Solitary Vulvar Metastasis from Early Stage Endometrial Cancer: Case Report and Literature Review

Vincenzo Dario Mandato (dariomandato@gmail.com)
AUSL-IRCCS Reggio Emilia
Valentina Mastrofilippo
AUSL IRCCS Reggio Emilia
Andrea Palicelli
AUSL IRCCS Reggio Emilia
Monica SILVOTTI
AUSL IRCCS Reggio Emilia
Silvia Serra
AUSL IRCCS Reggio Emilia
Lucia Giaccherini
AUSL IRCCS Reggio Emilia
Lorenzo Aguzzoli
AUSL IRCCS Reggio Emilia

Case report

Keywords: endometrial cancers, laparoscopy, recurrence, survival, vulvar metastasis, relapse, laparotomy, adjuvant treatment

Posted Date: July 8th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-40567/v1

Version of Record: A version of this preprint was published at Medicine on June 4th, 2021. See the published version at https://doi.org/10.1097/MD.0000000000025863.

Abstract

Background

Endometrial cancer is the most common gynaecological malignancy in developed countries. It is usually diagnosed at early-stage and presents a favourable prognosis. Conversely, advanced or recurrent disease result in low response to therapy and poor outcome. Most recurrences occur within two years postoperatively, typically in pelvic and para-aortic lymph nodes, vagina, peritoneum, and lungs; unusual localizations include abdominal organs/wall, bones, brain, muscle. Vulvar metastasis are indeed anecdotal probably because the different regional lymphatic drainage from corpus uterus. Here, we report a case of vulvar metastasis from an early endometrial cancer comprehensive staged by laparoscopy and reviewed the literature discussing the different mechanisms of vulvar metastasis pathogenesis and the prognosis.

Methods

We reported a case of vulvar metastasis from an early stage endometrial cancer. We also collected and analysed articles written in English regarding vulvar metastasis form endometrial cancer published between January 1966 and May 2020. PubMed was used as a database for this search. Clinical and pathological characteristics, treatments and outcomes were assessed.

In total, 19 cases of vulvar metastasis from endometrial cancer were found. Patients had a mean age of 66 years and were mostly asymptomatic. Labium major was the most common and usually unique site of metastasis. Vulvar metastasis were mostly nodular/mass-like lesions occurred in patients treated mostly for endometrial cancer at early stage. Median time to vulvar metastasis was ten months. Most of the metastasis were treated with surgery or radiotherapy. One third of patients presented a subsequent recurrence on average 11 months later. 61.1% of patients died of disease and 70 median overall survival was 16 months.

Vulvar metastasis can show different appearance, occurring as single or diffuse lesions on healthy

or injured skin, in patients treated for both early- and advanced-stage endometrial cancers. Surgical

approach seems not to influence the risk of subsequent metastasis, but tumor seeding and vaginal

injuries should be avoided. Whether isolated or associated with recurrence in other locations, vulvar

metastasis are characterized by severe prognosis despite radical treatment. Therefore, any suspected

vulvar lesion arisen during endometrial cancer follow-up should be biopsied, despite the vulva represents an unusual metastatic site.

Conclusions

Vulvar metastasis can show different appearance. Surgical approach seems not to influence the risk of subsequent metastasis. Vulvar metastasis are characterized by severe prognosis despite radical treatment. Therefore, any suspected vulvar lesion arisen during follow-up should be biopsied.

Background

Endometrial cancer (EC) is the most common gynaecological malignancy in developed countries [1]. When diagnosed at early-stage, it usually has favourable prognosis (77% 5-year overall survival, OS); conversely, advanced or recurrent disease result in low chemoresponse and poor outcome [2]. Sixty-four percent of recurrences usually occur within two years postoperatively (87% <3 years), typically in pelvic and para-aortic lymph nodes, vagina, peritoneum, and lungs; unusual localizations include abdominal organs/wall, bones, brain, and skeletal muscle [3].

Vulva seems the site of the female genital tract least-affected by secondary gynecologic and non-gynecologic tumors: vulvar metastases (VMs) are uncommon (5–8% of all vulvar cancers) and the tumor origin remains unknown in about 10% of the cases [4–5]. VMs from EC are anecdotal, probably because of the different regional lymphatic drainage of uterus (to pelvic and para-aortic lymph nodes) and vulva (to superficial inguinal lymph nodes); thus, EC-cells in inguinal lymph-nodes are considered a distant metastasis.

