Review

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Nektarios I. Koufopoulos *, Abraham Pouliakis, Menelaos G. Samaras, Kostantinos Skarentzos, Theofanis Nastos, Ioannis Boutas, Adamantia Kontogeorgi, Magda Zanelli *, Andrea Palicelli, Maurizio Zizzo, Giuseppe Broggi, Rosario Caltabiano, Serena Salzano, Dimitrios Goutas, Ioannis S. Pateras, John Syrios, Amanda Psyrri, Nikolaos Arkadopoulos, Ioannis G. Panayiotides

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Review

Invasive Lobular Carcinoma Metastases to the Female Genital Tract. A Review of Case Reports and Case Series

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Abstract

Invasive lobular carcinoma (ILC) is the most common special type of breast carcinoma, accounting for 5-15% of all breast carcinoma cases. It exhibits several unique features in morphology, clinical behavior, radiological features, molecular characteristics, and metastatic pattern. The latter differs from that of invasive breast carcinoma of no special type with ILC metastases to the peritoneum, gastrointestinal tract, and female genital tract being more frequent. We herewith review the demographic, clinicopathological, and therapeutic aspects of ILC metastases to the female genital tract and discuss separately the differential diagnosis and prognosis for each anatomic location of the female genital tract.

Keywords: breast carcinoma; invasive lobular carcinoma; female genital tract; metastasis; diagnosis

1. Introduction

Invasive lobular carcinoma (ILC) is the commonest special subtype of invasive breast carcinoma, accounting for 5-15% of breast carcinomas [1], thus being second in frequency only to invasive breast carcinoma of no special type (IBCNST) [2]. It was first described by Foote and Stewart in 1941 [2]. Its morphological, immunohistochemical, clinical, radiological, and molecular characteristics differ

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from those of IBCNST. It may remain undetectable or present as a palpable tumor [3]. In imaging studies, it may be detected with difficulty and tumor size may occasionally be underestimated, resulting in positive surgical margins [4]. The metastatic pattern also differs from that of IBC NST, with ILC metastases to the peritoneum, gastrointestinal tract, and female genital tract (FGT) being more frequent [5–8]. ILC lacks E-cadherin immunopositivity and displays an aberrant β-catenin immunostaining [9]. Its molecular profile is characterized by deleterious mutations in CDH1 paired with allelic loss of the remaining allele [4].

Histologically, ILC is characterized by small cells with a discohesive growth pattern forming single-cell files, and a minimal stromal response. Signet-ring-like cells may sometimes be found [4]. Apart from the classic variant, several histological variants have been described, including alveolar [10], tubulolobular [11], solid [12], trabecular [10], signet-ring [13], pleomorphic [14], and mixed [15]. Another three rare variants (ILC with extracellular mucin production, ILC with papillary features, and ILC with tubular elements) have recently been described [3].

ILC treatment usually includes hormonal therapy, since it is commonly positive for estrogen (ER) and progesterone receptors (PR) [3]. It displays a poor response to neoadjuvant chemotherapy when compared to IBCNST [3].

We herewith review case reports and case series describing ILC metastases to the FGT.

2. Materials and Methods

2.1. Search Strategy

A literature review was conducted using PubMed, Scopus, and Web of Science to identify all published cases in the English language of ILC metastasis to the FGT. The research utilized the following terms: “lobular carcinoma” AND “metastasis” AND “female genital tract OR ovary OR ovarian OR vulva OR vagina OR endometrium OR endometrial OR uterus OR uterine."We did not set any additional limitations while performing the search.

2.2. Inclusion and Exclusion Criteria

Two authors [MGS, KS] performed the literature review and collected data. Discrepancies were corrected in consensus. In cases where consensus could not be reached, the principal investigator (NK) resolved the discrepancy.

The timeline for the selected studies ranged from October 1993 to April 2024.

Both single case reports as well as case series (studies reporting at least two cases) on ILC metastasis to the FGT were included in the review. At the same time, we excluded narrative or systematic reviews, meta-analyses, opinion pieces, and other articles that did not present original research findings.

Papers available only as abstracts or those with text appearing too brief or noninformative were excluded from the present review.

The clinicopathological and treatment parameters analyzed included age (median and range), clinical presentation, primary tumor size, ER, PR, and HER-2 status both in primary focus and in the metastasis, tumor stage, location of metastatic involvement, metastases in organs or locations other than the FGT, surgical and neoadjuvant or adjuvant treatment, time interval to metastasis, median follow-up, outcome, and tumor grade (Tables 2–4).

In addition, cases with insufficient or too much aggregated data, as well as manuscripts in languages other than English, were excluded.

After applying inclusion and exclusion criteria, 54 manuscripts describing 61 cases of ILC with metastasis to the female genital tract [16–69] remained for data extraction.

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2.3. Statistical Analysis

As detailed patient characteristics were available in the studied case reports, it was feasible to perform statistical analysis. Specifically, the descriptive characteristics for the quantitative data that were expressed as median and Quartile 1 (Q1) to Quartile 3 (Q3), range and for completeness reasons via mean±standard deviation (SD), and for the qualitative data was reported the frequency of occurrence and the relevant percentage. It was also possible to evaluate overall survival (OS) via the Kaplan – Meier estimator and perform comparisons of OS with various characteristics via the log-rank method. The statistical analysis was performed using the R language for statistical analysis (version 4.4.0), and the significance level (p-value) was set to 0.05 when applicable tests were two-sided.The Materials and Methods should be described with sufficient details to allow others to replicate and build on the published results. Please note that the publication of your manuscript implicates that you must make all materials, data, computer code, and protocols associated with the publication available to readers. Please disclose at the submission stage any restrictions on the availability of materials or information. New methods and protocols should be described in detail while well-established methods can be briefly described and appropriately cited.

3. Results

3.1. Patients' Characteristics

In total, 61 patients were reported in the studied case reports and case series. The mean patient age was 57.4±12.2 years (min: 32, max: 86). The detailed descriptive statistics for patient characteristics are depicted in Table 1.

Table 1. Descriptive characteristics of the reported cases in the studied case reports. ANED: Alive, no evidence of disease, AWD: Alive with the disease, DOD: died of disease, SD: Standard deviation.

