Uterine Metastasis from Carcinoma of Breast – A Systematic Analysis

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Abstract: Breast cancer can metastasize to a wide range of organs, but reports about uterine metastases are rare. The current article systematically analyzes 55 patients reported in peer-reviewed literature from 2010–2022 with respect to nine variables, including: [i] age of the patient; [ii] clinical presentation of uterine metastasis; [iii] precise location of metastasis; [iv] primary (breast) cancer histopathology; [v] imaging modality utilized for detection of metastasis; [vi] timing of appearance of metastases: synchronous or metachronous; [vii] immunochemistry markers; [viii] management; and [ix] survival. Uterine metastases may appear in synchronous or metachronous fashion and may be asymptomatic or have symptoms like abnormal vaginal bleeding. Treatment of uterine metastases usually comprises of total abdominal hysterectomy with bilateral salpingo-oophorectomy along with chemotherapy. The long-term prognosis is unclear, but due to the development of metastases in other bodily parts, cases frequently have a poor outcome.

Keywords: Breast cancer, uterine cancer, uterine metastasis, hysterectomy, immunohistochemistry, invasive lobular breast carcinoma, invasive ductal cell carcinoma.

INTRODUCTION

Breast cancer is the most common cancer affecting women, and metastases from this cancer are a great clinical challenge as they account for the majority of deaths [1]. Their occurrence is on the rise, even at the sites that are regarded as uncommon, and this trend is attributed to the development of better imaging techniques that lead to detection, as otherwise the overall survival of BC patients has improved due to the availability of more effective therapy [2]. The American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care Guideline released in 2016 recommends that cancer survivors be educated and counseled about the presenting features of recurrence and even the lesser expected sites of metastases [3]. This would potentially result in early reporting, evaluation, and detection of metastases, thereby positively impacting survival [4]. Uterine metastases from breast cancer are relatively uncommon, and there are a limited number of reported cases in the literature.

This article has been compiled to systematically review the case reports from the recent literature in order to acquire a better understanding of the disease because uterine metastases from breast cancer are uncommon and have rarely been reported in the previous literature.

MATERIALS AND METHODS

Methods

A systematic literature search was conducted through electronic databases, including PubMed, ResearchGate, Google Scholar, Semantic Scholar, and Scopus, using the key words "breast cancer metastases; uterine metastases; endometrial Metastasis ". The search was carried out by using individual keywords: {[unusual (Title/Abstract)] OR [rare (Title/Abstract)] OR [unconventional (Title/Abstract)]} AND {[metastases (Title/Abstract)] OR [metastasis (Title/Abstract)]} AND {[breast (Title/Abstract)]} AND {[cancer (Title/Abstract)] OR [neoplasm (Title/Abstract)]}. The study was limited to article published in English language. In order to evaluate the recent literature only, the time frame fixed for the search was between 2010–2022.

Criteria for Considering Studies

Articles, including case series and case reports, that provided a clear account of the variables were included in the study.

Participants and Outcome Measures

Only those cases were included where the diagnosis of uterine metastases from breast cancer

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Table 1: Characteristics of the Patients of Uterine Metastases from Breast Cancer

Serial Number	Case Report / Series	Year of publication	Number of cases	Age (in years)	Clinical Presentation of uterine metastasis	Precise location of metastasis	Primary (breast) cancer histopathology	Imaging modality utilized for detection of metastasis	Synchronous (S) / Metachronous (M)	Immunochemistry markers	Management	Survival	Other relevant information
1	Bogliolo *et al.* [5]	2010	1	78	Asymptomatic ; detected during routine gynecological surveillance	Cervix uteri with parametrial involvement	Invasive lobular breast carcinoma	CT, MRI	S	-	Breast quadrantectomy with multi-systemic medical treatment including radiotherapy, chemotherapy and hormone therapy ; TAH-BSO	AAR	Primary breast cancer was asymptomatic and detected by screening mammogram; patient alive at 2.5 year follow-up. (AAR)
2	D'souza *et al.* [6]	2010	1	44	Abnormal vaginal bleeding	Cervix ueteri	Invasive lobular breast carcinoma	PET-CT	S	-	Palliative /supportive	AAR	Evaluation of uterine symptoms revealed bilateral breast cancer and PET-CT scan showed diffuse metastases.
3	Hara *et al.* [7]	2010	1	44	Abnormal vaginal bleeding two months after treatment of breast cancer (with surgery with chemotherapy)	Endometrium	Invasive lobular breast carcinoma	CT, MRI, TVS	M	ER +; PR - ; HER 2 +	Systemic chemotherapy	Death at 11 months	GCDFP-15 was found to be a diagnostic marker for metastatic uterine tumors arising from breast cancer ; patient passed away as a result of pleural carcinomatosis and multiple bone metastasis 11 months after the diagnosis of uterine metastases .

