Malignancies in Pleural, Peritoneal, and Pericardial Effusions

A 17-Year Single-Institution Review From 30 085 Specimens

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• ***Context.***—**The incidence and types of malignancies in effusion cytology are largely limited to studies performed in the 1970s through the 1990s.**

Objective.—**To examine how the incidence of different types of malignancies in effusions has changed with time.**

Design.—**A computerized search for fluid cytology from 2000 through 2016 (database included age, gender, cytologic diagnosis, and type of malignancy) was performed, and all cases were reviewed.**

Results.—**Of 30 085 effusion specimens, 3285 (11%) were positive for malignancy (2175 pleural, 955 peritoneal, and 155 pericardial). Of those, 1023 (31%) had known primary sites (648 pleural, 267 peritoneal, and 108 pericardial). Malignancy was more common in females than males in both pleural (15% versus 9%) and peritoneal (14% versus 5%) effusions ($P < .001$). The most common metastatic tumors in pleural fluid were lung for males and breast for females; in peritoneal fluid, hematolymphoid for males and Müllerian tumors for females; in pericardial fluid, lung for both genders. Among invasive mammary carcinomas, lobular carcinoma tended to metastasize to peritoneal fluid, whereas ductal carcinoma tended to metastasize to pleural fluid ($P < .001$). Plasma cell neoplasms metastasized to pleural and pericardial but not peritoneal fluid ($P = .002$).**

Conclusions.—**Although pulmonary and Müllerian tumors continue to be the most common origin of metastasis in pleural and peritoneal fluid for males and females, respectively, the frequencies for other malignancies have changed. Familiarity with the more common sites of metastasis in effusion cytology is important, especially in patients with unknown primary, as this will be valuable in judicious triaging of specimens for ancillary studies.**

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Effusions in body cavities, most commonly pleural, peritoneal, and pericardial, occur in a variety of clinical settings. Effusion samples provide important information for both diagnostic and therapeutic purposes. Existing data on the incidence and types of malignancies in serous fluids (pleural, peritoneal, and pericardial effusions) are largely limited to studies performed in the 1970s through the 1990s.[1–7] Given the large volume of specimens we receive in our institution, our goal was to perform the largest and most comprehensive study of malignant effusion fluids during a period of 17 years, and examine how incidences of the different types of malignancies have changed with time.

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DESIGN

This study was performed after an approval from the Cleveland Clinic Institutional Review Board (Cleveland, Ohio) was obtained.

Cases were selected after conducting a retrospective natural language search using our laboratory information system (Cerner Corporation, Kansas City, Missouri). The search was limited to cytology cases from pleural, pericardial, and peritoneal fluids from 2000 to 2016. The database included the cytopathology case number, age, gender, cytologic diagnosis (negative, atypical, suspicious, or positive for malignancy), and classification of malignancies.

When available, the origin of the primary tumor was included in the results. For cases that were positive for malignant cells, the primary site was determined based on known preexisting malignancies stated on the clinical history or from prior pathology reports, cytomorphologic features, and immunohistochemical stains performed on cell blocks. Cases reported as atypical or suspicious for malignancy were excluded from the study. Chi-square analysis was used for categorical data. A P value probability threshold of $<.05$ was considered statistically significant.

Table 1. Distribution and Diagnoses of Pleural, Peritoneal, and Pericardial Effusion Specimens From 2000 to 2016

Type of Effusion Fluid	No. (%) of Cases	
	Male	Female
Pleural (total 18 894; 63%)	9903 (64)	8991 (61)
Positive for malignancy	863 (9)	1312 (15)[a]
Atypical or suspicious	790 (8)	770 (9)
Negative	8250 (83)	6909 (76)
Peritoneal (total 9906; 33%)	4881 (32)	5025 (34)
Positive for malignancy	262 (5)	693 (14)[a]
Atypical or suspicious	196 (4)	236 (5)
Negative	4423 (91)	4096 (81)
Pericardial (total 1285; 4%)	627 (4)	658 (5)
Positive for malignancy	67 (11)	88 (13)[b]
Atypical or suspicious	31 (5)	27 (4)
Negative	529 (84)	543 (83)
Total = 30 085 specimens	**15 411** (51)	**14 674** (49)

[a] χ^2 $P < .001$.
[b] χ^2 $P = .14$, not statistically significant.