Characteristic	Measure
Number of cases	61
Age	
Mean±SD	57.4±12.2
Median [Min, Max]	56.0 [32.0, 86.0]
Tumor Size (cm)	
Mean±SD	3.65±2.11
Median [Min, Max]	3.65 [0.900, 10.0]
Missing	39 (63.9%)
Primary tumor ER status	
Negative	2 (3.3%)
Positive	34 (55.7%)
Missing	25 (41.0%)
Primary tumor PR status	
Negative	2 (3.3%)
Positive	34 (55.7%)
Missing	25 (41.0%)
HER-2/~~Ce~~-erbB-2 status	
Negative	21 (34.4%)
Positive	3 (4.9%)
Missing	37 (60.7%)
Secondary tumor ER status	
Negative	3 (4.9%)
Positive	31 (50.8%)
Missing	27 (44.3%)
Secondary tumor PR status	

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Negative	6 (9.8%)
Positive	24 (39.3%)
Missing	31 (50.8%)
HER-2 status	
Negative	9 (14.8%)
Positive	3 (4.9%)
Missing	49 (80.3%)
Stage pT component	
pT1	1 (1.6%)
pT1b	1 (1.6%)
pT1c	6 (9.8%)
pT2	15 (24.6%)
pT3	6 (9.8%)
pT4	1 (1.6%)
Missing	31 (50.8%)
Stage pN component	
N0	8 (13.1%)
N1	10 (16.4%)
N2	5 (8.2%)
N3	9 (14.7%)
Missing	29 (47.5%)
Stage pM component	
M0	22 (36.1%)
M1	6 (9.8%)
Missing	33 (54.1%)
Radiotherapy	
No	24 (39.3%)
Yes	27 (44.3%)
Missing	10 (16.4%)
Interval to Met (in months)	
Mean±SD	65.6±70.0
Median [Min, Max]	48.0 [2.00, 360]
Missing	20 (32.8%)
Last, follow up (in months)	
Mean±SD	71.1±67.6
Median [Min, Max]	54.0 [1.00, 308]
Missing	30 (49.2%)
Last, follow up status	
ANED	19 (31.1%)
AWD	9 (14.8%)
DOD	10 (16.4%)
Missing	23 (37.7%)
Tumor grade	
Grade II	10 (16.4%)
Grade III	2 (3.3%)
Missing	49 (80.3%)

3.2. Demographic and Clinicopathological Features

Metastasis of ILC to the female genital tract ILC metastasis to the FGT is uncommon. We were able to retrieve 54 manuscripts describing a total of 61 cases of ILC FGT secondaries. Primary tumor size was mentioned in 22/61 (36%) [17,18,21–23,25,28,32,34,36,39–41,43,50,53,58,59,63,65,66] cases. The mean tumor size was 36.5 mm (range 9–100 mm). The metastatic site was mentioned in all cases. Some of the patients had more than one FGT metastatic site. The most common metastatic site was

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the uterine corpus in 30/61 (49.2%) [20,24,27,28,30,35,36,38–41,43–47,49–51,53–56,59,61,62,64–66] patients, followed by the uterine cervix in 25/61 (41%) [21,22,24,27,28,30–32,34,35,39,44,46,50,53,54,58,59,62,65,66], and the ovary in 22/61 (36%) [28–30,35,36,38,42,44,48,51,53,54,57,63,65–67] patients. In 9/61 (14.7%) [16,20,26,27,52,60,68] cases, the metastatic site was an endometrial polyp; in 8/61 (13.1%) [17,23,27,33,37,38,44,45,52,59] a uterine leiomyoma, and in the vulva in 4/61 (6.5%) [18,25,37,42]. Less common metastatic sites were an ovarian granulosa cell tumor [19], the vagina [54], and an ovarian fibroma [69]. Metastases to sites other than the FGT were documented in 21/61 (34.4%) [18,20,21,23,36–38,40–46,49,57,59,62–64,66,67]. Metastatic spread to the bones was found in 12/21 (57.1%) [18,20,23,38,41,43,49,59,62–64,66] patients. Other metastatic sites were the pancreas [21], stomach [21,37,47,67], liver [36,38], pleura [37], peritoneum [37,42,43], lymph nodes [42,43,46], gallbladder [43], omentum [44], orbit [49], large bowel [57], and appendix [57].

Symptoms were mentioned in 60/61 (98.4%) [16–69] cases. Bleeding from the genitalia was the commonest symptom in 24/60 (40%) [17,20,21,24,26,28,33,35,37,41,43,44,49,52–56,58,60,61,64,65,68] cases followed by abdominal pain in 6/60 (10%) [19,22,57,59,60,69] patients, a mass in 5/60 (8.3%) [18,23,25,51] cases, abdominal distention in 3/60 (5%) [44,63,69] cases, abdominal discomfort in 3/60 (%) [39,67] patients. Less common symptoms included abdominal fullness [29], loss of appetite [29], urinary incontinence [38], polyuria [39], abdominal bloating [42,57], abdominal compression [45], postcoital bleeding [46], vaginal fullness and discomfort [51], altered bowel habits [57], and right shoulder pain [66] in 1/60 (1.7%) of patients each. Finally, 14/60 (23.3%) [16,27,30–32,34,36,40,47–51,62] patients were asymptomatic. In 42 cases, the FGT metastasis was metachronous, while in 12 cases, it was concomitant. The interval to metastasis ranged from 2 to 360 months (mean 65.6 months). The detailed demographic and clinicopathological features of the cases are shown in Table 2.

Table 2. Demographic and clinicopathological features of the reported cases.