4	Hooker *et al.* [8]	2011	1	83	Abnormal vaginal bleeding	Endometrial polyp	Invasive lobular breast carcinoma	Hysteroscopy	M	ER +	Resection of endometrial polyp	AAR	Vulvar metastasis were also detected in follow-up .
5	Abaid *et al.* [9]	2011	1	53	Abnormal vaginal bleeding, abdominal discomfort	Uterine fundus (endometrium, myometrium)	Invasive lobular breast carcinoma	USG	M	-	TAH-BSO	AAR	After diagnosis of breast cancer, she had declined recommended medical treatment and instead elected to undergo homeopathic therapy; then reported with uterine symptoms after 2 years .
6	Dirican *et al.* [10]	2012	1	47	Asymptomatic	Micro-metastases within leiomyoma	Invasive ductal cell carcinoma	CT	M	ER -, GCDFP-15 +	TAH-BSO, Chemotherapy	AAR	4 years after management of breast cancer with partial mastectomy, axillary dissection, chemotherapy and endocrine therapy (tamoxifen), elevated serum CA 15-3 levels detected during follow-up lead to discovery of uterine metastasis .
7	Van Meurs *et al.* [11]	2012	1	70	Asymptomatic	Myometrium	Invasive ductal cell carcinoma	CT scan	M	-	TAH-BSO	AAR	Ductal breast carcinoma was diagnosed in 1996, and treated with a mastectomy, radiation, and endocrine (tamoxifen)therapy until July 2002. Her disease had progressed, and she had developed multiple metastases to the bones. Uterine metastasis were detected on histopathological exam of uterus in 2010,which further revealed leiomyosarcoma .
8	Horikawa *et al.* [12]	2012	1	52	Lower abdominal discomfort and urinary frequency	Cervix uteri	Invasive lobular breast carcinoma	USG, MRI	S	ER+	TAH-BSO ; left modified radical mastectomy with axillary lymph node dissection followed by adjuvant chemotherapy	AAR	Primary asymptomatic invasive lobular carcinoma of the left breast, was discovered only after histopathology of uterus detected metastasis ; patient was alive at 7-year follow-up.

9	Arslan *et al.* [13]	2013	1	57	Abdominal pain and distension	Endometrium & myometrium	Invasive ductal cell carcinoma	MRI	M	-	TAH-BSO	AAR	Uterine metastasis detected after 2 years of MRM and radio-chemotherapy for stage IIIc Invasive ductal cell carcinoma of breast .
10	Muñoz-Iglesias *et al.* [14]	2013	1	50	Asymptomatic	Endometrium & myometrium	Invasive lobular breast carcinoma	PET-CT	M	-	TAH-BSO	AAR	After 6 years of management of bilateral lobular carcinoma of the breast with mastectomy, axillary lymphadenectomy, chemotherapy, and hormone therapy ; patient developed a progressive elevation of tumor markers and PET scan detected uterine metastasis .
11	Alheeti *et al.* [15]	2014	1	44	Asymptomatic	Cervix uteri extending to parametrium	Invasive lobular breast carcinoma	CT	S	ER +; PR + ; HER 2 -	Neo-adjuvant chemotherapy, modified right mastectomy & right axillary lymphadenectomy followed with adjuvant chemotherapy and radiotherapy.	AAR	Patient developed a breast lump but denied treatment, 3 months later she became pregnant and at labor, a fungating cervical mass was discovered .
12	Binstock *et al.* [16]	2014	1	43	Abnormal vaginal bleeding	Endometrium, myometrium, fallopian tubes, uterine serosa, ovaries and cul-de-sac	Invasive ductal cell carcinoma	TVS	M	ER +, PR -, HER 2 -, Ki-67 +	Robotic-assisted TAH-BSO	Death at 5 months	Patient passed away from progression of her primary disease 5 months following her surgery.
13	Bezpalko *et al.* [17]	2015	1	47	Abnormal vaginal bleeding	Endometrium	Invasive lobular breast carcinoma	CT, MRI	S	AE1/3 + ; GATA 3+	Chemotherapy ; hormonal therapy	Death at 6 weeks	Multiple co-morbidities including systemic lupus erythematosus, rheumatoid arthritis, thalassemia & fibromyalgia ; evaluation revealed invasive lobular carcinoma of the right breast with metastasis to the bone marrow, endometrium, gallbladder, regional lymph nodes, and peritoneum . Patient passed away about 6 weeks of diagnosis.

14	Haeri *et al.* [18]	2015	1	52	Abnormal vaginal bleeding	Uterine leiomyoma	Invasive ductal cell carcinoma	USG	M	GCDFP15 +	TAH-BSO	AAR	Patient developed metastasis to uterine leiomyoma 6 years after management of Invasive ductal cell carcinoma of right breast.
15	Huo *et al.* [19]	2015	1	66	Abnormal vaginal bleeding	Endometrium	Invasive lobular breast carcinoma	USG, CT	M	cytokeratin 5/6 + ; EGFR + ; GCDFP15 -	TAH-BSO along with pelvic and periaortic lymphadenectomy.	AAR	The patient had a history of MRM for left breast carcinoma 11 years prior .
16	Pekindil *et al.* [20]	2015	1	40	Asymptomatic	Cervix uteri, ovaries	Invasive lobular breast carcinoma	-	S	ER +, PR +, GCDFP15 +	TAH-BSO ; chemotherapy	AAR	Patient underwent TAH-BSO as a part of breast cancer management ; histopathology revealed metastasis to cervix and ovaries .
17	Toyoshima *et al.* [21]	2015	1	62	Abdominal discomfort; increase is size of previously present leiomyoma.	Myometrium, Fibroid tissue	Invasive lobular breast carcinoma	MRI, PET-CT	M	ER +, PR -, GCDFP15 + cytokeratin AE1/AE3 +, anti-cytokeratin CAM5.2 +	TAH-BSO ; chemotherapy	AAR	Uterine metastasis was reported 7 years after management of primary breast cancer with mastectomy and chemotherapy.
18	Lokadasan *et al.* [22]	2015	2	49	Abdominal discomfort and distension	Cervix uteri	Invasive lobular breast carcinoma	CT	M	ER +, PR +, E-cadherin -	TAH-BSO ; chemotherapy	AAR	4 years prior to onset of uterine symptoms, patient had undergone left MRM, chemotherapy and endocrine therapy (tamoxifen) .
				49	Abnormal vaginal bleeding	Endometrium, myometrium, fibroid, cervix, and bilateral ovaries	Invasive lobular breast carcinoma	TVS	S	-	TAH-BSO ; chemotherapy	AAR	Uterine symptoms led to evaluation and detection of primary left breast cancer.
19	Waks *et al.* [23]	2015	1	53	Postcoital vaginal bleeding	Cervix uteria	Invasive lobular breast carcinoma	USG	M	-	TAH-BSO	AAR	Patient reported with uterine symptoms after 15 years of putative "dormancy" post treatment of breast cancer .

