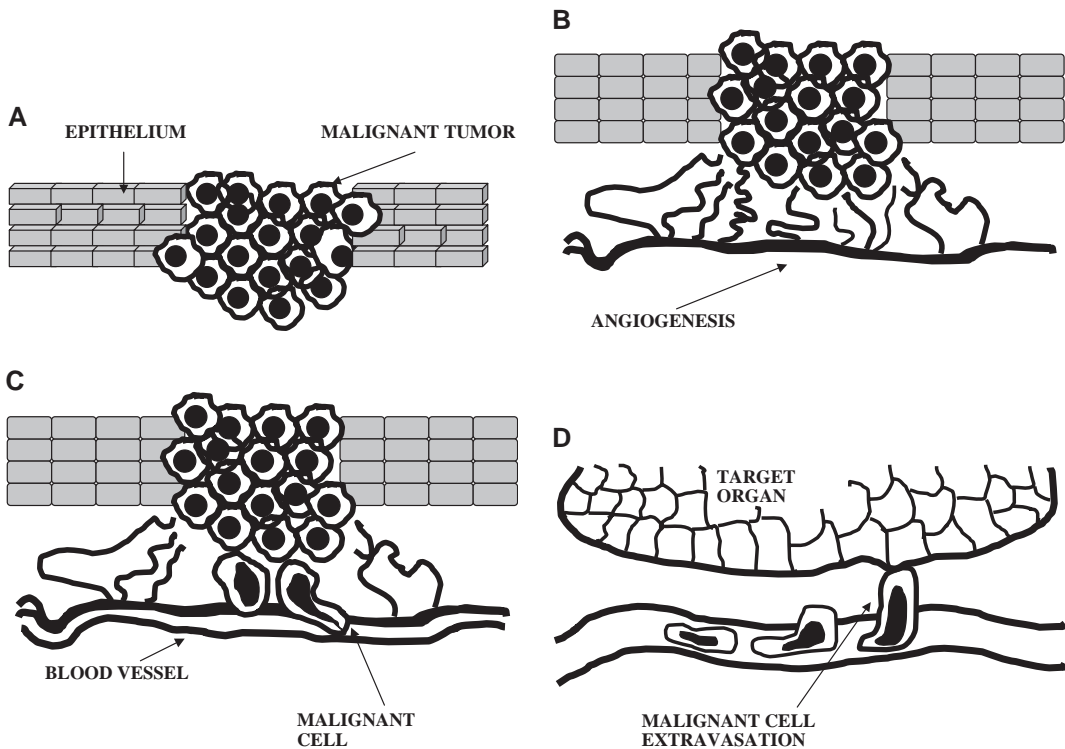


Fig. 1. Stepwise progression of tumor metastasis. (A) Tumor cells outgrow their native compartment and acquire independent growth potential. (B) Tumor cells secrete factor that attract new blood vessel growth and provide nutrients for further malignant cell expansion. (C) Malignant cells use extracellular matrix receptors to migrate and enter local vasculature. (D) Tumor cell extravasate out of vasculature and invade the target organ.

The more tumor cells shed into the blood stream, the higher the incidence of metastases. The link between angiogenesis and metastasis has been validated in many studies by using angiostatic molecules [8,9]. Furthermore, the vascular density of tumors was shown to be an accurate correlate of metastatic potential [10]. Acquisition of all of these traits enables a cancer cell to metastasize.

Examples of common molecular markers that are used in evaluating the gender-related malignancies are listed in Table 1. Markers are listed for each tumor by category of acquired metastatic trait. These markers are used for diagnosis and also as prognostic indicators of aggressive disease. Most of the tumors share similar markers; aggressive tumors have acquired many, if not all, of the traits that are listed (see Table 1).

### Patterns of pulmonary metastasis

It has long been recognized that certain tumors preferentially metastasize to certain organs. For ex-

ample, prostate cancer frequently metastasizes to the bone, whereas metastatic melanoma is frequently found in the lung. This can be explained, in part, by the architecture of the circulatory system. In the case of melanoma, the pulmonary circulation is the first capillary bed that is encountered by melanoma cells during the metastatic process. In addition, certain cancers show selective tropism; all organs have specific “area codes” and different tumors have a predilection for different area codes. Prostate cancer is a good example of this “address” system. It seems that prostate cancer prefers to metastasize to bone because specific adhesion molecules that are present on stromal bone cells are preferentially recognized by prostate tumor [2].