RESULTS

From 2000 to 2016, a total of 30 085 pleural, peritoneal, and pericardial effusion specimens were processed in our laboratory. The patients' age range was 3 to 97 years (median, 65 years). Roughly equal proportions of patients were male (15 411; 51%) and female (14 674; 49%). In both genders, the majority of the effusion specimens were pleural (total 18 894 [63%]; 9903 male, 8991 female), followed by peritoneal (total 9906 [33%]; 4881 male, 5025 female), and pericardial (total 1285 [4%]; 627 male, 658 female). Most of these effusions were negative for malignancy. There were 3285 cases (11%) classified as positive for malignancy (pleural 2175 [66%], peritoneal 955 [29%], pericardial 155 [5%]). Interestingly, malignant effusions were significantly more common in females than males in both pleural (male 863 [9%] versus female 1312 [15%], $P < .001$) and peritoneal (male 262 [5%] versus female 693 [14%], χ^2 $P < .001$) effusions. These findings are summarized in Table 1.

Of the 3285 cases that were positive for malignancy, 1023 (31%) had known primary malignancies (pleural 648 [63%], peritoneal 267 [26%], pericardial 108 [11%]). There were more females in this group (612; 60%) than males (411; 40%). For the remaining cases, the pathologists were able only to discern malignancy or place the case in a broad category, for example adenocarcinoma, but could not go further because of insufficient materials for further ancillary studies, lack of clinical history of a primary tumor site, or nonspecific morphology and/or immunohistochemical staining patterns.

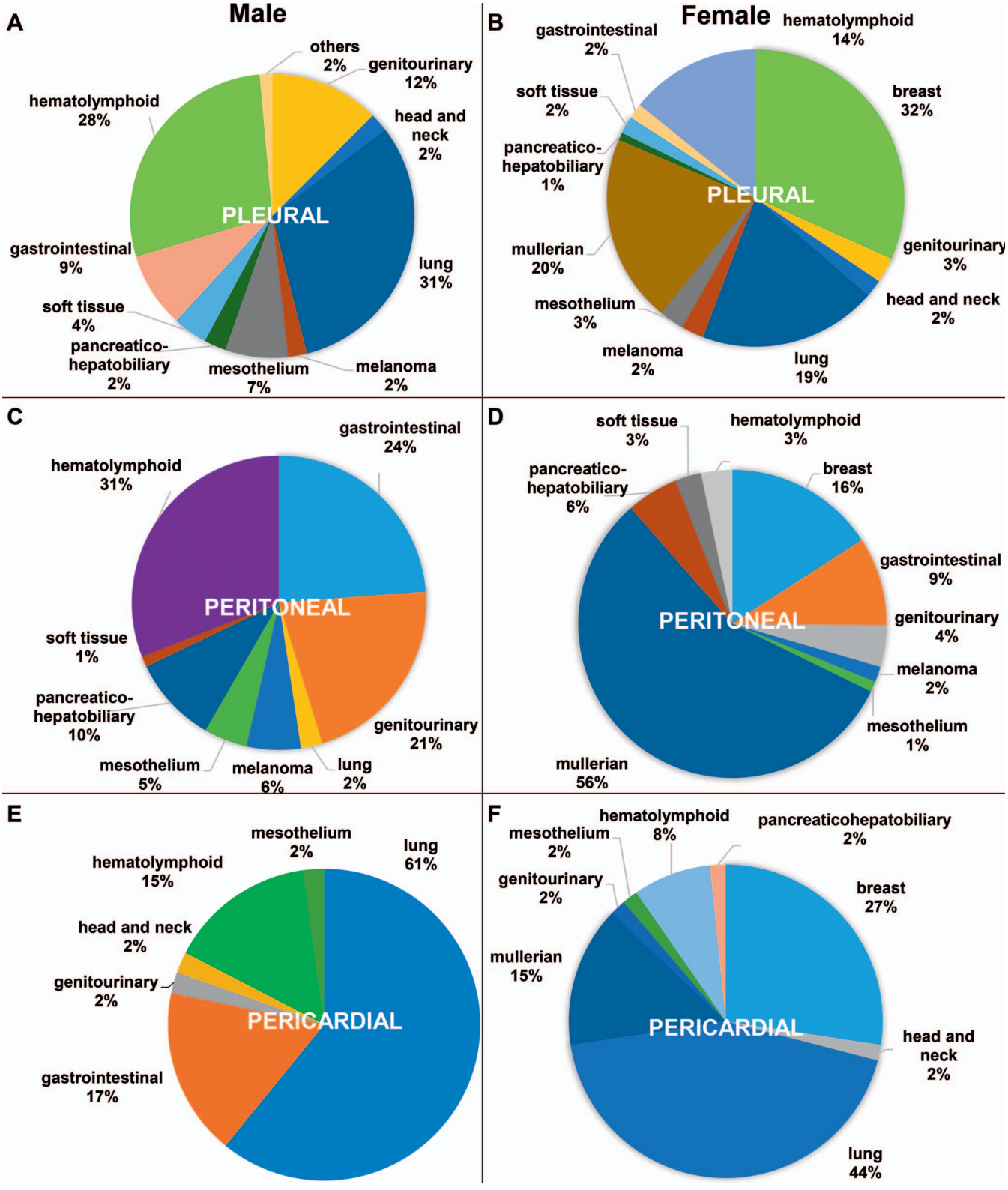
In pleural effusions, the most common metastatic tumors in males were lung (88 of 281 [31%]; most commonly adenocarcinoma, followed by small cell carcinoma), hematolymphoid (79 of 281 [28%]; most commonly lymphoma, followed by plasma cell neoplasms), and genitourinary (35 of 281 [12%]; most commonly renal cell carcinoma, followed by prostatic adenocarcinoma) (Figure, A; Table 2). In females, the most common metastatic tumors were breast (116 of 367 [32%]; most commonly invasive ductal carcinoma [IDC], followed by invasive lobular carcinoma [ILC]), Müllerian (75 of 367 [20%]; most commonly tubo-ovarian, followed by endometrial carcinoma), and lung (71 of 367 [19%]; most commonly adenocarcinoma) (Figure, B; Table 3).