20	Razia *et al.* [24]	2017	1	58	Abnormal vaginal bleeding	Endometrium, Myometrium	Invasive lobular breast carcinoma	TVS, MRI, PET-CT	M	ER +, PR +, HER 2 +, E-cadherin -	TAH-BSO, partial colectomy,	AAR	9 years prior, patient had undergone breast-conserving surgery for cancer of the right breast followed by chemotherapy and endocrine therapy (tamoxifen).
21	Seo *et al.* [25]	2017	1	46	Abnormal vaginal bleeding	Cervix uteri	Invasive lobular breast carcinoma	USG	M	ER +, PR +, GCDFP15 +	TAH-BSO	AAR	2 years prior, breast cancer had been managed with neo-adjuvant chemotherapy, breast conservation surgery, adjuvant chemotherapy, radiotherapy and endocrine therapy (tamoxifen, goserilin).
22	Hajal *et al.* [26]	2017	1	65	Asymptomatic	Endometrium	Invasive lobular breast carcinoma	-	M	-	10 cycles of Aredia (pamidronate)	AAR	2 years prior, patient had undergone Right MRM and axillary lymph node dissection followed by adjuvant chemotherapy, radiotherapy and endocrine therapy (tamoxifen). Multiple bony metastasis were also discovered.
23	Chupryna *et al.* [27]	2017	1	56	Abnormal vaginal bleeding, bloating, fatigue, difficulty in breathing, polyuria	Cervix uteri, Endometrium	Invasive lobular breast carcinoma	USG, CT, TVS	S	ER +, PR +, GCDFP15 + HER 2 – CK7 +	Chemotherapy, TAH-BSO, Breast lumpectomy	AAR	Patient had bilateral hydronephrosis managed by nephrostomy . Uterine symptoms led to evaluation and discovery of breast cancer.
24	Trihia *et al.* [28]	2017	1	82	Abnormal vaginal bleeding	Endometrial polyp	Invasive lobular breast carcinoma	-	M	ER -, PR -, GCDFP15 -,	TAH-BSO	AAR	Uterine recurrence 19 years after management of primary breast cancer (with left MRM and axillary lymph node dissection and tamoxifen) .

25	Akinpeloye *et al.* [29]	2017	2	47	Abnormal vaginal bleeding	Endometrium	Invasive lobular breast carcinoma	USG	S	pan-cytokeratin (AE1/AE3)+, GATA3 +	-	Death at 2 months	Patient reported with severe bleeding per vaginum and thrombocytopenia; on evaluation, multiple metastases were found; patient passed away after 2 months due to disease dissemination.
				59	Abnormal vaginal bleeding	Endometrium	Invasive lobular breast carcinoma	CT	M	-	-	AAR	Uterine symptoms after 7 years of management of primary breast cancer (with left MRM and right simple mastectomy with adjuvant chemotherapy and endocrine therapy which included Tamoxifen) .
26	Akhtar *et al.* [30]	2017	2	42	Abdominal distension (enlarged uterus)	Endometrium ; left ovary	Invasive ductal cell carcinoma	PET-CT	S	GATA-3 +, pancytokeratin, +, ER +	Neoadjuvant chemotherapy, TAH-BSO, adjuvant chemotherapy	AAR	During evaluation of breast lump, enlarged uterus detected .
				62	Asymptomatic	Endometrium; Cervix uteri	Invasive lobular breast carcinoma	USG	S	-	-	Lost to follow up	Patient had been offered plan of neoadjuvant chemotherapy followed by TAH-BSO but decline and was lost to follow up.
27	Abdalla *et al.* [31]	2018	1	32	Abnormal vaginal bleeding	Endometrium, Cervix uteri	Invasive ductal cell carcinoma	TVS, CT	M	CK7 +, GCDFP15 +, ER -, PR-	-	AAR	1 year after treatment of breast cancer with neoadjuvant chemotherapy, mastectomy, axillary clearance followed with, radio-chemotherapy .
28	Berger *et al.* [32]	2018	1	70	Abnormal (severe) vaginal bleeding	Endometrium ; myometrium ; cervix uteri ; adnexa	Invasive lobular breast carcinoma	PET-CT	M	-	Robotic assisted TAH-BSO ; chemotherapy	AAR	5 years after management of breast cancer with surgery, chemotherapy and endocrine therapy, patient underwent palliative hysterectomy to control metastasis induced bleeding per vaginum ; patient had multiple bony metastasis .