Metastasis to the lung can take many forms. These include solitary and multiple parenchymal nodules, lymphangitis carcinomatosa, tumor emboli, endobronchial metastasis, and pleural effusion. These patterns can occur by direct extension or by systemic spread. In the case of systemic spread, tumor cells lodge in the lung as the vessel lumen narrows and

Table 1

A list of various markers that have been used in studies for prognosis and diagnosis of the four gender related tumors

Tumor marker	Breast cancer	Ovarian cancer	Cervical cancer	Uterine cancer
Growth factors				
Progesterone receptor	+			+
Estrogen receptor	+			+
Her2/neu	+	+	+	+
Epidermal growth factor Receptor	+	+		+
Cathepsin-D	+			
K-ras		+	+	+
CSF-1		+		
HPV e6,7			+	
IL-6		+		
TGF- $\beta$		+		
CA19-9				+
CA-125		+		+
Cell division/cycle				
BRCA-1,2	+	+		
S-phase	+	+	+	+
Ploidy	+	+	+	+
Antiapoptosis				
p53	+	+	+	+
Bcl-2	+			
Angiogenesis/invasion				
$\beta$ 1 Integrin		+		+
CD44		+		+
Microvessel density	+	+	+	
VEGF	+	+	+	
MMP-2		+	+	
TIMP-1,2			+	

*Abbreviations:* BRCA, breast cancer susceptibility; CA, carbohydrate antigen; CD, cluster determinant; CSF-1, colony stimulating factor-1; HPV, human papilloma virus; MMP, matrix metallo-proteinase; TGF, transforming growth factor; TIMP, tissue inhibitor of metalloproteinase.

*Data from* Devita V, Hellman S, Rosenberg S. Cancer: principles and practice of oncology, vol. 2. Philadelphia: Lippincott; 2001.

grow into the parenchyma or along the pulmonary lymphatics. Venous blood is filtered by the lung, which makes it a frequent site of metastasis [11].

#### *Parenchymal nodules*

Parenchymal nodules are the most frequent representation of pulmonary metastasis. These nodules are usually multiple, peripheral, and basal in anatomic distribution and correspond with areas of increased blood flow in the lung [12]. They may be symmetric, variable in size or miliary, or even present as large, well-defined cannonball-like masses. Symmetric, equally-sized nodules likely reflect a single embolic shower of tumor emboli, whereas nodules of variable size may reflect embolic events that occurred at different time periods [11].

Solitary nodules represent a distinct form of pulmonary metastasis that is rare. In one study of solitary pulmonary nodules, 11% had an extrapulmo-

nary source [13]. By convention, patients who present with a solitary pulmonary nodule and a history of nonpulmonary cancer often have it excised because the nodule may represent a primary bronchogenic carcinoma. Resection of solitary metastatic nodules can be curative and is reviewed in greater detail.

#### *Lymphangitic carcinomatosis*

When tumor spreads by way of the lymphatic system, it does so in two ways. Tumor spread initially can be hematogenous and spread to the interstitial space and then the lymphatics or retrograde from the lymph node toward the periphery [14]. Radiographically, lymphangitic carcinomatosis appears similar to interstitial edema with thickened bronchovascular markings and septal Kerley B lines [15]. Lymphangitic carcinomatosis may be focal or diffuse. Approximately 40% of patients who have lymphangitic carcinomatosis have concomitant pleural effusion or

mediastinal adenopathy [15]. Bronchoscopy with transbronchial biopsy frequently is successful in making the diagnosis because of the proximity of lymphatics to the peribronchial space [16].

#### *Endobronchial obstruction*

Although endobronchial and tracheal metastases have been reported commonly in autopsy studies, clinically manifest disease is far less common [17]. Metastasis to the airways occurs most often by direct extension from adjacent parenchymal or mediastinal tumor and rarely by hematogenous spread. Patients typically present with cough, dyspnea, wheeze, or hemoptysis [18]. Radiographically, the lesions usually are occult on plain films, but may include atelectasis distal to the obstruction, focal air trapping (mosaic pattern), or postobstructive pneumonia. CT scan can detect endobronchial disease with greater sensitivity than plain films [19].