Authors	Year	Age	Clinical Presentation	Tumor Size (cm)	Stage	Site of metastasis FGT[16–69	Other metastatic sites
Aranda et al.	1993	76	Asymptomatic	NM	pTx, N0	Endometrial polyps	-
Sugiyama et al.	1995	51	Hypermenorrhea	4	pT2, N1, M1	Uterine leiomyoma	-
Menzin et al.	1998	53	Vulvar tumor	2,5	pT2, N0, M1	Vulva	Vertebrae and pelvic bones.
Arnould et al.	2002	59	Abdominal and pelvic pain	-	-	Ovarian granulosa cell tumor	-
Alvarez et al.	2003	69	Metrorrhagia	-	pT2, N1, M0	Endometrial polyps and uterus	Skull and spine.
Ogino et al.	2003	49	Abnormal genital bleeding	3.5	pT2, N0, M0	Cervix	Pancreas, stomach
Rau et al.	2003	55	Abdominal pain	5	pT4, N1, M0	Cervix	-
Blecharz et al.	2004	46	Enlarged uterus	1	pT1c, N2	Uterine leiomyoma	Bone
Famoriyo et al.	2004	78	Postmenstrual bleeding	-	NM	Uterus and cervix	-
Sheen-Chen et al.	2004	32	Vulvar tumor	3	pT2, N0, M0	Vulva	-
Al-brachim et al.	2005	53	Vaginal bleeding	NM	pTxN1	Endometrial polyps	-
Lee et al.	2005	76	Asymptomatic	NM	NM	Uterine leiomyoma, myometrium, endometrial polyps, cervical stroma and soft tissue adjacent to the uterus and the cervix	-
Scopa et al.	2005	50	Vaginal bleeding	6	pT3N3	Endometrium, endocervix, ovaries, and fallopian tubes.	-
Scopa et al.	2005	81	Vaginal bleeding	1,6	pT1c, N3	Endometrium	-
Chen et al.	2006	47	Poor appetite and abdominal fullness		pT3, N0, M0	Ovary	-
Erkanli et al.	2006	63	Asymptomatic	NM	pT2, N3, M0	Endometrium, cervix, and ovaries.	-
Perisic et al.	2007	65	Asymptomatic	NM	pT2, N1, M0	Cervix	-
Manci et al.	2008	41	Asymptomatic	1	pT1c, N0, M0	Cervix	-
Manipadan et al.	2008	70	Vaginal bleeding	NM	NM	Endometrial polyps	-
Bogliolo et al.	2009	78	Asymptomatic	0,9	pT1b, N2, M1	Cervix	-
Ustaalioglu et al.	2009	56	Vaginal bleeding	NM	pT2, N2, M0	Endometrium, myometrium, cervix, left uterine tube and left ovary.	-
Engelstaedter et al.	2011	64	Asymptomatic	4	pT3, N3, M1	uterus, adnexa	Liver
Hooker et al.	2011	83	Postmenopausal uterine bleeding	NM	NM	Endometrial polyps, vulva	Pleura, peritoneum, stomach

Isci et al.	2011	48	Increased abdominal girth urinary incontinence	NM	NM	Both the ovaries, tubes, abdominal washing fluid, myometrium, and the huge leiomyoma	Liver, bone
Horikawa et al.	2012	52	abdominal discomfort, polyuria.	5	pT2, N3, M1	Cervix, endometrium	-
Komeda et al.	2012	59	Asymptomatic	3,8	pT3, N2, M0	Uterus	multiple metastases
Vicioso et al.	2013	67	Metrorrhagia	3,2	pT2, N2, M0	Uterus	Left femur, calvarial skull, axial skeleton, and rib cage.
Alligood-Percoco et al.	2015	36	Abdominal bloating	NM	NM	Ovaries / vulva	Peritoneum, lymph nodes
Bezpalko et al.	2015	47	Vaginal bleeding	1,8	pT1c, Nx, M1	Endometrium	gallbladder, bone marrow, lymph nodes, and peritoneum.
Lokadasan et al.	2015	49	Menorrhagia	NM	NM	Endometrium, myometrium, fibroid, cervix, bilateral ovaries.	-
Lokadasan et al.	2015	49	Abdominal distention, pain	NM	pT3, N3, M0	Cervix, bilateral adnexa	Omentum
Toyoshima et al.	2015	62	Abdominal compression.	NM	pT2, N1, M0	Uterine leiomyomata, myometrium	-
Waks et al.	2015	53	Postcoital bleeding	NM	pT2, N1, M0	Cervix, corpus uteri	Pelvic and para-aortic lymph nodes
Lai et al.	2016	54	Asymptomatic	NM	pT3, N3, M0	Endometrium	Stomach
Makris et al.	2016	45	Asymptomatic	NM	pT2, N1, M0	Ovary	-
Martinez et al.	2016	40	Vaginal bleeding	NM	NM	Endometrium	Orbit, bone
Martinez et al.	2016	48	Asymptomatic	NM	NM	Endometrium, myometrium	-
Akhtar et al.	2017	62	Asymptomatic	2,9	NM	Endometrium, cervix	-
Bennett et al.	2017	53	Asymptomatic	NM		Bilateral ovaries	-
Bennett et al.	2017	64	Vaginal fullness and discomfort	NM		Bilateral ovaries, uterus, fallopian tubes	-
Bennett et al.	2017	54	Adnexal mass	NM		-	-
Bennett et al.	2017	41	Adnexal mass	NM		Bilateral ovaries, fallopian tube	-
Bennett et al.	2017	48	NM	NM		Left ovary, uterine serosa	-
Razia et al.	2017	58	Abnormal uterine bleeding	NM	NM	Endometrial polyps, uterine leiomyoma, cervix	-
Seo et al.	2017	46	Vaginal bleeding	4	pT1, N0, M0	Uterine corpus, endocervix, left ovary	-
Aytekin et al.	2018	38	Vaginal bleeding	NM	pT2, N3, M0	Uterus, bilateral ovaries, vaginal cuff, cervix	-

Briki et al.	2018	50	Postmenopausal uterine bleeding	NM	pT2, N1, M0	Endometrium	-
Franko-Marquez et al.	2019	86	Abnormal uterine bleeding.	NM	NM	Endometrium	-
Kachi et al.	2019	58	Altered bowel habits, abdominal pain, bloating.	NM	NM	Bilateral ovaries	large bowel, appendix
Fontinele et al.	2019	57	Abnormal uterine bleeding	10	ypT0, N0, M0	Cervix	-
Abdallah et al.	2020	59	Lower abdominal pain	5	NM	Endometrium, myometrium, leiomyoma, cervix	Scapula
Arif et al.	2020	55	Vaginal bleeding, lower abdominal pain.	NM	NM	Endometrial polyp	-
Gomez et al.	2020	69	Post menopausal bleeding	NM	NM	Endometrium	-
Yuan et al.	2020	64	Asymptomatic	NM	NM	Endometrium, cervix	Bones
Akizawa et al.	2021	49	Abdominal distention	5	NM	Ovary	Bones
Awazu et al.	2021	66	Abnormal genital bleeding	NM	NM	Endometrium	Bones
Lim et al.	2021	57	Vaginal bleeding	5,6	NM	Uterus, cervix, bilateral ovaries, fallopian tubes	-
Kong et al.	2022	64	Right shoulder pain	1,5	pT1c, N3 M0	Uterus, cervix, bilateral ovaries, fallopian tubes	Bones
Li et al.	2022	61	stomach discomfort	NM	pT1c, N1, M0	Bilateral ovaries, peritoneum	Stomach
Benlghazi et al.	2024	56	abnormal uterine bleeding	NM	NM	Endometrial polyps	-
Faur et al.	2024	82	abdominal distension and pain	NM	NM	Ovarian fibroma	-

Abbreviations: FGT: female genital tract; HBSO: hysterectomy and bilateral salpingo-oophorectomy; Met: metastasis; Mo: months; N: No; Neoadj.: neoadjuvant; NM: not mentioned; OM: omentectomy; RT: radiotherapy; Y: Yes.