We report an EC treated with comprehensive surgical staging and adjuvant radiotherapy that showed a vulvar recurrence one year later. We also performed a literature review discussing the different mechanisms of VM-pathogenesis.

Methods

Systematic review of the literature

We performed a literature review of EC-VMs-cases published from January 1966 to May 2020. Combinations of “endometrial cancer” with “vulvar metastasis”, “vulvar recurrence”, “vulvar relapse” or “vulvar spread” were searched in Pubmed database, without limitations.

Statistical analysis

Statistical analysis was performed using R-3.2.3 software. Quantitative variables are reported as mean ± standard deviation or median and interquartile range. The categorical variables are expressed in absolute frequency and percentage. OS was computed as the time period from the date of surgery to either the date of death or last follow-up.

Case presentation

A 73-year-old woman presented with an endometrial biopsy diagnosis of grade 1-endometrioid carcinoma. She had a history of tuberculosis, HBV-infection and seropositive erosive rheumatoid arthritis associated with scleroderma. A laparoscopic total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH + BSO) and pelvic bilateral systematic lymphadenectomy was performed: frozen section examination identified a 5-cm EC, deeply invading the myometrium. The final diagnosis was of a FIGO-stage IB, grade 2 endometrioid carcinoma of the endometrium (myoinvasion depth of 12 mm on 15 mm of myometrial thickness), showing lymphovascular invasion. The 18 pelvic lymph nodes were reactive. External radiotherapy (ERT) and vaginal brachytherapy (BRT) were administered. A 3-cm, reddish, bleeding lesion of posterior commissura/right labia was found 11 months later on follow-up examination: biopsy confirmed the EC-recurrence. The lesion was weakly-contrasted on pelvic magnetic resonance imaging (MRI) (Fig. 1), with high standardized uptake value (SUV: 5.2) on Positron Emission Tomography (PET) (Fig. 2). The VM was radically resected with free-margins (Fig. 3). As imaging exams (also including computed tomography) excluded other metastases, the patient was followed-up without additional treatment. Six month later, PET (Fig. 4) showed only a 1.5-cm lesion with high uptake (SUV: 8.1) in the VI° hepatic segment: a wedge resection was laparoscopically performed. Histological exam confirmed an EC-recurrence, focally invading the perihepatic fat; surgical margins were uninvolved (Fig. 5). On immunohistochemical examination, tumor cells were positive for Estrogen receptor (75%), lacking expression of Progesterone receptor. The mismatch repair system proteins (MLH1; MSH2; MSH6, PMS2) resulted positive. Six cycles of Carboplatin and Taxol are going to be administered to the patient (27 months after primary surgery).

IRB approval was not requested for “case report” but patient signed consent is available if requested. Our patient provided standard written consent for the use of data, pictures and videos for teaching and research purposes at the time of operation.

Details of immunohistochemical antibodies

Estrogen Receptor: clone SP-1, rabbit monoclonal, Ventana Medical Systems, Tucson, AR, US.

Progesterone receptor: clone 1E2, rabbit monoclonal, Ventana Medical Systems, Tucson, AR, US.

MLH1: clone M1, mouse monoclonal, Ventana Medical Systems, Tucson, AR, US.

MSH2: clone G219-1129, mouse monoclonal, Ventana Medical Systems, Tucson, AR, US.

MSH6: clone 44, mouse monoclonal, Cell Marque, Rocklin, CA, US.

PMS2: clone EPR3947, rabbit monoclonal, Ventana Medical Systems, Tucson, AR, US.

Results

Nineteen VM-cases were found [5–14] (Table 1), excluding a case [7] lacking information.