#### *Pleural disease*

Pleural effusion is a common finding in metastatic disease and can occur through a variety of mechanisms. It can occur by way of tumor spread along the peripheral lymphatics; in this situation, it frequently is associated with parenchymal disease. Pleural disease also can spread through the diaphragm by way of lymphatic channels [20]. It is critical to appreciate that the presence of a pleural effusion in the setting of cancer is not always indicative of pleural metastatic disease. For example, serous nonmalignant effusion can occur secondary to obstruction of intrathoracic lymphatics. Exudative and bloody pleural effusion is much more likely to represent metastatic involvement [11]. Pleural fluid cytology often can establish the presence of malignant cells within the pleural space, although the highest yield occurs with direct observation of the pleura at thoracoscopy.

The patterns of pulmonary metastases for four gender-related malignancies (breast, ovarian, cervical, and uterine cancer) are discussed below. The frequency of the patterns of metastasis is represented in Table 2. These data have been collated from the largest published trials of pulmonary metastases in this defined subset of patients. Data from small case series and case reports were not included, unless otherwise noted.

### **Breast carcinoma**

Breast cancer is the most common malignancy of women. It is the second leading cause of cancer-related death among women, after lung cancer [21]. Recent studies suggest that its incidence is on the rise [22]. Increased awareness and improved screening mammography likely have contributed to the increase in newly-diagnosed disease. Metastatic breast cancer remains common and currently is considered to be incurable, although surprisingly long survival times can be achieved with therapy of metastatic disease. The spread of breast cancer can be localized and extend through the lymphatic system, or can be systemic by way of the bloodstream. The pulmonary manifestations of metastatic breast cancer are influenced by the method of tumor spread. Pulmonary complications of treatment have been reviewed extensively and will not be discussed here. Traditional staging strategies offer some predictive value in metastatic disease but remain crude and imprecise [23]. Recent evidence suggests that the patient's smoking status can affect the likelihood of thoracic metastases [24].

Breast cancer has two main histologic variants: infiltrating ductal carcinoma (IDC) and infiltrating lobular carcinoma (ILC). Although there are conflicting reports regarding survival in metastatic breast cancer, several studies have demonstrated distinct

Table 2  
Frequency of metastatic patterns among the four gender-related cancers

Tumor	Parenchymal nodules	Solitary nodules	Pleural disease	Endobronchial disease	Lymphangitic carcinomatosis
Breast	++++	++	++++	+	++
Uterine	+++	++	+	+/-	+
Ovarian	++	+	+++	+/-	++
Cervical	+++	++	++	+	+

++++ 50–80% (most common cause of particular pattern).

+++ 30–60%.

++ 10–30%.

+ 1–5%.

+/- case reports only.

metastatic patterns for each histology [25–27]. In a review of 1238 patients who had metastatic disease, IDC was associated with lung, pleural, and brain metastases, whereas ILC more commonly metastasized to the bone marrow and peritoneum [26]. Recurrent or metastatic breast cancer most commonly presents as local/regional lymph node metastases but can, and often does, present as metastasis at distant sites such as bone, skin, lung, brain, meninges, and the peritoneal surface. Although tumor biology dictates metastatic behavior, a reliable measurement of such tumor biology is still lacking. Clinically, the most useful indicator of tumor biology is the cancer stage at the time of diagnosis. These data often are used as a prognostic indicator. Using the Surveillance, Epidemiology, and End Results Program data, tumor size and lymph node status were correlated with survival. This study evaluated the 5-year survival data in 24,740 cases of breast cancer; it was concluded that tumor diameter was predictive of survival and lymph node involvement [23]. The study also demonstrated that disease progression to distant sites can occur without axillary lymph node involvement. Additionally, the study identified a small subset of patients who had a tumor that had metastasized to four or more nodes at the time of initial diagnosis. This subset of patients demonstrated a pattern of aggressive tumor behavior that began early in their disease.

Metastatic patterns of breast cancer are variable. The thorax is the most common place for recurrent disease after local/regional sites and bone [28]. At autopsy, 57% to 77% of patients who had breast cancer have evidence of lung metastasis, usually multinodular [29,30]. In addition to parenchymal disease, breast cancer frequently involves the lymphatics, pleura, and the tracheobronchial tree. In a retrospective study of patients who had recurrent disease, almost 40% of patients who had metastatic breast cancer had pulmonary involvement. More than 60% of patients had recurrence to a single site—typically bone—and only 8% had solely thoracic involvement. This study demonstrated that thoracic involvement in recurrent disease most often was part of multiple systemic metastases. The relative frequency and type of pulmonary involvement is summarized (see Table 2).