Table 2. Distribution of Metastatic Tumors in Malignant Pleural Effusions (in Descending Order of Frequency) in Males

Primary Tumor Origin	No. (%) of Cases
Lung	88 (31)
Adenocarcinoma	66
Small cell carcinoma	10
Squamous cell carcinoma	8
Large cell neuroendocrine	2
NSCLC, NOS	2
Hematolymphoid	79 (28)
Lymphoma	47
Plasma cell neoplasm	22
Leukemia	10
Genitourinary	35 (12)
Kidney	22
Prostate	9
Urothelium	4
Gastrointestinal	24 (9)
Esophagus/GE junction	13
Stomach	6
Others (colon, anus, appendix)	3
NOS	2
Mesothelium	20 (7)
Soft tissue	11 (4)
Ewing sarcoma	3
Synovial sarcoma	2
EHE	2
Osteosarcoma	1
Chondrosarcoma	1
Angiosarcoma	1
DSRCT	1
Pancreaticohepatobiliary	7 (2)
Adenocarcinoma	6
Small cell carcinoma	1
Melanoma	6 (2)
Head and neck	6 (2)
Salivary duct carcinoma	2
Squamous cell carcinoma	1
PTC	1
Adenocarcinoma, NOS	2
Others	5 (2)
Breast	2
Skin	2
Thymoma	1
Total	**281**

Abbreviations: DSRCT, desmoplastic small round blue cell tumor; EHE, epithelioid hemangioendothelioma; GE, gastroesophageal; NOS, not otherwise specified; NSCLC, non–small cell lung carcinoma; PTC, papillary thyroid carcinoma.