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3.3. Histological Findings

No information regarding the subtype of ILC was available, apart from one case of ILC with extracellular mucin production [69], which is a very rare subtype with around forty cases in the English literature [70,71].

3.4. Estrogen Receptors (ER) /Progesterone Receptors (PR) /HER-2 Status

Concerning hormonal and HER-2 status, 36/61 (59%) [18,20,21,23,29–48,50,54–56,58,59,63,65,66,68] cases reported ER and PR in the primary focus and 34/61 (55.7%) [18–21,23,26–29,32,35,37,39–42,44–48,50,52,56–59,62–64,66,68] in the metastatic setting. HER-2 status was reported in 24/61 (39.3%) [29,30,32,34,35,37–41,43–45,47,50,54–56,58,59,63,65,66,68] in the in the primary focus and 12/61 (19.7%) [28,29,32,35,46,47,52,58,62,64] in the metastatic location. ER, PR, and Her-2 status of the cases and the histological grade are shown in Table 3.

Table 3. ER, PR, and Her-2 status and histological grade of the reported cases.

Authors	Primary tumor			Metastatic tumor			Tumor grade
	ER status	PR status	HER-2 status	ER status	PR status	HER-2 status	
Aranda et al.	NM	NM	NM	NM	NM	NM	NM
Sugiyama et al.	NM	NM	NM	NM	NM	NM	NM
Menzin et al.	+	+	NM	+	+	NM	NM
Arnould et al.	NM	NM	NM	+	+	NM	NM
Alvarez et al.	+	+	NM	+	+	NM	NM
Ogino et al.	-	+	NM	-	+	NM	NM
Rau et al.	NM	NM	NM	NM	NM	NM	NM
Blecharz et al.	+	+	NM	+	-	NM	NM
Famoriyo et al.	NM	NM	NM	NM	NM	NM	NM
Sheen-Chen et al.	NM	NM	NM	NM	NM	NM	NM
Al-brachim et al.	NM	NM	NM	+	+	NM	NM
Lee et al.	NM	NM	NM	+	+	NM	Grade II
Scopa et al.	-	+	NM	-	+	+	NM
Scopa et al.	NM	NM	NM	+	+	NM	NM
Chen et al.	+	+	-	+	+	-	Grade III
Erkanli et al.	+	+	-	NM	NM	NM	-
Perisic et al.	+	+	NM	NM	NM	NM	Grade II
Manci et al.	+	+	-	+	+	+	NM
Manipadan et al.	Not done	Not done	Not done	NM	NM	NM	NM
Bogliolo et al.	+	+	-	NM	NM	NM	Grade II
Ustaalioglu et al.	+	+	-	+	+	-	NM
Engelstaedter et al.	+	+					Grade II
Hooker et al.	+	+	-	+	-	NM	NM
Isci et al.	+	-	-	NM	NM	NM	NM
Horikawa et al.	+	+	-	+	NM	NM	NM
Komeda et al.	+	+	-	-	-	NM	NM
Vicioso et al.	+	+	-	+	-		Grade II
Alligood-Percoco et al.	+	+	NM	+	NM	NM	NM
Bezpalko et al.	+	+	-	NM	NM	NM	Grade II
Lokadasan et al.	+	+	-	NM	NM	NM	NM
Lokadasan et al.	+	+	NM	+	+	NM	Grade II
Toyoshima et al.	+	+	+	+	-	NM	NM

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Waks et al.	+	+		+	+	-	NM
Lai et al.	+	+	-	+	+	-	Grade II
Makris et al.	+	+	NM	+	+	NM	NM
Martinez et al.	NM	NM	NM	NM	NM	NM	
Martinez et al.	NM	NM	NM	NM	NM	NM	NM
Akhtar et al.	+	+	-	+	+	NM	NM
Bennett et al.	NM	NM	NM	NM	NM	NM	NM
Bennett et al.	NM	NM	NM	NM	NM	NM	NM
Bennett et al.	NM	NM	NM	NM	NM	NM	NM
Bennett et al.	NM	NM	NM	NM	NM	NM	NM
Bennett et al.	NM	NM	NM	NM	NM	NM	NM
Razia et al.	NM	NM	NM	+	+	+	NM
Seo et al.	+	+	NM	+	+	NM	NM
Aytekin et al.	+	+	-	NM	NM	NM	NM
Briki et al.	+	+	-	NM	NM	NM	NM
Franko-Marquez et al.	+	+	+	+	NM	NM	NM
Kachi et al.	NM	NM	NM	+	+	NM	NM
Silva Fontinele et al.	+	+	-	+	+	-	Grade II
Abdallah et al.	+	+	-	+	+	NM	NM
Arif et al.	NM	NM	NM	NM	NM	NM	NM
Gomez et al.	NM	NM	NM	NM	NM	NM	Grade II
Yuan et al.	NM	NM	NM	+	+	-	NM
Akizawa et al.	+	+	-	+	NM	NM	NM
Awazu et al.	NM	NM	NM	+	+	-	NM
Lim et al.	+	+	+	NM	NM	NM	NM
Kong et al.	+	-	-	+	+	-	NM
Li et al.	NM	NM	NM	NM	NM	NM	NM
Benlghazi et al.	+	+	-	+	-	-	Grade III
Faur et al.	NM	NM	NM	NM	NM	NM	NM

Abbreviations: ER: estrogen receptors; NM: not mentioned; PR: progesterone receptors.