#### *Parenchymal metastasis*

The most common thoracic manifestation of metastatic breast carcinoma involves the lung parenchyma. Initially, many patients are asymptomatic, but eventually all develop respiratory complaints [31]. Multiple, bilateral, well-circumscribed nodules

were the most common thoracic presentation in several case series [28,29,32]. Kamby et al [28] reported that 71% of patients who had metastatic disease in the thorax had bilateral, round nodules. The nodules tended to vary in size, to predominate in the lower to mid lung zones, and were more often peripheral than central [12].

There are case reports of metastatic lung nodules cavitating in patients who had breast cancer. These examples are rare; most examples of lung cavitation occurred with squamous cell cancer of the lung, head, and neck or with genitourinary cancer of women. Cavitation occurs when central desquamation or central necrosis of the tumor takes place because the cancer has outgrown its blood supply. Mermershtain and colleagues [33] described a patient who developed cavitation of a metastatic breast cancer lung nodule after treatment with herceptin and taxol. The investigators speculated that the cavitation occurred as a result of treatment.

#### *Pleural effusion*

Metastatic breast cancer is a common cause of malignant pleural effusion. Pleural effusion that occurs in the setting of malignant disease is due to a variety of mechanisms. Metastases can involve the pleura directly or obstruct pleural lymphatics by involving mediastinal lymph nodes and interrupting lymphatic drainage. Endobronchial obstruction can lead to “trapped lung” physiology and the presence of a transudative effusion [34]. In cases where the pleural effusion is caused by mediastinal lymph node obstruction without pleural surface involvement, the pleural effusion is best termed “paramalignant” rather than malignant. In contrast to malignant effusions, paramalignant effusions are less acidotic, less cellular, have lower levels of lactate dehydrogenase, and do not contain malignant cells [35]. Published series of pleural effusions secondary to metastatic breast cancer do not necessarily distinguish between malignant and paramalignant effusions.

Several investigators showed that metastatic breast cancer is one of the top three causes of malignant effusion [34]. Often, the tumor also spreads systemically and involves the liver at the same time [36]; however, spread of tumor also can occur directly through the chest wall to the parietal pleura. Fentiman et al [37] reviewed 105 patients who had pleural effusions that were due to metastatic breast cancer. Most patients had a unilateral primary tumor; 50% developed an ipsilateral effusion, 40% developed a contralateral effusion, and 10% developed bilateral effusions [37]. Pleural effusion was the first presen-

tation of breast cancer recurrence in 43% of the patients. Moreover, in patients who had multifocal metastasis, only 2% demonstrated hepatic involvement. By contrast, in an analysis of 122 patients who had breast cancer–related pleural effusion, Raju and Kardinal [38] identified nearly 50% of patients who had ipsilateral effusions and concurrent chest wall involvement. Both of these studies demonstrate the frequency of thoracic manifestation of metastatic disease that occurs by way of local spread.

Most studies that have attempted to address mode of spread were done before modern therapeutic approaches. Accordingly, the true etiology in patients who were treated with modern chemotherapy is not known. Autopsy studies revealed that 50% to 75% of patients who died from breast cancer had pleural involvement [39]. More recent studies that related radiologic manifestation of recurrent metastatic breast cancer that presented as pulmonary disease showed a 40% incidence of pleural effusion [32]. Kamby et al [28] found that only 10% of patients who presented with a first-time recurrence of breast cancer had pleural involvement. As with parenchymal lung recurrence, patients who had pleural disease often had disease at other sites. These data, taken together with the studies by Fentiman et al [37] and Raju and Kardinal [38] imply that the tumor biology of breast cancer recurrence is different from that of initially metastatic breast cancer. This suggests that a patient who has a single-site breast cancer recurrence has a different prognosis from that of a patient who presents with a new diagnosis of breast cancer that has metastasized already. The relative differences between recurrent breast cancer with thoracic metastasis and initially metastatic breast cancer have not been studied extensively.