Table 1

Clinical features of 19 patients with vulvar metastasis from endometrial cancer reported in the English liter

Author Year	Age	Type of EC	Gradig	Stage	Fisrt Therapy	Adju Ther.	First recurr. (mo.)	Vulvar site	Other site of recurr.	Size of recurr. (cm)	Symptoms of vulvar recurr.	Surgica treatme recurr.
Dehner LP; 1973 [5]	56				*ERT, BRT	NO	12	Labium major	No	1	Solitary painful nodule	NO
	78				*ERT BRT	IRT	Sync VM	Labium major	Vaginal	6,5	Solitary bleeding lesion	NO
	69				*ERT, BRT	NO	4	Labium major Clitoris	No		Multiple painful nodule	NO
	71				ERT, BRT TAH, BSO	NO	5	Labium major	No	1	Solitary painful nodule	NO
Mazur MT et al; 1984 [7]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Neto AG et al; 2003 [6]	62							Labius minus	Yes		Mass	Wide lo excisior
	63							Labius major	No		Mass	NO
	54							Labia majora	Yes		Mass	NO
	68								Yes		Ulceration	NO
	51							Labius minus	Yes		Ulceration	NO
	73							Introitus	Yes		Mass	NO
Giordano G. et al; 2005 [8]	66	EH	G3	IIIC	TAH, BSO, PLS	NO	7	Posterior commissura	Liver		Mass	Tumor e
Ray K. et al; 2006 [9]	53	EH	G1	IB	TAH, BSO, SPL, SLL	NO	10	Introitus on Marsupialization site	No	1	Post-coital bleeding nodule	Tumor e
Temkin SM et al; 2007 [10]	63	SH		IB	TAH, BSO, PLS, LLS	BRT	84	Labium major	Homolateral groin mass	8	Exophytic vulvar lesion and groin mass	Radical hemivu and left dissecti
	83	EH	G1	IB	TAH	ERT/BRT on vaginal cuff relapse 5 month later	36	Right labium major	No	4	Exophytic vulvar itching and bleeding	Radical excisior radical dissecti
Wimmer JL et al; 2013 [11]	79	EH	G2	IA	TAH, BSO	ERT	5	Right labium major in a squamous cell carcinoma	No	1	Exophytic mass	Partial resectio
Fakor F et al; 2013 [12]	52	EH	G3	IB	TAH, BSO, PLS, LLS	BRT	18	Clitoris	No	4	Clitoro megally	Wide lo excisior clitoris
Abdullah A et al; 2014 [12]	87	EH	G1	IB	TLH, BSO, PLS, LLS.	BRT	8	Posterior commissura	No	1,9	Asymptomatic exophitic lesion	Partial vulvect

NR: not reported; EH: endometrioid histotype, SH: serous histotype; G: grading; TAH: total abdominal hysterectomy; BSO: bilateral salpingo-oophorectomy; IRT Exclusive external radiation and brachytherapy; TLH: total laparoscopic hysterectomy; LFN: lymphadenectomy; SPL: systematic pelvic lymphadenectomy; SL sampling; LLS: lombo-aortic lymph-nodes sampling. PG: progesteron. CHE: chemotherapy. DOD: died of disease; AWD: alive with disease; FOD: free of diseas

Author Year	Age	Type of EC	Gradig	Stage	Fisrt Therapy	Adju Ther.	First recurr. (mo.)	Vulvar site	Other site of recurr.	Size of recurr. (cm)	Symptoms of vulvar recurr.	Surgica treatme recurr.
Rottenstreich M et al; 2019 [13]	60	EH	G2	IIIA	TAH, BSO PLS, LLS.	CHE	36	Vulva and extending to the pubis and lower abdomen and vaginal vault	No		Painfull lesion	NO
Mandato VD et al; 2020	73	EH	G2	IB	TLH, SOB, SPL	ERT/BRT	12	Posterior commissura	No	1.2 x0.9 x0.5	Exophitic bleeding lesion	Radical resectio

NR: not reported; EH: endometrioid histotype, SH: serous histotype; G: grading; TAH: total abdominal hysterectomy; BSO: bilateral salpingo-oophorectomy; IRT Exclusive external radiation and brachytherapy; TLH: total laparoscopic hysterectomy; LFN: lymphadenectomy; SPL: systematic pelvic lymphadenectomy; SL sampling; LLS: lombo-aortic lymph-nodes sampling. PG: progesteron. CHE: chemotherapy. DOD: died of disease; AWD: alive with disease; FOD: free of diseas