3.5. Treatment

Surgical treatment information was available in 51/61 (83.6%) [17–49,52,54–59,61–68] cases. In 32/51 (62.7%) [17,20–23,25–31,35,39,40,42,44,47,49,54–58,61,62,65–68] cases, surgical treatment consisted of a modified radical mastectomy. Breast-conserving surgery was performed in 9/51 (17.6%) [18,32,34,36,41,45,46,48,53] cases, hysterectomy and bilateral salpingo-oophorectomy in 5/51 [23,36,39,59,63] (9.8%), breast biopsies in 3/51 (5.9%) [33,43,44]. Omentectomy was performed in 2/51 (3.9%) [36,63] cases. Endometrial and cervical biopsies were performed in 2/51 (3.9%) [34,49] cases, cervical biopsy in 1/51 (1.9%) [34], and partial vulvectomy in 1/51 (1.9%) [18] cases. Additionally, two manuscripts reported that surgical treatment was performed without any additional detail concerning the type of intervention [52,64]. In cases with metachronous FGT metastasis, second-line treatment was reported in 43/49 (87.7%) [16,19–23,25,27–33,35,37,38,40–42,44–49,52–58,60–62,64–66,68] cases. Surgical treatment consisted in hysterectomy and bilateral salpingo-oophorectomy in 22/43 (51.2%) [16,21,26,28–30,32,35,38,41,42,45,48,49,52–55,58,60,64–66,68] patients, bilateral oophorectomy in 2/43 (4.6%) [19,57], pancreatoduodenectomy in 1/43 (2.3%) [21], wide tumor excision in 1/43 (2.3%) [25], omentectomy in 4/43 (9.3%) [29,30,48,64], pelvic lymph node sampling in 1/43 (2.3%) [29], pelvic lymphadenectomy in 2/43 (4.6%) [30,32], excision of an endometrial polyps in 2/43 (4.6%) [33,37], appendectomy in 2/43 (4.6%) [42,57], endometrial biopsy in 1/43 (2.3%) [47], peritoneal biopsies in 2/43 (4.6%) [48,64], partial colectomy in 1/43 (2.3%) [52], anterior resection in 1/43 (2.3%) [57]. Biopsy of the metastatic lesion was performed in 5/43 (11.6%) cases [20,46,56,61,62].

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Information regarding adjuvant treatment was provided in 50/61 (83.6%) [17,19–23,25–50,52–59,62–68] cases. Chemotherapy either in the adjuvant or neoadjuvant setting was offered in 43/50 (86%) [17,19,20,22,23,25,27–29,31,33–36,38,40–49,52–59,62–68] cases and radiotherapy in 27/50 (54%) [19,20,22,27–29,31,32,34,35,42,44–49,52–55,57,58,62,65,67,68] cases. In two cases, patients refused chemotherapy [30,50], and in another two, radiotherapy [30,66]. The most common regimen used consisted of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF regimen). In contrast, the second most common regimen consisted of adriamycin, cyclophosphamide (AC regimen), and paclitaxel administered in four [20,25,31,42] and three cases [54,58,63], respectively. Hormonal treatment was provided to 48/50 (96%) [17,19–23,25–32,34–47,49,52–59,62–68] patients. Among 43 cases with metachronous metastasis, 13 received additional chemotherapy [21,25,30,32,40,42,44,46–48,54,56,66,67], one received targeted therapy [65], two received additional radiotherapy [23,41], and 13 received additional hormonal treatment [19,21,23,32,35,41,42,45,52,58,64,65,68].

3.6. Outcome

Follow-up information was available in 40/61 (65.6%) [17–19,21–23,25,28,30–32,34–43,45,47,48,50–54,58,60,62–64,66–68] cases. Briefly, 16/40 (40%) [17,19,32,35–39,45,48,52,53,58,60,64,67,68] patients were alive without evidence of disease, 9/40 (22.5%) [18,23,25,30,34,41,42,47,51] were alive with disease, and 10/40 (25%) [21,28,31,40,43,51,54,66] died of disease in a period of time that ranges from 1 to 308 months. In 2/40 (5%) [22,50] cases, patients were lost to follow-up. Treatment and follow-up data are shown in Table 4.

Table 4. Treatment and follow-up features of the reported cases.

Authors	Surgery	CHT	RT	Hormonal therapy	Interval to Met (Mo)	Second-Line Therapy	Outcome
Aranda et al.	NM	NM	NM	NM	36	HBSO	NM
Sugiyama et al.	MRM	5-FU, mitomycin C, and pirarubicin	N	Tamoxifen	Concomitant	-	48 ANED
Menzin et al.	Quadrantectomy, ALND, and partial vulvectomy.	NM	N	Tamoxifen	Concomitant	-	18 AWD
Arnould et al.	NM	CHT	Y	Tamoxifen	48	Bilateral oophorectomy, letrozole	60 ANED
Alvarez et al.	MRM	6 x CMF	Y	Tamoxifen	48	Biopsy	NM
Ogino et al.	MRM	No	N	Tamoxifen	128	Pancreatoduodenectomy, HBSO, ADM-TXL CHT and anastrozole.	136 DOD
Rau et al.	MRM	6x CHT	Y	Tamoxifen	48	Patient refused	Lost to follow-up
Blecharz et al.	MRM, HBSO	6 x ADR, CTX, 5-FU.	N	Tamoxifen	Concomitant	Aromatase inhibitors and biphosphonates and palliative radiotherapy of the thoracic and lumbar vertebrae.	59 AWD
Famoriyo et al.	NM	NM	NM	Tamoxifen	NM	NM	NM
Sheen-Chen et al.	MRM	6 x CMF	N	Tamoxifen	40	Wide excision of the tumor, cyclophosphamide, epirubicin, and 5-FU.	40 AWD
Al-brachim et al.	MRM	No	N	Tamoxifen	48	NM	NM
Lee et al.	MRM	CHT	Y	Tamoxifen	18	HBSO	
Scopa et al.	MRM	4 x epirubicin	Y	Tamoxifen and LH-RH agonist	36	HBSO	54 DOD
Scopa et al.	MRM	4 x cyclophosphamide and adriamycin.	N	Tamoxifen and LH-RH agonist	24	HBSO	30 DOD
Chen et al.	MRM	6 x CHT	Y	Tamoxifen	56	HBSO, partial OM, and pelvic lymph node sampling	NM
Erkanli et al.	MRM	Patient refused CHT	Patient refused RT	-	8	HBSO, omentectomy, and pelvic lymphadenectomy. Cyclophosphamide, epirubicin, and 5-FU	8 AWD