#### *Pulmonary lymphangitis*

Lymphangitic carcinomatosis another common manifestation of metastatic breast cancer. Several different mechanisms have been proposed. The current belief is that tumor spreads hematogenously to the lungs and then penetrates the local endothelium, because tumor typically is present in the interstitium that surrounds the lymphatics [11]. The involvement most often is diffuse, but can be focal. In cases of focal disease, the etiology is likely hematogenous. Lymphangitic carcinomatosis can be silent radiologically, but when present, usually manifests as a reticulonodular pattern. The typical radiographic findings on a chest radiograph (CXR) are patchy, coarse, interstitial opacities that can be associated with a pleural effu-

sion. High-resolution CT has enhanced the sensitivity of these findings [40].

In an autopsy study of patients who had breast cancer, 24% had lymphangitic involvement. The majority had axillary node involvement [41]. Other investigators reported lymphangitic spread in more than 80% of autopsy cases [29]. In addition, Kamby et al [28] showed that approximately 5% of their patients who had recurrent breast cancer had radiologic evidence of pulmonary lymphangitis. A smaller review of radiographic patterns in patients who had breast cancer with known thoracic recurrence revealed that 18% of patients had evidence of lymphangitis. Older studies that were performed before the current therapeutic era suggested that the incidence of lymphangitis in all patients who had breast cancer is approximately 9% [42].

#### *Tumor emboli*

All patients who have cancer are at risk for venous thromboembolism; patients who have breast cancer are no exception. The risks of thromboembolic disease have been reviewed extensively and are not discussed here; however, the phenomenon of tumor microemboli within the pulmonary vascular is not uncommon in breast cancer. An autopsy review of 100 patients who had breast cancer revealed the presence of microscopic emboli in 17% of cases [43]. Patients typically complain of dyspnea that has worsened over several weeks, have evidence of cor pulmonale, and have abnormal ventilation perfusion scans [44,45]. A case of a large pulmonary tumor embolus that was diagnosed by endovascular biopsy was reported [46].

#### **Ovarian carcinoma**

Ovarian cancer is not as common as breast cancer; however, its lower incidence is offset by a higher fatality rate. Approximately 24,000 new cases are diagnosed each year, with approximately 13,900 associated deaths [47]. Most patients present at an advanced stage, frequently with peritoneal involvement [48]. Risk factors for this disease include family history, nulliparity, infertility, and the use of fertility drugs, such as clomid [49,50]. All ovarian cell types have the potential for malignancy. Of the three general cell types (germ cell, stromal cell, epithelial cell), epithelial cells are the most likely to transform into a malignancy [48]. Epithelial ovarian cancer is further subdivided into four distinct cell types: papillary serous, endometrial, clear cell, and mucinous; papil-

lary serous is the most common type [51]. There is a higher incidence of clear cell histology among Japanese women [52]. Tumors that originate from a non-epithelial cell type tend to occur in younger women, have a better prognosis, and may be benign [3].

Stage IV ovarian cancer implies that the tumor has spread beyond the peritoneal space. Although stage IV disease is not common—it occurs in 10% to 15% of cases—it is associated with a particularly poor outcome [3]. The pleural space is the most frequent site of extraperitoneal involvement [53]. Predictors of poor outcome include poor performance status, sub-optimal surgical debulking, and histology; mucinous and clear cell histology are associated with a worse prognosis [52].

The frequency of pulmonary involvement in patients who were diagnosed with ovarian cancer ranged from 21% to 45% and is as high as 70% in autopsy studies [51,53]. Patients typically have pleural involvement, but parenchymal, endobronchial, and embolic phenomena have been described [51,53,54]. Right-sided ovarian cancer was more likely to produce thoracic metastases. Many studies have highlighted the lack of symptoms, particularly respiratory, in patients who present with advanced disease [51,53]. In one study of patients who had pulmonary involvement, only 3% had respiratory symptoms [53].

#### *Pleural disease*

In a large review of malignant pleural effusions, ovarian carcinoma was the fourth most common etiology after lung, lymphoma, and breast cancer [34]. Among thoracic metastases, pleural effusion is present in 77% and represents an estimated 31% to 40% of all extraperitoneal metastases [52,55]. The presence of a pleural effusion does not, however, always represent a malignant etiology to the effusion. Many studies that reported on the presence of pleural effusions in ovarian cancer did not differentiate cytology positive from cytology negative effusions [53]. In some studies, patients in whom pleural effusion was the only manifestation of metastasis may have a survival advantage over patients who have visceral involvement [56]. Similarly, in a retrospective review of patients who presented with peritoneal or liver involvement without evidence of primary ovarian carcinoma, such patients showed improved survival if they had a pleural effusion rather than other visceral involvement [57]. Taken together, these observations imply a different tumor biology for ovarian carcinoma that is metastatic to the pleura only. In general, pleural disease rarely is the only site of metastatic disease [53].