Primary endometrial cancer

EC-histotype was reported in 10/18 (55.5%) cases: one was a serous carcinoma [10], one was a clear cell carcinoma [5] while 8/10 (80%) tumors were endometrioid carcinomas [5, 8–14] and grade (G) was reported in seven cases (G1: 3/7, 42.8%; G2: 2/7, 28.6%; G3: 2/7, 28.6%) [8–14]. FIGO stage was reported in 8/18 (44.4%) cases: 5/8 (62.5%) were stage IB [9, 10, 12, 13], 1/8 (12.5%) IA [11], 1/8 (12.5%) IIIA [14] and 1/8 (12.5%) IIIC [8]. Treatment information of primary uterine ECs was available for 11/18 (61.1%) patients [5, 8–14]. 3/18 (16.7%) patients were treated by exclusive external radiotherapy and brachytherapy (followed by interstitial radiotherapy in 1/3 cases) [5]. 9/18 (50%) were treated with TAH [5, 8–14] (+ BSO except for 1 case) [10]. A patient underwent to neoadjuvant ERT + BRT [5]. Systematic pelvic and lombo-aortic lymphadenectomy was performed in 1 case (1/9 cases, 11.1%) [9], while 5 patients underwent sampling of pelvic (1/9 cases, 11.1%) [8] or pelvic and lombo-aortic lymph nodes (4/9 cases, 44.4%) [10, 12–14] In 12/18 (66.7%) patients, information about adjuvant therapy was reported [5, 8–14]: 1/12 (8.3%) received ERT [11], 3/12 (25%) BRT [10, 12, 13] and 1/12 (8.3%) exclusive chemotherapy [14].

Vulvar metastasis

Patients' age range was 51–87 years (mean 66). Labium major was the most common site of recurrence (9/17, 52.9%) [5, 6, 10, 11], followed by labium minus (2/17, 11.8%) [6], introitus (2/17, 11.8%) [6, 9], posterior commissure (2/17, 11.8%) [8, 13] and clitoris (2/17, 11.8%) [4, 12]. A VM extended to pubis/lower abdomen and vaginal vault [14]. VMs were nodular/mass-like (9/18, 50%) [5, 6, 8, 9], exophytic (4/18, 22.2%) [10, 11, 13], ulcerated (3/18, 16.7%) [6, 10] or papular (1/18, 5.5%) [14], causing clitoromegally in 1 case (5.5%) [12]. Bleeding (3/18, 16.7%) [5, 9, 10] and pain (4/18, 22.2%) [5, 14] were reported, but most of patients (61.1%) were asymptomatic [6, 8, 10–13].

In 7/18 (38.9%) cases VM were associated with recurrences in other sites [6, 8, 9], whilst in one case VM was synchronous to the diagnosis of EC with vaginal involvement [5]. The mean size of VMs was 3.1 ± 2.6 cm (available information for 50% of cases) [5, 9–13]. VMs were treated by radiotherapy (5/18, 27.8%) [5, 6], surgery (4/18, 22.2%) [9–11, 13], chemotherapy (2/18, 11.1%) [6], surgery and radiotherapy (2/18, 11.1%) [6, 12], chemoradiation (2/18, 11.1%) [6, 14], surgery and chemoradiation (1/18, 5.5%) [10], surgery and progestin therapy (1/18, 5.5%) [8], or only follow-up (1/18, 5.5%) [5].

Follow up data

Information about follow-up were reported in all 18 cases. Time to VM was reported in 11/17 (64.7%) cases [5, 8–14]. Median time to VM was 10 months (range 4–84 months). In one case before the VM, a tumor recurred on the vaginal cuff 5 months after primary treatment: the vaginal metastasis was treated with ERT + BRT [10]. 6/18 (33.3%) cases presented a subsequent recurrence after VM [5, 10, 12]. Median time to subsequent recurrence was 11 months (range 5–26 months). 6/18 (33.3%) cases were free of disease (FOD) [6, 9–11, 13, 14], 11/18 (61.1%) died of disease (DOD) [5, 6, 8, 10, 12] and 1/18 (5.6%) was alive with disease (AWD) [6]. Median OS was 16 months (3–84 months). The OS from VM treatment was 76.5% after 6 months, 58.8% after 12 months, 23.5% after 24 months, 11.8% after 36 months, and 5.9% after 60 months (Fig. 6).