Perisic et al.	MRM	6 x CMF	Y	Tamoxifen	52	The patient refused CHT	72 DOD
Manci et al.	quadrentectomy	No	Y	Tamoxifen	130	HBSO, pelvic lymphadenectomy, CHT, Femara.	150 ANED
Manipadan et al.	Biopsy	6 x docetaxel and zoledronic acid	N	No	2	Polypectomy	NM
Bogliolo et al.	Quadrantectomy, SLNB, endometrial and cervical biopsy.	6 x 5-FU, epirubicin, cyclophosphamide, and docetaxel	Y	Letrozole	Concomitant	-	30 AWD
Ustaalioglu et al.	MRM	4 x doxorubicine, cyclophosphamide / 4 x docetaxel	Y	Anastrozole	36	HBSO, exemestane	45 ANED
Engelstaedter et al.	HBSO, OM, lumpectomy, ALND.	Navelbine.	N	Tamoxifen	Concomitant	-	65 ANED
Hooker et al.	No	No	N	Letrozole, Tamoxifen, Fulvestrant	60	Polypectomy	72 ANED
Isci et al.	No	CHT	N	Letrozole and ibandronate.	15	HBSO, CHT	27 ANED
Horikawa et al.	HBSO, MRM	No	N	Anastrozole, S-1	Concomitant	-	84 ANED
Komeda et al.	MRM	4 x doxorubicin, cyclophosphamide/ 6 x paclitaxel	N	Letrozole	15	The patient refused HBSO, doxorubicin, and cyclophosphamide.	28 DOD
Vicioso et al.	Quadrantectomy, ALND.	6 x taxotere, adriamycin, and cyclophosphamide.	N	Tamoxifen	72	HBSO, letrozole, RT.	163 AWD
Alligood-Percoco et al.	MRM	4 x doxorubicin, 8 x CMF.	Y	Tamoxifen	116 / 240	HBSO, appendectomy, debulking, Taxotere, and Xeloda / Arimidex	240 AWD
Bezpalko et al.	Biopsy	CHT	N	Hormonal therapy	Concomitant	-	1 DOD
Lokadasan et al.	Biopsy	5-FU, epirubicin, cyclophosphamide	N	Hormonal therapy	Concomitant	-	NM
Lokadasan et al.	MRM	3 x 5-FU, adriamycin, cyclophosphamide / 3 x docetaxel	Y	Tamoxifen	48	Carboplatin, gemcitabine.	NM
Toyoshima et al.	Breast conserving surgery	6 x 5-FU, epirubicin, cyclophosphamide.	Y	Anastrozole	84	HBSO, exemestane	ANED
Waks et al.	Breast conserving surgery, ALND	methotrexate, cyclophosphamide, 5-FU	Y	Tamoxifen	180	Biopsy, CHT	NM

Lai et al.	MRM	CHT	Y	Tamoxifen / anastrozole / exemestane	84	endometrial biopsy, CHT	AWD
Makris et al.	Lumpectomy, ALND	6 x docetaxel, doxorubicin, cyclophosphamide	Y	No	24	HBSO, omentectomy, peritoneal biopsies, 6 x carboplatin, paclitaxel	18 ANED
Martinez et al.	MRM, endometrial biopsy	CHT	N	Tamoxifen	Concomitant	-	
Martinez et al.	MRM	CHT	Y	Tamoxifen	18	HBSO	NM
Akhtar et al.	Biopsy	Patient refused CHT	N	N	Concomitant	-	Lost to follow-up
Bennett et al.	NM	NM	NM	NM	NM	NM	49 DOD
Bennett et al.	NM	NM	NM	NM	NM	NM	84 AWD
Bennett et al.	NM	NM	NM	NM	NM	NM	9 DOD
Bennett et al.	NM	NM	NM	NM	NM	NM	NM
Bennett et al.	NM	NM	NM	NM	NM	NM	NM
Razia et al.	Surgery	doxifluridine, cyclophosphamide, docetaxel	Y	Goserelin acetate, Tamoxifen, toremifene citrate	108	HBSO, a partial colectomy, an aromatase inhibitor	ANED
Seo et al.	Breast conserving surgery, ALND	2 x neoadj. Cyclophosphamide, adriamycin 4 x adj. cyclophosphamide, adriamycin	Y	Goserelin, TamoxifenTamoxifenTamoxifen	24	HBSO	ANED
Aytekin et al.	MRM	4 x adriamycin, cyclophosphamide / 12 x paclitaxel	Y	tamoxifen and luteinizing hormone-releasing hormone analog	10	HBSO, CHT	16 DOD
Briki et al.	MRM	CHT	Y	Tamoxifen	24	HBSO	NM
Franko-Marquez et al.	MRM	CHT	N	NM	360	Biopsy, CHT	NM
Kachi et al.	MRM	9 x CHT	Y	Tamoxifen	60	Anterior resection, BO, appendectomy	NM
Silva Fontinele et al.	MRM	Neoadj. 4x doxorubicin, cyclophosphamide/ 12 x paclitaxel	Y	Tamoxifen	39	HBSO, anastrozole	66 ANED
Abdallah et al.	HBSO	6 x cycolphosphamide, epirubicin 5-FU	N	Hormonal therapy	Concomitant	-	NM

Arif et al.	NM	NM	N	Tamoxifen	84	HBSO	96 ANED
Gomez et al.	MRM	NM	NM	Tamoxifen	60	Biopsy	NM
Yuan et al.	MRM	CHT	Y	Hormonal therapy	132	Biopsy	ANED
Akizawa et al.	HBSO, OM	Palbociclib, denosumab	N	Letrozole	Concomitant	-	ANED
Awazu et al.	Surgery	CHT	NM	aromatase inhibitors/tamoxifen	276	HBSO, partial OM, a biopsy of the peritoneum, fulvestrant, toremifene citrate, and tegafur	308 ANED
Lim et al.	MRM	4 x cyclophosphamide, adriamycin, 5-FU/ 4 x taxotere	Y	Tamoxifen	30	HBSO, fulvestrant, ribociclib	NM
Kong et al.	MRM	4 x epirubicin, cyclophosphamide / 4 x paclitaxel	patient refused RT	Letrozole	29	Radiotherapy, zoledronate / HBSO, 6 x paclitaxel, capecitabine, radiotherapy, zoledronate / 2 x gemcitabine, cisplatin	49 DOD
Li et al.	MRM	6 x docetaxel, doxorubicin, cyclophosphamide	Y	Anastrozole	36	hyperthermic perfusion chemotherapy (paclitaxel)	ANED
Benlghazi et al.	MRM	3 x Epirubicine, cyclophosphamide, 5FU / 3 x Docetaxel	Y	Tamoxifen	60	HBSO, hormonal treatment	78 ANED
Faur et al.	NM	NM	NM	NM	NM	NM	NM

Abbreviations: Adj.: Adjuvant; Adriamycin-Cyclophosphamide (AC), ADR: Adriamycin; ADM-TXL: doxorubicin (ADM), paclitaxel (TXL); ANED: Alive no evidence of disease; AWD: Alive with disease; BO: Bilateral oophorectomy; Cyclophosphamide-adriamycin-5-Fluorouracil (CAF); Cyclophosphamide- Methotrexate- 5 Fluorouracil (CMF); CHT: chemotherapy (not specified); CTX: Cyclophosphamide; Docetaxel-doxorubicin- cyclophosphamide (TAC); DOD: Died of disease; Epirubicin-Cyclophosphamide (EC); Epirubicin-cyclophosphamide-5FU (FEC); FGT: female genital tract; 5-FU: 5 Fluorouracil; HBSO: hysterectomy and bilateral salpingo-oophorectomy; Met: metastasis; Mo: months; N: No; Neoadj.: neoadjuvant; NM: not mentioned; OM: omentectomy; RT: radiotherapy; Y: Yes.