Meig's syndrome describes a benign ovarian fibroma with associated ascites and pleural effusion. It is important to distinguish Meig's syndrome from malignant ovarian cancer because of obvious prognostic differences [58]. Pseudo-Meig's syndrome refers to nonovarian tumors that also present with ascites and pleural effusion and typically are benign [59].

#### *Parenchymal disease*

Parenchymal disease represents the second most frequent presentation of thoracic metastasis in ovarian cancer. Solid parenchymal disease has been reported in 3% to 10% of extraperitoneal malignancies [52,53]. Despite the lack of evidence for a survival advantage in patients who have solid parenchymal disease, resection for discrete lesions was performed in patients who had recurrent ovarian cancer [60]. Multi-nodular lung disease and alveolar hemorrhage also have been reported in patients who had nonepithelial ovarian carcinoma [61,62]. Nodal involvement is part of the spectrum of thoracic involvement; it occurs in a reported 2.5% of thoracic lesions [53]. Lymphangitic involvement, however, is described rarely with ovarian carcinoma. It is reported to be the principal thoracic lesion in only 1.8% of cases and frequently is associated with negative CXR findings [53].

#### *Endobronchial disease*

Metastatic disease that involves the tracheobronchial tree is extremely rare in patients who have ovarian cancer. Evidence of this process exists in the literature as a handful of case reports only [54,63]. The cell type that is involved in tracheobronchial metastasis is typically papillary or serous cystadenocarcinoma, although a granulosa cell tumor also was described [54]. In some cases, the presentation of tracheobronchial metastases occurred several years after the original diagnosis [64,65]. Patients who had endobronchial disease also tended to be younger with a more favorable course [54].

#### **Uterine and cervical carcinoma**

Uterine and cervical cancers when combined are more common than ovarian cancer, but are less likely to present as disseminated disease [47]. Metastatic disease is clinically symptomatic in 5% to 10% of cases, but is detected more frequently in autopsy studies [66]. Distant metastasis frequently is associated with intra-abdominal spread. Generally, multiple pulmonary nodules are more common than solitary

nodules [67]. Typically, patients present with metastases early in the course of their disease and outcomes are poor [67].

Cervical cancer has the lowest incidence of the gynecologic cancers. Because of effective screening programs that detect precancerous lesions, the incidence of invasive cervical cancer has declined dramatically [47]. Most patients who have cervical cancer present in the fifth and sixth decades of life, whereas precancerous lesions are detected in women who are younger than 40 years of age. Cervical cancer is associated closely with human papilloma virus infection [3]. Accordingly, risk factors for the disease include beginning sexual intercourse at an early age, multiple sexual partners, smoking, and an immunosuppressed state [68]. The most common histology is squamous cell carcinoma followed by adenocarcinoma. Rarely, small cell carcinoma is reported and usually is associated with an aggressive metastatic potential [3].

The incidence of pulmonary metastasis in patients who have carcinoma of the uterine cervix is rare. In one Japanese study, the incidence was 6.1% among 817 patients [69]. An earlier study with a similar design found an incidence of 7% to 9% in patients who were admitted to the hospital with a new diagnosis of cervical cancer [66]. By contrast, many autopsy studies have revealed a much higher rate of pulmonary metastasis [70]. Pulmonary involvement is associated with cancer stage and tissue histology. Although squamous cell is the most common cell type, adenocarcinoma and poorly differentiated carcinoma have a much higher likelihood of lung involvement [69,71]. The most common thoracic manifestation consists of multiple pulmonary nodules; however, mediastinal disease and pleural effusions are not infrequent [66,69,72]. Lymphangitic carcinomatosis, solitary pulmonary nodules, and endobronchial disease occur rarely [69,72,73].