Discussion

Despite EC is the most common gynecological cancer in Western countries, VMs from ECs are very rare: only 19 cases were reported in the last 50 years. Like our case, VM is usually an isolated recurrence, being associated with other metastatic sites in In 7/18 (38.9%) 3/18 (16.7%) patients [6, 8, 9]. VM was mostly diagnosed in patients with low-intermediate risk ECs (66.7%) [9–13]: only two ECs presented at advanced stage (IIIA, IIIC) [8, 14]. According to the stage, 7–15% of stage I-II ECs recur [15, 16]: the relapse rate is higher in case of adjuvant-RT administration (12.9% vs 7.2%) except for local recurrences, which show a lower rate after adjuvant-RT (3.7%) [15]. As our patient, 6/13 (46.1%) primary ECs received adjuvant therapy with radio- [5, 11–13] or chemo-therapy [14]; and in one cases VM appeared 5 months after a vaginal cuff recurrence has been treated with radiotherapy [10]. VMs usually arose in labia majora as asymptomatic [6, 8, 10–13] nodular/mass [5, 6, 8, 9], however also painful bleeding exophitic [5, 10, 11, 13] and ulcerated [6, 10] or papular lesions [14] have

been reported. As for other sites frequently-involved by EC-recurrences, VMs were diagnosed within two years (median time 10 months) [3, 16] from initial treatment. VMs occurred most frequently in postmenopausal women, frequently representing a worrisome prognostic event: the median survival after VM was 20 months [17, 18]. In distant recurring ECs, 3-year OS varied from 14 [15] to 54.3% [19]; 5-year OS was 55% for pelvic recurrences and reduced to 17% for extrapelvic relapses [20]. To our review, 61.1% (11/18) of VM-patients DOD [5–8, 10, 12, 14]: the maximum OS was 84 months [6]. As other extrapelvic recurrences, VMs may be a prognostic risk factor [3, 16, 20] causing a rapid halving of survival 12 months after diagnosis (Fig. 4). 4/17 (23.5%) patients were alive 2 years after VM-treatment [5, 13, 6], 2/17 (11.8%) after 3 years [6] and only one patient (5.9%) after 5 years [6]. VMs may be due to direct tumor spread through vagina [10, 14], which also represents the most frequently preoperatively-contaminated site because of tumor bleeding [24]. Moreover, EC-recurrences may occur on incisional abdominal wounds/scars of either laparotomy or mini-invasive surgery [21–23], usually due to microscopic tumor seeding during primary surgery [9]. EC-seeding on Bartholin's gland incision during preoperative hysteroscopy can also justify VMs [9]. Hematogenous [12] or lymphatic spread [5, 8–11, 14] may represent alternative pathways of tumor spread, like in our case: moreover, extensive radical pelvic surgery or radiotherapy can enhance lymphatic stasis with a possible retrograde spread of tumor emboli to the vulvar lymphatics and vulvar colonization [5, 8–11, 14]. Although limited and conflicting data suggested that pneumoperitoneum may alter the peritoneal surfaces favoring cancer cell adherence or spread [25], it's certainly questionable to consider laparoscopy a risk factor for VMs: most of patients with VM were primary treated by laparotomy [5, 8–12, 14] (only 1 by laparoscopy) [13]. Synchronous tumors may attract the implantation of tumor cells, as suggested for a vulvar squamous cell carcinoma [11, 26]. According to Paget's "seed and soil" theory, tumor development occurs as a consequence of the provision of a fertile environment (the soil) in which the tumor cells (the seed) can proliferate [26]. However, it's impossible to know when tumor cells were released from EC, if during tumor bleeding, hysteroscopy or hysterectomy. Tumor seeding during surgery should be prevented and injuries of genital mucosa should be avoided to break the "seed and soil" binomial. Abdullah et al. [13] suggested to use a bag during transvaginal specimen removal in selected patients with an inelastic, atrophic vagina, in which the posterior fourchette may be fragile and easily-traumatized from the passage of a large uterus.