Among peritoneal effusions, the most common metastatic tumors in males were hematolymphoid (26 of 84 [31%]; most commonly lymphoma), gastrointestinal (20 of 84 [24%]; most commonly colorectal, followed by gastric adenocarcinoma), and genitourinary (18 of 84 [21%]; most



Summary of the frequencies of site of origins of malignant effusions in males (A, C, and E) and females (B, D, and F) in pleural (A and B), peritoneal (C and D), and pericardial (E and F) fluids.

commonly urothelial and renal cell carcinoma) (Figure, C; Table 4). In females, the most common metastatic tumors were Müllerian (103 of 183 [56%]; most commonly tubo-ovarian), breast (29 of 183 [16%]; most commonly ILC, followed by IDC), and gastrointestinal (18 of 183 [9%]; most commonly gastric adenocarcinoma) (Figure, D; Table 5).

For pericardial effusions, the most common metastatic tumors in males were lung (28 of 46 [61%: most commonly

Table 3. Distribution of Metastatic Tumors in Malignant Pleural Effusions (in Descending Order of Frequency) in Females

Primary Tumor Origin	No. (%) of Cases
Breast	116 (32)
Invasive ductal carcinoma	66
Invasive lobular carcinoma	18
Mixed ductal and lobular carcinoma	4
Angiosarcoma	1
NOS	27
Müllerian	75 (20)
Tubo-ovarian	40
Endometrium	8
Cervix	6
Uterus	3
NOS	18
Lung	71 (19)
Adenocarcinoma	58
Small cell carcinoma	5
Squamous cell carcinoma	4
Large cell neuroendocrine	1
NSCLC, NOS	3
Hematolymphoid	52 (14)
Lymphoma	40
Plasma cell neoplasm	10
Leukemia	2
Genitourinary	10 (3)
Kidney	9
Urothelium	1
Mesothelium	10 (3)
Melanoma	9 (2)
Soft tissue	8 (2)
EHE	2
MPNST	1
ARMS	1
Synovial sarcoma	1
Angiosarcoma	1
Ewing sarcoma	1
High-grade sarcoma, NOS	1
Head and neck	7 (2)
Squamous cell carcinoma	2
Adenoid cystic carcinoma	2
ARMS	1
Adenocarcinoma, NOS	1
Carcinoma, poorly differentiated	1
Gastrointestinal	6 (2)
Adenocarcinoma	6
Pancreaticohepatobiliary	3 (1)
Adenocarcinoma	2
Neuroendocrine	1
Total	**367**

Abbreviations: ARMS, alveolar rhabdomyosarcoma; EHE, epithelioid hemangioendothelioma; MPNST, malignant peripheral nerve sheath tumor; NSCLC, non–small cell lung carcinoma; NOS, not otherwise specified.

Table 4. Distribution of Metastatic Tumors in Malignant Peritoneal Effusions (in Descending Order of Frequency) in Males

Primary Tumor Origin	No. (%) of Cases
Hematolymphoid	26 (31)
Lymphoma	23
Leukemia	3
Gastrointestinal	20 (24)
Colorectal	9
Stomach	6
Esophagus/GE junction	3
Small bowel	1
Appendix	1
Genitourinary	18 (21)
Urothelium	8
Kidney	8
Prostate	2
Pancreaticohepatobiliary	8 (10)
Adenocarcinoma	6
Hepatocellular carcinoma	2
Melanoma	5 (6)
Mesothelium	4 (5)
Lung	2 (2)
Adenocarcinoma	2
Soft tissue	1 (1)
Rhabdomyosarcoma	1
Total	**84**

Abbreviation: GE, gastroesophageal.

adenocarcinoma), gastrointestinal (8 of 46 [17%]; most commonly stomach), and hematolymphoid (7 of 46 [15%]; most commonly lymphoma) (Figure, E; Table 6). In females, the most common metastatic tumors were lung (27 of 62 [44%]; most commonly adenocarcinoma), breast (17 of 62 [27%]; most commonly ductal), and Müllerian (9 of 62 [15%]; most commonly tubo-ovarian) (Figure, F; Table 7).

Among metastatic breast tumors in the pleural fluid (total 116 cases), IDC was more frequently found in pleural fluid than ILC: 66 (57%) versus 18 (16%), χ^2 $P < .001$. In contrast, of the 29 peritoneal fluid breast metastases, ILC was more common than IDC: 10 (34%) versus 5 (17%), χ^2 $P < .001$.