#### *Parenchymal disease*

Most studies that have evaluated the incidence and pattern of lung metastasis in cervical carcinoma have been retrospective in nature. Accordingly, the incidence and type of thoracic metastasis in these studies is affected by the method in which the patients were screened for advanced disease. Most studies relied on screening CXRs or specific respiratory symptoms. In one study, multiple pulmonary nodules were present in 46% of patients who had thoracic metastasis [69]. In this same study, a pneumonia-type pattern favored adenocarcinoma, whereas a reticular pattern was more commonly representative of squa-

mous cell carcinoma. Tellis et al [66] also reported that 13 of 22 patients (59%) exhibited multiple pulmonary nodules as the main radiographic finding. Another study reviewed patients who had squamous cell cervical carcinoma who died with evidence of thoracic metastases. Multiple pulmonary nodules was the most typical pattern and was seen in 71% of patients [72]. Nodules ranged in size from 0.5 cm to 7.0 cm and a significant percentage showed cavitation. Other studies demonstrated that cavitating nodules frequently are a part of the spectrum of metastatic disease in cervical carcinoma. Sostman et al [71] found that adenocarcinoma was associated solely with multiple nodules, whereas squamous cell carcinoma had pulmonary nodules in 67% of cases of metastatic disease.

#### *Pleural disease*

Pleural effusions represent a significant proportion of thoracic metastasis in cervical carcinoma. Early autopsy studies reported pleural metastasis in 11% of cases. The incidence of pleural effusion in patients who had newly-diagnosed cervical carcinoma or in those who were followed over several years has ranged from 9% to 44% [69,71,72]. Sostman and Matthay [71] found that pleural effusions were related to histology; squamous cell carcinoma was associated more commonly with a pleural effusion than adenocarcinoma. It is rare for a pleural effusion to be the sole manifestation of metastatic disease [71,72].

#### *Lymphangitic carcinomatosis and endobronchial disease*

Lymphangitic carcinomatosis and endobronchial metastasis in cervical carcinoma are rare, with only a handful of case reports in the literature [73–75]. Shin et al [72] reviewed squamous cell cervical carcinoma metastatic to the lung and found that lymphangitic carcinomatosis or endobronchial obstruction was present in only 3% to 5% of cases. By contrast Sostman and Matthay [71] and Tellis and Beechler [66] found no cases of either. Imachi et al [69] reported that in the few patients who had lymphangitic carcinomatosis, many had positive sputum cytology.

Uterine cancer is the most common gynecologic malignancy and accounts for almost 6500 deaths annually [47]. Most uterine cancers are derived from the endometrium, although sarcomas occur rarely. Risk factors are associated with prolonged estrogen exposure, such as nulliparity, early menarche, late menopause, obesity, and tamoxifen use [76]. Estradiol-secreting ovarian tumors can be associated with



synchronous uterine malignancy. Typically, patients present with complaints of postmenopausal bleeding. Consequently, most patients present in an early stage of disease [76].

Compared with cervical cancer, cancer of the uterus has a low incidence of pulmonary metastasis. In one study that simultaneously reviewed metastatic cervical and endometrial carcinoma, the incidence of pulmonary metastasis was 5.1% and 3.6%, respectively [67]. As seen in other malignancies, the autopsy-based rate of pulmonary metastasis is much higher [77]. Because most patients present with early stage disease, pulmonary metastasis frequently is diagnosed as a recurrence during the course of initial treatment. Most pulmonary metastases occur within 30 months and frequently are associated with other sites of spread [67]. Other studies have reported that up to 34% of patients presented with pulmonary metastasis as the only site of recurrence [78]. Patients who have metastases that are confined to the lungs had a higher response to chemotherapy [79].

Few studies have focused solely on the patterns of thoracic involvement in metastatic uterine cancer. One large study reviewed 1550 patients who were admitted with a diagnosis of uterine cancer over a 27-year experience. The study identified 90 (5.8%) patients who had pulmonary involvement, with varying histopathology [78]. Multiple pulmonary nodules of various sizes were the most common radiographic abnormality and were present in 72% of the 90 patients. Older series similarly reported multiple bilateral nodules as the primary pattern of thoracic metastasis [79]. Solitary pulmonary nodules are not as common, and represent between 12% and 18% of all thoracic metastases [78,79]. Similarly, the incidence of lymphangitic carcinomatosis, endobronchial disease, and cavitating nodular disease has been reported rarely in clinical series of metastatic uterine malignancy [67,78,79].