29	Briki *et al.* [33]	2018	2	50	Abnormal vaginal bleeding	Endometrium ; myometrium	Invasive lobular breast carcinoma	USG, MRI	M	-	TAH-BSO	AAR	2 years prior to uterine symptoms, patient had undergone radical mastectomy with axillary lymph node dissection followed by chemotherapy and endocrine therapy (tamoxifen) .
				67	Abnormal vaginal bleeding	Endometrium ; myometrium	Invasive ductal cell carcinoma	USG, MRI	M	-	TAH-BSO	AAR	Patient had undergone a left radical mastectomy and a right breast tumerectomy associated with bilateral axillary lymph node dissection bilateral breast carcinoma 3 years ago . Bony metastasis.
30	Thouvenot *et al.* [34]	2018	1	82	Abnormal vaginal bleeding, abdominal pain	Cervix uteri, myometrium, adnexa	Invasive ductal cell carcinoma	CT, MRI, PET-CT	M	ER -, PR –, E-cadherin +, EGFR -	Supportive care	Death at 3 months	Patient reported with uterine symptoms 2 years after right mastectomy and axillary lymphadenectomy with adjuvant endocrine therapy (letrozole). Evaluation revealed heavy burden of metastasis due to which patient passed away in 3 months.
31	Rahmani *et al.* [35]	2018	1	51	Abnormal vaginal bleeding	Endometrium, ovary	Invasive ductal cell carcinoma	TVS	S	ER +, PR +, GCDFP15 + E-cadherin +	Chemotherapy	AAR	Uterine symptoms led to workup and discovery of occult breast cancer with bony metastasis and axillary lymphadenopathy.
32	Cimpeanu *et al.* [36]	2019	1	76	Asymptomatic	Cervix uteri, with parametrial involvement	Invasive lobular breast carcinoma	USG, PET-CT	S	ER +, PR +, , EGFR -	Chemotherapy	AAR	Reported with right hip pain ; evaluation led to discovery of skeletal and uterine metastasis from occult breast cancer with axillary lymphadenopathy .

33	Franco-Márquez *et al.* [37]	2019	1	86	Abnormal vaginal bleeding	Endometrium	Invasive lobular breast carcinoma	TVS	M	GATA-3 +, ER +, Mammaglobin +	-	AAR	Patient reported with uterine symptoms, after 30 years of radical mastectomy, axillary node dissection and chemotherapy for lobular carcinoma of breast .
34	Homsi *et al.* [38]	2019	1	37	Asymptomatic	Cervix uteri, Myometrium,	Invasive ductal cell carcinoma	PET-CT, MRI	S	-	TAH-BSO	AAR	The asymptomatic uterine metastasis mimicked fibroids and were detected during workup and staging of breast cancer .
35	Silva Fontinele *et al.* [39]	2019	1	57	Abnormal vaginal bleeding	Cervix uteri, myometrium	Invasive lobular breast carcinoma	CT	M	ER +, PR +, HER 2 –, Cadherin -	TAH-BSO	AAR	Uterine symptoms, 4 years after management of left breast cancer with neoadjuvant chemotherapy, MRM, adjuvant radiotherapy and endocrine therapy (tamoxifen) .
36	Arif *et al.* [40]	2020	1	55	Abnormal vaginal bleeding, abdominal discomfort	Endometrial polyp	Invasive lobular breast carcinoma	USG	M	-	TAH-BSO	AAR	Uterine symptoms 7 years after treatment of primary breast cancer with left mastectomy and endocrine (tamoxifen) therapy .
37	AbdallahH *et al.* [41]	2020	1	59	Lower abdominal discomfort	Endometrium Cervix uteri, Myometrium	Invasive lobular breast carcinoma	TVS	S	ER +, PR +, GATA3 +, CK7 +	TAH-BSO, Palliative chemotherapy	AAR	Abdominal pain led to evaluation and discovery of uterine metastasis and primary breast cancer ; further evaluation discovered diffuse metastases to other organ-systems .
38	Farkas *et al.* [42]	2020	1	47	Abnormal vaginal bleeding	Endometrium Cervix uteri, Myometrium	Invasive ductal cell carcinoma	PET-CT	M	ER +, HER 2 +	TAH-BSO	AAR	Uterine symptoms 7 years after treatment of primary breast cancer with right mastectomy, radiation therapy, chemotherapy, and endocrine (tamoxifen) therapy . On evaluation, metastases to brain, bone and lymph nodes detected.

39	Qawasmeh *et al.* [43]	2020	1	65	Abnormal vaginal bleeding	Cervix uteri ; Recurrence at vaginal vault	Invasive ductal cell carcinoma	TVS, MRI	M	ER +, GATA3 +,	TAH-BSO Chemotherapy ; recurrence treated with radio-chemotherapy	AAR	Uterine symptoms 7 years after staged bilateral MRM, endocrine (tamoxifen) therapy for bilateral breast cancer. After 4 years of TAH-BSO, patient had recurrence at vaginal vault .
40	Goel *et al.* [44]	2020	1	45	Asymptomatic	Cervix uteri	Invasive ductal cell carcinoma	USG, PET-CT	S	-	Chemotherapy	Death at 8 months	Uterine metastasis was detected during routine evaluation of left breast cancer ; diffuse lymphatic metastasis in axillae, chest and abdomen ; patient passed away at 8 months .
41	Danolić *et al.* [45]	2020	1	55	Abnormal vaginal bleeding	Endometrium	Invasive lobular breast carcinoma	PET-CT	M	-	Chemotherapy	AAR	2 years prior to the onset of uterine symptoms, patient had undergone segmental mastectomy with sentinel lymph node dissection, adjuvant chemotherapy and endocrine therapy with anastrozole for breast cancer . She was found to have diffuse osseous metastases.
42	Gomez *et al.* [46]	2020	1	69	Abnormal vaginal bleeding	Endometrium	Invasive lobular breast carcinoma	USG	M	CK AE1/AE3 +, CAM5.2 +, GATA-3 +, mammaglobin +, ER+	-	AAR	5 years prior to the onset of uterine symptoms, patient MRM followed by hormonal therapy (Tamoxifen) .
43	Cochrane *et al.* [47]	2020	1	62	Abnormal vaginal bleeding	Cervix uteri	Invasive ductal cell carcinoma	MRI	M	GATA3 +, ER +, PR+	Total abdominal hysterectomy, intravaginal brachytherapy	AAR	10 years prior to the onset of uterine symptoms, patient had undergone right mastectomy, right axillary lymph node dissection, chemotherapy ; due to intolerance to endocrine (tamoxifen) therapy, had undergone bilateral salpingo-oopherectomy for estrogen reduction.