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3.5. Patient Survival

Patient survival time information was available for 31 patients. Of these patients, 10 were deceased due to their disease; the restricted mean survival time was 186±30.7 months.

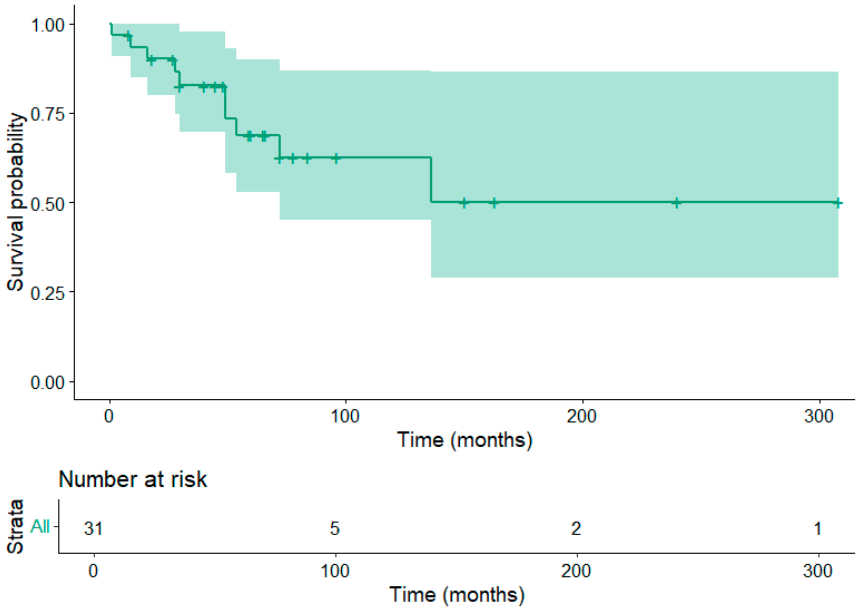

Figure 1. Kaplan Meier estimator for the patient overall survival. The shaded area corresponds to the 95% confidence interval.

Further analysis was based on the evaluation of the role of all recorded characteristics in patient survival. The results are depicted in Table 5. Notably, a negative ER on a secondary tumor was found to be linked to worst patient survival (HR: 0.13, 95% CI: 0.02-0.8, p=0.01); see Figure 2.

Table 5. Role of the study variables in patient overall survival. HR: Hazard Ratio, CI: Confidence interval, N: Number of valid cases.

Characteristic	HR and 95% CI	p-value	N
Primary tumor ER status	0.41 (0.08-2.18)	0.283	22
Primary tumor PR status	0.27 (0.03-2.6)	0.223	22
Secondary tumor ER status	0.13 (0.02-0.8)	**0.01**	18
Secondary tumor PR status	2.04 (0.23-18.39)	0.518	16
HER-2 status	1.73 (0.11-27.89)	0.695	7
Stage pN	4.91 (0.2-118.15)	0.31	20
Stage pM	0.64 (0.07-5.76)	0.686	18
Other metastasis	0.82 (0.22-3.03)	0.76	31
RT	0.72 (0.17-3.02)	0.65	27

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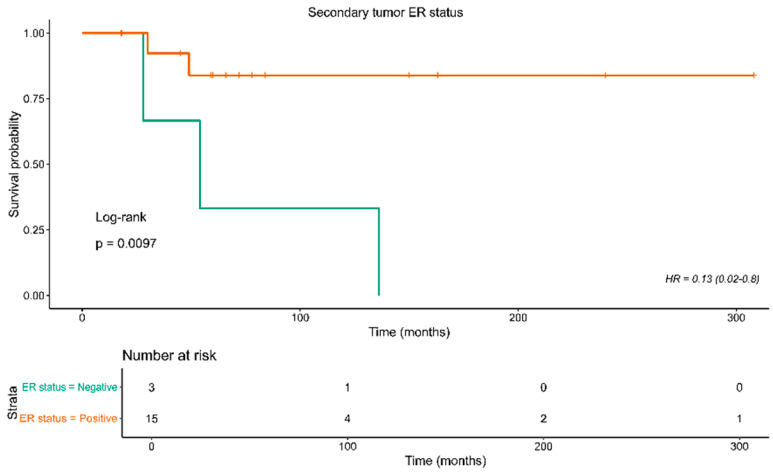

Figure 2. Kaplan Meier curves for overall survival in relation to ER status of the secondary tumor.

4. Discussion

Extragenital metastases to the FGT are relatively uncommon. Concernng specific locations of secondaries, One study reported that, among 149 metastatic neoplasms to the FGT from primary extragenital tumors reported in one study, the ovary (75.8%) and vagina (13.4%) were the most frequent locations, followed by the endometrium (4.7%) and cervix (3.4%) [72]. The majority of FGT metastases from breast cancer occurred in advanced cases during hormonal treatment or follow-up [53].

In the literature, the incidence of ILC metastasis to the FGT ranges from 2% to 5% in clinical series [5,73] and from 36% to 52% in autopsy series [74,75]. This difference is probably due to the fact that autopsy may discover clinically occult micrometastases. Adnexal involvement was reported in 21% of patients in a series [76].

The ovaries frequently receive metastases from primary malignant tumors both of genital and extragenital sites [77,78]. This can be explained by the fact that they provide an excellent environment for malignant cell implantation due to their rich vasculature and extensive lymphatic network, as well as due to a favorable pH and oxygen pressure in the ovarian stroma [31].