Conclusion

VMs can show different appearance (exophytic, nodular, papular, ulcerated), occurring as single or diffuse lesions on healthy or injured skin, in patients treated for both early- and advanced-stage ECs. Surgical approach seems not to influence the risk of subsequent VMs, but tumor seeding and vaginal injuries should be avoided. Whether isolated or associated with recurrence in other locations, VMs were characterized in most cases by a severe prognosis despite radical treatment. Therefore, any suspected vulvar lesion arisen during EC-follow-up should be biopsied, despite the vulva represents an unusual metastatic site.

Abbreviations

EC
endometrial cancer; OS:overall survival; VM:vulvar metastasis; TAH:total abdominal hysterectomy; BSO:bilateral salpingo-oophorectomy; FIGO:International Federation of Gynecology and Obstetrics; ERT:External radiotherapy, BRT:brachytherapy:MRI:magnetic resonance imaging, SUV:standardized uptake value; PET:Positron Emission Tomography; G:grade; FOD:free of disease; DOD:died of disease; AWD; alive with disease.

Declarations

Ethics approval and consent to participate

Written informed consent was not necessary because our patient provided standard written consent for the use of data, pictures and videos for teaching and research purposes at the time of laparoscopy.

Consent to publish

Not applicable.

Availability of data and materials

Data collected and analyzed during this study are included in this review and are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests. All authors deny any found, financial and personal relationships with other people or organizations/companies that could inappropriately influence their work.

Funding

The funding body had no role in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

Authors' contributions

VDM conceived of the manuscript, performed operations, collected data, and wrote the manuscript. **VM** collected data, performed statistical analysis and wrote the manuscript. **AP** performed pathological evaluation and wrote the manuscript. **MS** performed radiologic follow-up, provided imaging and wrote the manuscript. **SS** performed pathological evaluation and wrote the manuscript. **LG** conceived of the manuscript, performed adjuvant therapy, performed follow-up and wrote the manuscript. **LA** performed operations, collected data, and wrote the manuscript.

All authors read and approved the final manuscript.

Author information

[1] Unit of Obstetrics and Gynecology, Azienda Unità Sanitaria Locale, IRCCS, Reggio Emilia, Italy. [2]Unit of Surgical Gynecol Oncology, Azienda Unità Sanitaria Locale, IRCCS, Reggio Emilia, Italy. [3] Unit of Pathology, Azienda Unità Sanitaria Locale, IRCCS, Reggio Emilia, Italy. [4] Unit of Radiology, Azienda Unità Sanitaria Locale, IRCCS, Reggio Emilia, Italy. [5] Unit of Radiation Oncology, Azienda Unità Sanitaria Locale, IRCCS, Reggio Emilia, Italy.

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Figures

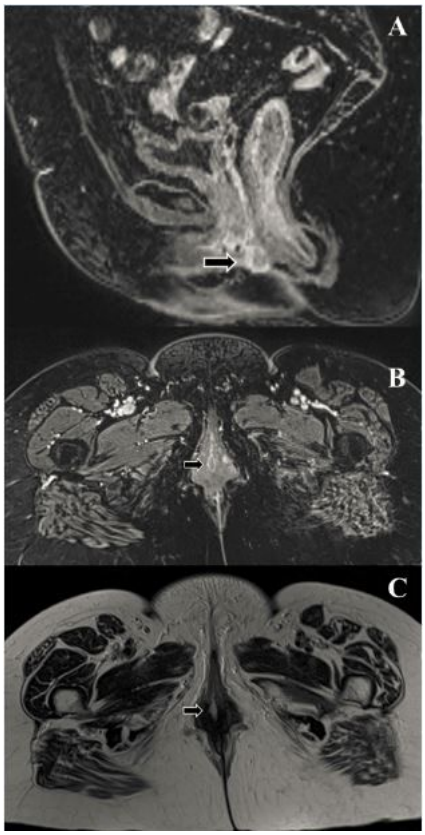

Figure 1

Magnetic Resonance (MR): A) Sagittal contrast-enhanced T1-weighted MR image shows enhancing mass (arrow) in vulva; B) Axial contrast-enhanced T1-weighted MR image shows enhancing mass (arrow) in right vulva; C) Axial T2-weighted MR image shows hyperintense mass (arrow) in right vulva.