44	Landolfo *et al.* [48]	2021	1	52	Abnormal vaginal bleeding	Myometrium; ovary	Invasive ductal cell carcinoma	USG	M	-	TAH-BSO	AAR	2 years prior to the onset of uterine symptoms, breast cancer treated with neoadjuvant chemotherapy, followed by left total mastectomy, axillary lymph node dissection and hormonal therapy.
45	Awazu *et al.* [49]	2021	1	66	Abnormal vaginal bleeding		Invasive lobular breast carcinoma	MRI	M	ER +, PR+, HER 2 +, GCDFP15 + E-cadherin -, CD10 -	TAH-BSO, partial omentectomy and biopsy of the peritoneum	AAR	Patient reported with features of uterine and multiple bony metastases after 23 years of treatment of breast cancer (mastectomy, chemotherapy).
46	Azhar *et al.* [50]	2021	1	49	Abnormal vaginal bleeding	Endometrium Cervix uteri, Myometrium	Invasive ductal cell carcinoma	TVS, PET-CT	M	ER +, PR+, GCDFP15 +, Mammaglobin +	TAH-BSO	AAR	Uterine symptoms reported after 8 months of breast cancer treatment with neoadjuvant chemotherapy followed by MRM and radiotherapy/endocrine therapy.
47	Lim *et al.* [51]	2021	1	57	Abnormal vaginal bleeding	Endometrium, myometrium, cervix uteri, adnexa	Invasive lobular breast carcinoma	TVS, CT	S	CK7 +, ER +, GATA-3+	TAH-BSO, Chemotherapy, CDK4/6 inhibitor	AAR	The patient had left radical mastectomy for breast cancer 2 years prior and was undergoing tamoxifen treatment. Then presented with a right breast cancer and synchronous uterine metastasis ; the patient also had colonic adenocarcinoma 1 year prior to synchronous uterine metastasis .
48	Varghese *et al.* [52]	2021	1	47	Abnormal vaginal discharge, lower limb edema, low backache	Cervix uteri with extension to anterior vaginal wall.	Invasive lobular breast carcinoma	CT	M	ER +, PR +, GATA-3+	Palliative chemotherapy	AAR	6 years prior to the onset of uterine symptoms, left breast cancer treated with left MRM, axillary lymph node dissection and endocrinology therapy (tamoxifen).

49	Dominguez *et al.* [53]	2021	1	42	Abdominal distension and vomiting	Uterus, ovaries	Invasive lobular breast carcinoma	-	S	-	TAH-BSO	Lost to follow up	Left breast lobular cancer detected on detailed examination ; patient lost to follow up ;this case series had two more cases but not affecting the uterus.
50	Bouvier *et al.* [54]	2021	1	50	Asymptomatic	Myometrium	Invasive ductal cell carcinoma	CT, PET-CT	M	-	TAH-BSO, Chemotherapy	AAR	Uterine metastases after 6 years of breast cancer ; at 17 months after hysterectomy, patient developed bone and lung metastases .
60	Kong *et al.* [55]	2022	1	64	Asymptomatic	Endometrium Cervix uteri, Myometrium	Invasive lobular breast carcinoma	PET-CT	M	ER +, PR +, GATA-3+, E-cadherin -	TAH-BSO, Chemotherapy	Death at 2 years	The patient had undergone MRM with chemotherapy for advanced right breast cancer and after two years, reported with bone pain . Evaluation revealed multiple bony and uterine metastasis.

Footnotes: AAR: Alive at time of report; TVS: Transvaginal ultrasound; TAH-BSO: Total abdominal hysterectomy with bilateral salpingo-oophorectomy ; GCDFP-15: Gross cystic disease fluid protein-15 ; CK7: Cytokeratin 7 ; MRM : Modified radical mastectomy

had been clearly established. The nine variables (Table **1**) analyzed include: [i] age of the patient; [ii] clinical presentation of uterine metastasis; [iii] precise location of metastasis; [iv] primary (breast) cancer histopathology; [v] imaging modality utilized for detection of metastasis; [vi] timing of appearance of metastases: synchronous or metachronous; [vii] immunochemistry markers; [viii] management; and [ix] survival.

Exclusion

All such articles that were deficient in information related to the multiple variables under study were excluded. Editorials, comments, conference letters, systematic reviews, and meta-analyses were also excluded.

Risk of Bias

There is a chance that a few important details may have been overlooked because the study relied on complete texts of the literature that were collected through open access, institutional subscriptions (Saudi Digital Library), and requests to the authors via ResearchGate.

Methodological Quality Checking

Checklist items used in Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) and previously published articles from peer-reviewed literature were selected and considered for comparison with the checklist self-drafted for this study.

Data Synthesis (Extraction and Analysis)

Data related to the nine variables was extracted and arranged in Table **1**. The collected data was then analyzed with Microsoft Excel (Office Version 2019). The characteristics of participants were described with descriptive statistical analyses, and the information was presented using frequencies, summary measures, figures, and tables, as shown in the results. Drawing a conclusion was based on previously published, peer-reviewed literature.