For hematolymphoid neoplasms, in both males and females, plasma cell neoplasms (plasmacytomas and plasma cell myelomas) had a propensity to metastasize to pleural (32 [24%] among a total of 131 hematolymphoid cases for both genders) but not to peritoneal fluid (0 among a total of 32 hematolymphoid cases for both genders) (χ^2 $P = .002$).

DISCUSSION

Cytologic evaluation remains the mainstay of diagnostic modality for effusion specimens, particularly in the setting of preexisting malignancies or workup of an underlying tumor.[8–10] For certain tumors, such as ovarian and lung tumors, peritoneal effusion (ascites) and pleural effusions could, respectively, be the initial presentation of malignancy.[11] The presence of malignancies in effusions also provides valuable staging and prognostic information for downstream treatments. For instance, following diagnoses of malignant pleural effusions, patients who received com-

Table 5. Distribution of Metastatic Tumors in Malignant Peritoneal Effusions (in Descending Order of Frequency) in Females

Primary Tumor Origin	No. (%) of Cases
Müllerian	103 (56)
Tubo-ovarian	36
Endometrium	8
Uterus	5
Cervix	2
Omentum	1
NOS	51
Breast	29 (16)
Invasive lobular carcinoma	10
Invasive ductal carcinoma	5
Mixed ductal and lobular carcinoma	3
NOS	11
Gastrointestinal	18 (9)
Stomach	8
Colorectal	5
Others (small bowel, stomach, esophagus/GE junction)	5
Pancreaticohepatobiliary	10 (6)
Adenocarcinoma	9
Hepatocellular carcinoma	1
Genitourinary	8 (4)
Kidney	5
Urothelium	3
Hematolymphoid	6 (3)
Lymphoma	4
Leukemia	2
Soft tissue	4 (3)
Rhabdomyosarcoma	2
EMC	1
High-grade sarcoma, NOS	1
Melanoma	3 (2)
Mesothelium	2 (1)
Total	**183**

Abbreviations: EMC, extraskeletal myxoid chondrosarcoma; GE, gastroesophageal; NOS, not otherwise specified.

Table 6. Distribution of Metastatic Tumors in Malignant Pericardial Effusions (in Descending Order of Frequency) in Males

Primary Tumor Origin	No. (%) of Cases
Lung	28 (61)
Adenocarcinoma	23
Poorly differentiated	5
Gastrointestinal	8 (17)
Stomach	6
Esophagus	1
Colorectal	1
Hematolymphoid	7 (15)
Lymphoma	4
Leukemia	2
Plasma cell neoplasm	1
Genitourinary	1 (2)
Kidney	1
Head and neck	1 (2)
Mesothelium	1 (2)
Total	**46**

bined chemoradiation therapy had a significantly longer survival compared with those who received no therapy.[12] In addition to morphologic assessment and immunohistochemical studies, cytologic specimens from effusion are also highly amenable to molecular testing.[13] This ancillary study plays an important role in providing more precise identification, subtyping, and prognostic and therapeutic markers for a variety of tumor types, such as *EGFR* and *ALK* mutation testing for lung adenocarcinoma.[14]

Although we had a total of 30 085 effusions in a span of 17 years, our study showed that only a small percentage (11%) were positive for malignancies. This could either be due to low cellularity rendering the specimen inadequate for definitive diagnosis, or because a large number of effusions are transudates or reactive in nature, even in the setting of preexisting malignancy.

The incidence of malignant effusions was significantly higher in females compared with males in both pleural and peritoneal fluids. In females, breast and Müllerian were the most common primaries in pleural and peritoneal fluid, respectively. This is consistent with the known fact that carcinomas originating from either the ovaries or fallopian tubes tend to undergo peritoneal spread.[15] Among our cases of metastatic breast tumors, IDC was more frequently found in pleural fluid, whereas ILC was more commonly present in peritoneal fluid. This finding is supported by an earlier study by Inoue et al,[16] which showed that the frequency of lung metastases was significantly lower in the ILC group (6.3%) than in the IDC group (53.7%) ($P = .01$), whereas the frequency of peritoneal metastases was significantly higher in the ILC group (68.8%) than in the IDC group (1%) ($P < .001$). Although the reason underlying the difference in metastatic patterns between these 2 tumors is unclear, one possible reason is that in ILC, there is loss of expression of the intercellular adhesion molecule E-cadherin as a result of mutational inactivation, a finding not present in ductal carcinoma.[17,18]