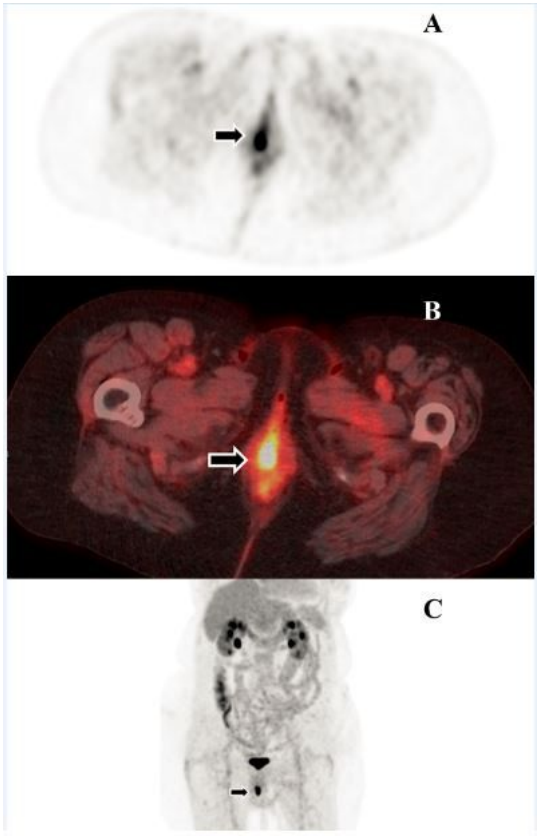

Figure 2

Positron emission thomography (PET): A) Axial PET/CT image shows vulvar mass (arrow) with FDG avidity. B) Axial PET/CT image shows vulvar mass (arrow) with FDG avidity. C) Coronal maximum-intensity-projection PET/CT shows vulvar mass (arrow) with FDG avidity.