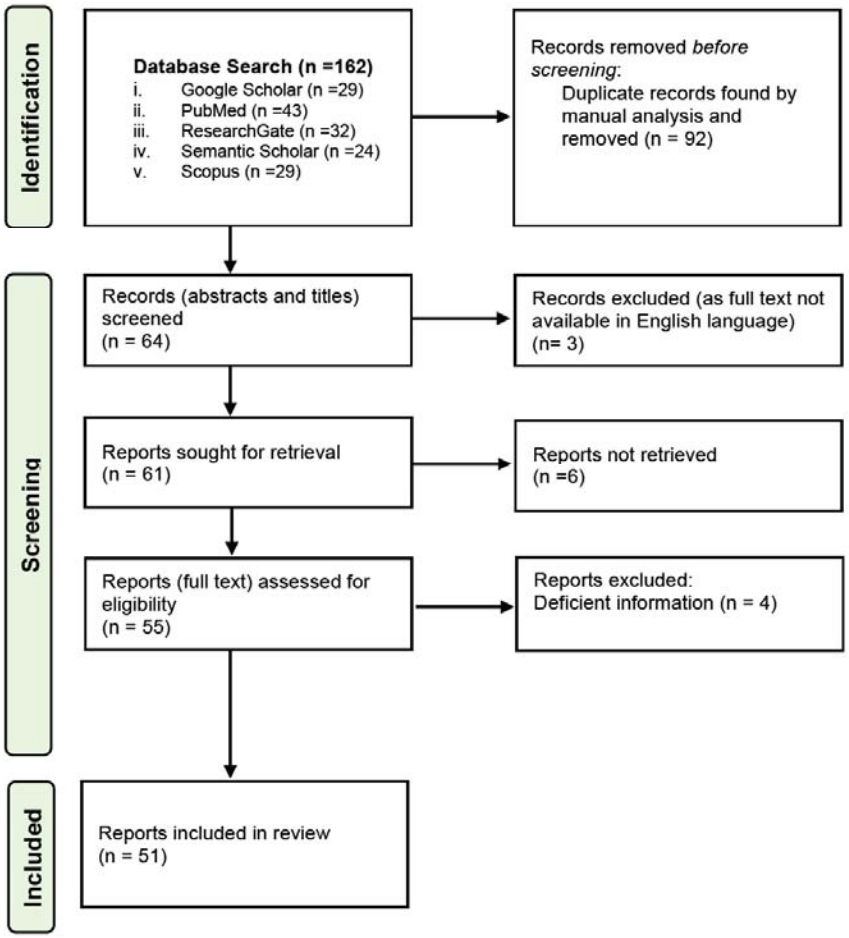

Figure 1: Flowchart of the reviewed articles.

RESULTS

Study Selection

The electronic database search resulted in a total of 162 articles: 43 were identified in PubMed, 34 in ResearchGate, 32 in Google Scholar, 29 in Scopus, and 24 in Semantic Scholar. After excluding 92 duplicated articles, 64 were used to screen titles and abstracts, after which 61 potentially relevant articles in English were sought for retrieval. 5 could be retrieved from the available sources, and 55 were assessed for the eligibility criteria. Finally, 51 articles were included in the review after the detection of deficient or unrelated data in four articles, as shown in Figure **1**.

Study Characteristics

There were 47 case reports (each with a single patient) and 4 case series (each with two patients), thereby giving a total of 55 cases for inclusion in this study, as shown in Table **1**.

Patients ranged in age from 32 years to 86 years (mean 56.2 years). There were 18 synchronous cases wherein uterine metastases were detected during the full-body evaluation of freshly diagnosed breast cancer or else led to further evaluation and the discovery of otherwise unknown primary breast cancer. There were 37 metachronous cases where in uterine cancer was detected after treatment of primary breast cancer, at periods ranging from 5 months to 30 years (mean 6.2 years), as depicted in Figure **2**.

The histopathology and immunochemistry of uterine metastases revealed features of invasive lobular breast carcinoma in 37 (67%) cases and invasive ductal cell carcinoma in 18 (33%), as depicted in Figure **3**. The features matched the primary breast cancer in all the cases.

Abnormal vaginal bleeding (including postmenopausal and post-coital) was the commonest symptom, being present in 33 (60%) cases, followed by abdominal discomfort with or without distension in 9 (116%) cases. 13 (24%) patients were asymptomatic. In 10 cases (19%), metastases affected the cervix uteri; in 9 (17%), the endometrium was affected; and in the rest (n = 35; 69%), multiple layers and parts of the uterus were involved. Multiple imaging modalities were utilized, either singly or in combination, to assist in diagnosis, including 18F-FDG PET/CT (n = 15; 27%), MRI (n = 14; 26%), USG of the abdomen and pelvis (n = 16; 30%), CT scan of the abdomen and pelvis (n = 14; 26%), and transvaginal ultrasound (n = 12; 22%). In 34 (63%) cases, detailed immunochemistry studies were undertaken to arrive at a definite diagnosis. 36 (65%) cases required total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH-BSO) with or without adjuvant chemotherapy, whereas in 1 (2%) case, only total abdominal hysterectomy was undertaken as bilateral salpingo-oophorectomy had