#### *Pleural disease*

Of all the gender-related malignancies that are covered in this article, uterine cancer is the least likely to demonstrate pleural disease. In a study by Bouros et al [78], only 6 of the 90 patients who had pulmonary metastasis manifested a pleural effusion. Of those patients, 50% had concurrent parenchymal disease. In an older review of 33 patients who had pulmonary metastasis, only 2 had evidence of pleural involvement [79]. D'Orsi et al [67] also reported that pleural disease was rare among patients who had pulmonary metastasis. They found that only 5 of 42 patients had a pleural effusion, all of whom had

concurrent parenchymal disease. Again, a few reported cases of “pseudo-Meig's syndrome” are noted, whereas patients who have uterine leiomyoma present with ascites and pleural effusion [80–82].

#### **Survival and prognostic factors**

Although conventional wisdom dictates that metastatic cancer carries a morbid prognosis, differences exist among various cancers; however, in general, the prognosis is poor in most cases. One of the likely reasons is that pulmonary metastases rarely are isolated and also reflect a high tumor burden. Solitary pulmonary nodules, however, show different traits.

Solitary pulmonary nodules can occur in all four of the gender-related tumors that are discussed in this article. Of the four cancers, ovarian carcinoma is the only one that does not demonstrate a favorable outcome with surgical resection [60]. There is compelling evidence among the other three tumor types to suggest that solitary pulmonary nodules demonstrate a separate tumor biology from other forms of pulmonary metastasis.

Solitary pulmonary nodules are not as common as multiple nodules. In contrast to multiple pulmonary nodules, Kamby et al [28] found a solitary pulmonary lesion in only 27% of patients who had thoracic disease from the first recurrence of breast cancer. In another review of 1416 patients who had breast cancer, the incidence of solitary pulmonary nodules was 3% [83]. One of the difficulties in evaluating solitary pulmonary nodules is establishing if the lesion is metastatic or a primary bronchogenic tumor. Casey et al [83] found that 52% of patients who had breast cancer and presented with a solitary pulmonary nodule had primary lung cancer. Although no randomized trials exist, pulmonary metastectomy has been proposed as a potential treatment modality. Freidel et al [84] reported the largest series of patients who underwent pulmonary metastectomy for breast cancer. Disease-free survival (DFI) of at least 36 months and complete resection were associated with a 5-year survival rate of 45%, a 10-year survival rate of 26%, and a 15-year survival rate of 21%. They concluded that in this subset of patients, a 15-year survival of 21% argues that metastatic breast cancer is not incurable [83].

Uterine and cervical cancers that recur or present as solitary pulmonary masses also were studied with regard to surgical resection. A recent study reviewed 60 patients who had uterine cancer and 22 patients who had cervical cancer; 25 patients underwent pulmonary resection. Among patients who had uterine

cancer, three or fewer metastases and a DFI of greater than 1 year were associated with improved survival. By contrast, Levenback et al [85] reported a 50% 5-year survival rate among patients who had leiomyosarcoma. Patients who had uterine adenocarcinoma seemed to fare better than patients who had leiomyosarcoma [86]. The median survival of 36 months for patients who had cervical cancer was similar to that for other studies of surgical metastectomy for cervical cancer [86,87].

Despite presenting at a favorable stage, some patients progress to metastatic disease over a short interval. These patients represent a poor prognosis profile that is not predicted reliably by current staging protocols. Early efforts focused on single elements as prognostic indicators of aggressive cancer. Many of the markers (see Table 1) have been evaluated as independent predictors of advanced disease; however, with current molecular biology techniques, it is possible to evaluate thousands of genes simultaneously. Of the four gender-related malignancies, the greatest amount of research in this area has been done on breast cancer. A recent study used gene microarray analysis on primary breast tumors of 117 young patients. This strategy identified a molecular signature for the poor prognosis profile [88]. Genes that regulate cell cycle, invasion, metastasis, and angiogenesis made up the poor prognosis molecular signature.

## Summary

Metastatic, gender-related, nonpulmonary malignancy can exhibit different patterns of tumor spread and different natural histories. The pulmonologist often is involved in the diagnosis and treatment of patients with pulmonary metastases; and a thorough understanding of the patterns of metastasis from these cancers can help to guide appropriate work-up and therapy. In the case of solitary pulmonary metastases, a surgical approach may not be unreasonable based on current clinical evidence. Knowledge of the clinical spectrum of these diseases, together with their unique molecular biology, may improve the clinical care of patients.

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