Among the hematolymphoid neoplasms, lymphoma was the most common metastatic tumor in pleural, peritoneal, and pericardial effusions, whereas leukemia was the least common. Interestingly, plasma cell neoplasms were present in pleural and pericardial fluids but were not detected in peritoneal effusions. The latter finding is not unusual because myelomatous ascites is extremely rare, with only a handful of case reports to date.[19] The reason why plasma cell neoplasms preferentially metastasize to pleural and pericardial but rarely to peritoneal is unclear. Although different gene signatures (metastasis initiation genes, metastasis progression genes, and metastasis virulence genes) for invasion and colonization have been identified in solid tumors,[20] none have been studied for their role in tumor initiation or colonization in multiple myelomas.[21,22] Another important factor to consider is how well-adapted the malignant cells are to the new host microenvironment.

With the advancement in early detection and treatment modalities of malignancies, we were interested in whether the incidences of the different types of malignancies have changed, particularly with the advent of targeted therapies

Table 7. Distribution of Metastatic Tumors in Malignant Pericardial Effusions (in Descending Order of Frequency) in Females

Primary Tumor Origin	No. (%) of Cases
Lung	27 (44)
Adenocarcinoma	26
Squamous cell carcinoma	1
Breast	17 (27)
Ductal	10
Lobular	1
Metaplastic	1
NOS	5
Müllerian	9 (15)
Tubo-ovarian	8
Endometrium	1
Hematolymphoid	5 (8)
Lymphoma	4
Leukemia	1
Pancreaticohepatobiliary	1 (2)
Head and neck	1 (2)
Genitourinary	1 (2)
Mesothelium	1 (2)
Total	**62**

Abbreviation: NOS, not otherwise specified.

in the current era of personalized medicine, such as imatinib for chronic myelocytic leukemia, trastuzumab for *HER2*-amplified breast cancer, and erlotinib for non–small cell lung cancer.[23]

Regarding pleural effusions, in a 1985 study by Johnston et al,[1] which focused mainly on 584 malignant pleural effusions, results were similar to our findings in the order of frequency as follows: among males, lung, hematolymphoid, gastrointestinal, and genitourinary tumors, and among females, breast, Müllerian, lung, and hematolymphoid tumors. Comparable results were reported by Sears and Hajdu[2] in 1986. However, in a study by Hsu,[3] of the 781 malignant pleural effusion specimens between 1974 and 1984, lung adenocarcinoma was the most frequent type of malignancy identified for both genders. Our findings indicate that among malignant pleural effusions, the most common primary site in males is lung, and that in females is breast rather than lung.

As for peritoneal effusions, in a study by DiBonito et al,[4] of 215 malignant peritoneal effusions collected between 1984 and 1990, among males, stomach was the most common primary site of metastasis, followed by pleural mesothelioma. In contrast, our results showed that in males, hematolymphoid neoplasm was the most common, followed by colorectal carcinoma. Although our study supports the finding that gynecologic tumors continues to be the most common cause of malignant ascites in females, our results showed that the second most common tumor was breast, not stomach, in contrast to what was reported by DiBonito et al.[4]

For pericardial effusions, our results were consistent with previous reports showing lung adenocarcinomas as the most common metastatic tumor for both sexes. In females, breast was the second common metastatic tumor in pericardial effusions, a finding similar to that of prior papers by Dragoescu and Liu[24] and He et al.[25] However, our results of gastrointestinal and hematolymphoid malignancies as second and third most common pericardial malignancies in males were not reported in the series by Dragoescu and Liu.[24]

In conclusion, our study shows that although lung and ovary continue to be the most common primary sites of metastasis in pleural and peritoneal fluid in males and females, respectively, there have been differences in types of malignancies in other sites, depending on gender. Familiarity with the more common sites of metastasis in effusion cytology is important, especially in patients who present with unknown primary, as this will be valuable in judiciously triaging specimens for ancillary studies.

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