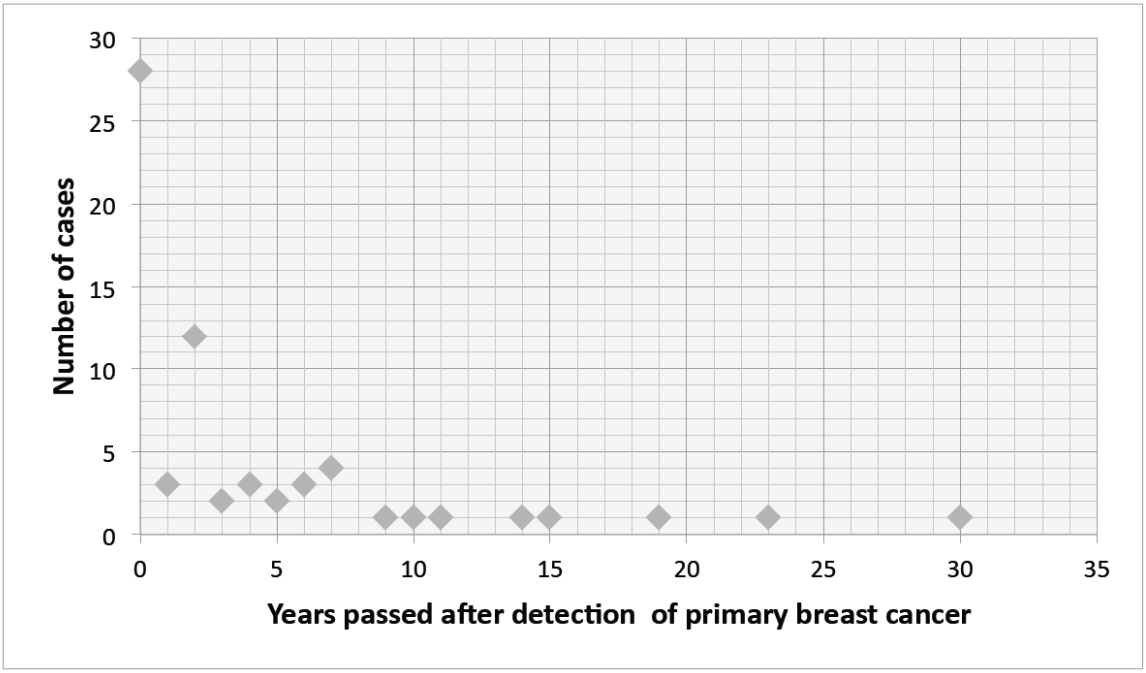

Figure 2: Time duration of uterine metastases after detection of primary breast cancer.

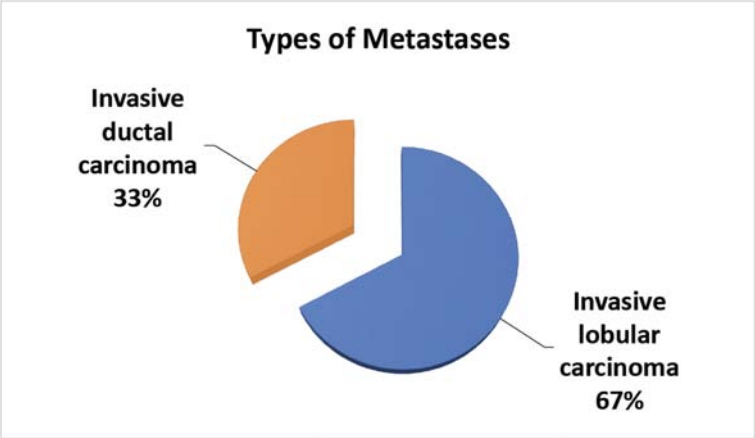

Figure 3: Histopathology of uterine metastases.

previously been undertaken as management of primary breast cancer. In 12 (22%) cases, only palliative chemotherapy and supportive care were provided in view of the disease burden. 46 (84%) cases were alive at the time of reporting in the literature, and 7 (13%) had passed away at periods ranging from 6 weeks to 2 years (mean 7 months). 2 (4%) patients had been lost to follow-up, and their outcomes were hence unknown.

DISCUSSION

Metastases from breast cancer to the uterus are rare, and they may be mistaken for primary uterine cancer as both entities have identical local symptoms and signs (viz., abnormal vaginal bleeding, vaginal discharge, and pain in the pelvis and abdomen). Endocrine therapy (e.g., Tamoxifen), which is a frequent adjuvant therapy in the treatment of hormone-receptor-positive breast cancer, is also known to raise the risk of endometrioid adenocarcinoma, complex atypical hyperplasia, and simple endometrial hyperplasia, which can cause abnormal uterine bleeding [16]. Hence, an important step in the management of uterine metastases is to confirm their tissue of origin and distinguish them from primary uterine disorders, as there are marked differences in the treatment strategy and outcome. This requires (a) a proper clinical history of the patient, (b) appropriate imaging, and (c) histopathological and immunohistochemical analysis of the retrieved specimen.

The imaging modalities utilized for the evaluation of patients in this study include computed tomography (CT) scans, transvaginal ultrasound (TVS), abdominal and pelvic ultrasound (USG), magnetic resonance imaging (MRI), and FDG PET-CT (2-fluorine-18] fluoro-2-deoxy-D-glucose positron emission tomography in combination with computed tomography). In recent studies, the role of FDG PET-CT has been rapidly growing in recent years, and this tool has been found to be very sensitive and specific in the assessment of female gynecological malignancies [2, 10, 56]. However, FGD uptake varies with the menstrual cycle, and furthermore, common benign entities like fibroids may also be hypermetabolic and hence display a positive image [57]. However, the increased uptake in a postmenopausal woman should raise the suspicion of malignancy and initiate further workup. In this study, the case reported by Muñoz-Iglesias *et al*. [14] had no uterine symptoms, but the progressive elevation of tumor markers after 6 years of management of bilateral lobular carcinoma of the breast led to PET-CT and the discovery of uterine metastasis. In the cases reported by Thouvenot *et al*. [34], D'souza *et al*. [6], and Danolić *et al*. [45] , PET-CT revealed widespread metastatic lesions.