In a number of studies, the most common primary site varies between the gastrointestinal tract and the breast [79]. Ovarian metastasis from breast carcinoma constitutes 3–38% of all ovarian neoplasms, with a variable incidence depending on diagnostic methods, geographic distributions, and other variables [80–82]. Studies have shown that breast cancer patients have an incidence of ovarian metastases in 13–47% of cases, either in autopsy or surgical material [83–85].

ILC ovarian metastasis usually manifests as bilateral solid and cystic masses, the so-called Krukenberg tumor(s). Micrometastatic disease may remain undetected both on clinical examination and imaging studies [86].

Metastases in the ovaries may occasionally mimic clinical and histological characteristics of primary ovarian carcinomas [79]. The distinction of metastatic versus primary ovarian carcinoma is of paramount importance since their management differs [77,87–89]. To date, there are no clear guidelines concerning the management of carcinomas metastatic to the ovary. However, surgical resection may increase patient survival [79].

Some clinicopathologic factors of primary breast carcinoma have been identified to be related to increased risk for ovarian metastasis. ILC has an increased metastatic potential to the ovaries [5,74,75,90–92]. Also, young age and premenopausal status are factors related to increased risk [81,93–96]. Other factors related to the development of ovarian metastases are other co-existent metastatic sites [85], large primary tumor size [85,97], inflammatory breast cancer [85], positive lymph nodes [85,97], higher stage (III-IV)[97–99], and bilaterality [81].

The incidental finding of an ovarian mass in an asymptomatic patient may be the first sign of ovarian metastasis [77,98–102]. Usually, they are bilateral, small, and solid [81,82,87,103–108]. Other

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symptoms, including gastrointestinal symptoms, ascites, pelvic pain, and vaginal bleeding, can be observed in some patients [77,94]. However, none of these clinical manifestations is related to either breast metastasis or primary ovarian carcinoma [78,82,107]. In our review, only 3/20 (15%) [30,48,51] cases were asymptomatic.

Imaging examinations are also widely used for diagnosis, staging, and monitoring of curative effects.

The pathologic examination of a specimen includes gross, microscopic, and immunohistochemical testing. These are considered the 'gold standard' in the diagnosis of metastatic breast cancer to the ovaries [109].

On gross examination, bilateral involvement, small size, and a solid mass are clues related to metastatic breast carcinoma [81,82,87,98,103,105,106,108,109]. Metastases in the ovaries are usually located in the ovarian medulla and/or cortex [94]. On the other hand, primary tumors are typically located in the ovarian surface epithelium and superficial cortex [102].

Microscopically, ovarian metastases sometimes mimic histological features of primary ovarian carcinomas [103,110,111], which makes their distinction difficult. The characteristic pattern of ILC with small, discohesive cells forming single-cell files will usually allow to make the diagnosis on hematoxylin and eosin stains. In difficult cases, immunohistochemical analysis typically resolves any diagnostic problem. Immunostaining for GATA-3, GCDFP-15, and Mammaglobin is diagnostic for metastatic ILC, whereas PAX-8, WT-1 p53, and p16 are positive in primary ovarian carcinoma.

Concerning treatment options, most breast cancer patients have other non-FGT metastases at the time of ovarian metastasis. The treatment should be for systemic disease. The regimen should be tailored to the clinicopathological aspects of the metastatic site, the burden of disease and the eventual visceral crisis, the symptoms, and the performance status of the patient. Drug toxicity profile and patient preferences are of utmost importance [85,103].

The prognosis of patients with breast carcinoma ovarian metastases is poor since the median progression-free survival ranges from 9 to 30 months, the median overall survival is 16 to 38 months, and the 5-year survival rate is 6 to 26% [79].

Clinicopathologic factors that affect survival are age [103], time interval to ovarian metastasis [82], unilaterality [109], adenocarcinoma [112], and menstrual status [89].

Uterine metastases from extragenital cancers are much less common than ovarian metastases ones [52]. Metastases confined to the uterus, without ovarian involvement, are very rare and can occur through hematogenous spread [52]. The myometrium is the most commonly involved location within the corpus uteri that metastatic ILC involves, followed by the endometrium. The first manifestation of metastatic disease may be abnormal uterine bleeding [86].

ILC is, in most cases, ER-positive. Premenopausal patients regularly receive Tamoxifen as part of the adjuvant treatment, which, increases the risk for endometrioid carcinoma of the endometrium [86].

Differentiating metastatic ILC from a primary endometrial carcinoma can be difficult but is of huge importance since the treatment is different for these carcinomas.

Metastasis from breast carcinoma to the cervix uteri is very rare, with an estimated frequency of 0.8–1.7% [113]. This is possibly due to its small size, its reduced blood flow and distal circulation, and the presence of abundant fibrous tissue [114]. The true incidence of cervical metastasis from ILC remains unknown. Other distant metastases were found at the time of diagnosis of cervical metastasis in 67%–89% of the cases [115].

In our review, we found 22 cases of ILC metastatic to the cervix.

Differential diagnosis between a cervical primary and ILC cervical metastasis may occasionally prove difficult. Dedifferentiation of cervical adenocarcinoma and squamous cell carcinoma with acantholytic changes may result in the simulation of the morphology of ILC [116,117]. Again, the finding of the characteristic morphology of ILC, i.e., discohesive cells and the formation of single cell files within the cervical stroma, especially when the cervical epithelium is spared, should raise the

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suspicion of metastatic disease. Appropriate immunohistostaining with GATA3, mammaglobin, and GCDFP-15 will give the diagnostic solution in ambiguous cases.

Vaginal metastasis is second in frequency after ovarian involvement in the FGT. Treatment consists of surgical debulking chemotherapy and/or radiotherapy. For patients with vaginal metastasis from breast carcinoma, a very important prognostic feature is the finding of metastases in other sites [118]. A lot of times, when vaginal metastases occur, there are already metastases in other organs. Whenever this happens, the prognosis is poor [119].

Breast cancer metastasis to the vulva is very rare. In these cases, the differential diagnosis is done with primary breast carcinoma of the vulva [120]. The most important distinguishing feature is the previous history of breast cancer. Additionally, the histological similarity between the primary breast and the metastatic lesion, as well as the absence of an in situ element, will guide the pathologist in diagnosing a metastatic lesion [120].

5. Conclusions

In summary, we reviewed cases and case series of ILC metastasis to the FGT, describing the clinical, pathological, therapeutical, and follow-up data. We also discussed the current literature focusing on the differential diagnosis, treatment, and prognosis of ILC metastasis to the FGT.

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