Immunohistochemistry, in recent times, has evolved as a crucial technique in finding out the tissue of origin of the lesions [58]. GCDFP-15 (Gross cystic disease fluid protein-15) is a glycoprotein originally detected in the fluid from cystic mastopathy, and positive immunohistochemical staining for this biomarker proves the mammary origin of a lesion (49). GATA-3 is another highly conserved essential transcription factor that serves as a sensitive biomarker for the identification of metastatic breast cancer. Tozbikian and Zunger in 2018, after analysis of biopsy specimens from 57 cases of metastatic breast cancer, found GATA-3 positivity in 82% of metastatic breast cancer [59]. Similarly, negative staining for the CD10 biomarker indicates that the tumor did not originate from the uterine tissues. Positive staining for the cellular adhesion molecule E-cadherin suggests that

the tumor is ductal carcinoma rather than lobular carcinoma (49) which underpins the discohesive pattern of the latter with cells arranged in single file and dispersed widely in the stroma. Mammaglobin is another 93-amino acid protein biomarker largely confined to breast tissue, and Han *et al*. have developed antibodies to mammaglobin and found high sensitivity (84.3%) and specificity (85%) for the discrimination of breast cancer [60].

The metastatic spread of breast cancer has been found to be unpredictable and dependent upon various factors, including phenotypic evolution and tumoral heterogeneity. In 2014, Cummings *et al*., after analysis of the autopsy findings in 197 women who had succumbed to metastatic breast cancer, found that younger females are at a greater risk for metastasis to gynecological sites, and this is attributed to the estrogen-rich environment provided by pre-menopausal ovaries [61]. In our analysis, however, the mean age of patients was 56.2 years. 37 (67%) cases had invasive lobular breast carcinoma metastasis, and 18 (33%) cases had invasive ductal cell carcinoma. This trend concurs with the data in the previously available peer-reviewed literature. Lamovec and Bracko [62], on the basis of autopsy studies, found that invasive lobular breast cancers are responsible for more than 80% of metastases in gynecologic organs. The precise reason for this difference in metastatic pattern between the two variants of breast cancer is not clear, though certain studies have suggested that in infiltrating lobular carcinoma, there is a differential loss of expression of E-cadherin, which could potentially lead to disease progression [63–64]. Kowalski *et al*. have confirmed the difference in pattern of E-cadherin expression (membranous or cytoplasmic, normal or aberrant) at the primary and metastatic sites of ductal and lobular cancers, indicating that this protein may play different roles in the progression of each cancer type [65].

In our study, 37 (68%) cases underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH-BSO). In a retrospective analysis conducted by Rodrigues *et al*. [66], enrolling all the women with uterine metastasis from breast cancer managed at Instituto Português Oncologia Francisco Gentil, Porto, Portugal, from 1995–2011, it was found that even though the women who underwent hysterectomy had a greater median survival, the difference was not statistically significant ($p = 0.159$), and it was concluded that more studies are needed to determine the best course of treatment in metastatic disease restricted to the uterus. In that study, it was not clear if hysterectomy actually prolongs disease-free survival. However, Berger *et al*. [32] have suggested that whenever appropriate, hysterectomy should be explored for otherwise good surgical candidates since it can provide long-term palliation for vaginal bleeding.

46 (84%) cases were alive at time of reporting in literature. Hence it is not possible to deduce any conclusions about the prognosis and ultimate survival and larger studies with follow-up till death are required to determine the long-term outcomes. Furthermore, the 7 (13%) cases that had passed away at periods ranging from 6 weeks to 2 years (mean 7 months) did not have isolated uterine metastases but had a significant disease burden with widespread metastases and hence, cannot shed light on prognosis. Karvouni *et al*. [67] however suggests that the metastasis to the uterus and to other organs of the genital tract can be considered as a pre-terminal event and hence any unusual uterine bleeding in a patient with breast cancer should alert the treating physicians to the possibility of metastatic disease. Because 7 (13%) of the patients in the current study reported having uterine metastases more than 10 years after the main tumor was treated, this warning should be in place throughout the duration of a breast cancer survivor's life. The patients reported by Franco-Márquez *et al*. [37] and Awazu *et al*. [49] were reported 30 years and 23 years, respectively, following their diagnosis of cancer.

CONCLUSION

Breast cancer seldom spreads to the uterus. Every woman who receives a breast cancer diagnosis ought to undergo a full gynecologic evaluation, regardless of whether or not she has uterine symptoms. Uterine metastases can appear synchronously or metachronously and are more likely to develop from primary invasive lobular cancer. Because there are distinctly different treatment options and prognoses for primary uterine carcinoma and uterine metastatic carcinoma, it is essential to make this distinction. The assessment of the lesions' histopathology and immunohistochemistry is essential for making an accurate diagnosis. Chemotherapy and total abdominal hysterectomy with bilateral salpingo-oophorectomy are the main interventions for uterine metastases from breast cancer. The long-term prognosis following uterine metastases is unclear, but due to the development of metastases in other bodily parts, cases frequently have a poor outcome.

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COMPETING INTERESTS

The Authors declare that there are no relevant financial or non-financial competing interests to report.

AUTHORS' CONTRIBUTION

Author 1 (SAS) has conceived and drafted the final version of the manuscript. Authors 2 (MAF), 3 (LSA) and 4 (SAA) have conducted the literature analysis. Author 5 (MAE) has contributed in statistical analysis of data.

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