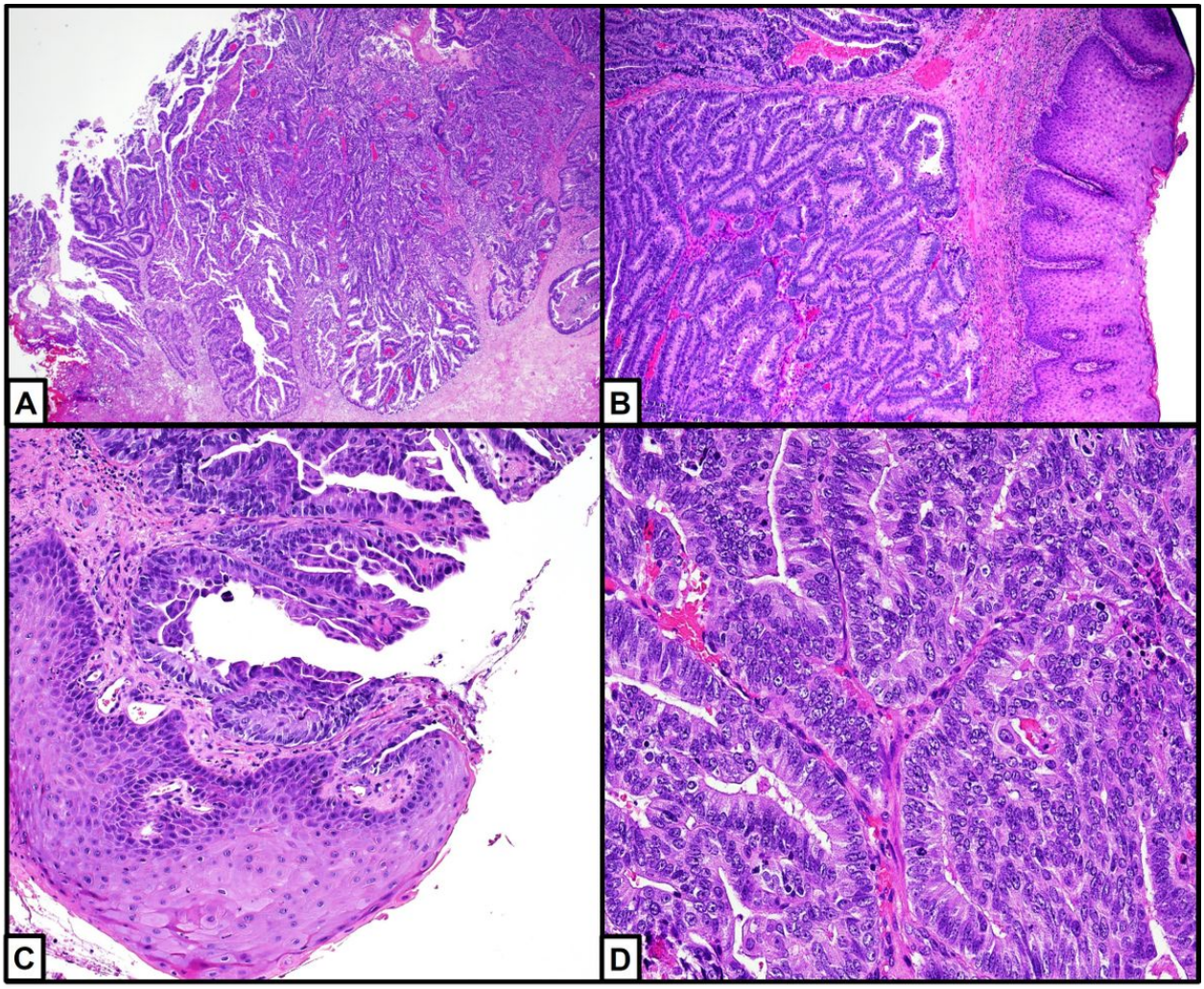

Figure 3

Vulvar metastasis: histopathological features. A) The metastatic tumor extensively replaced and ulcerated the vaginal mucosa; the tumor showed surface papillary, cribriform and glandular histological patterns (Hematoxylin and Eosin, HE, 4 x). B) In this area, the tumor (on the left) grew under the normal vaginal epithelium (on the right) (HE, 10 x). C) Detail. The tumor (top) replaced the normal vaginal epithelium (bottom) (HE, 20 x). D) Detail of tumor morphology. Cribriform pattern. Moderate nuclear atypia (HE, 40 x).

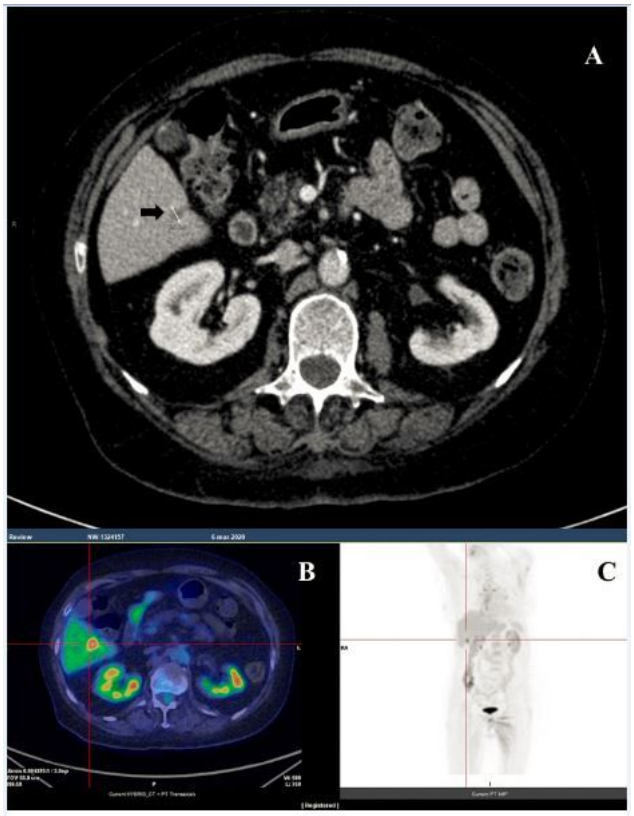

Figure 4

Computed Tomography (CT): A) Axial contrast-enhanced T1-weighted MR image shows enhancing mass (arrow) in the liver; B) Axial Positron emission thomography (PET) PET/CT image shows liver mass (arrow) with FDG avidity. C) Coronal maximum-intensity-projection PET/CT shows liver mass (arrow) with FDG avidity.

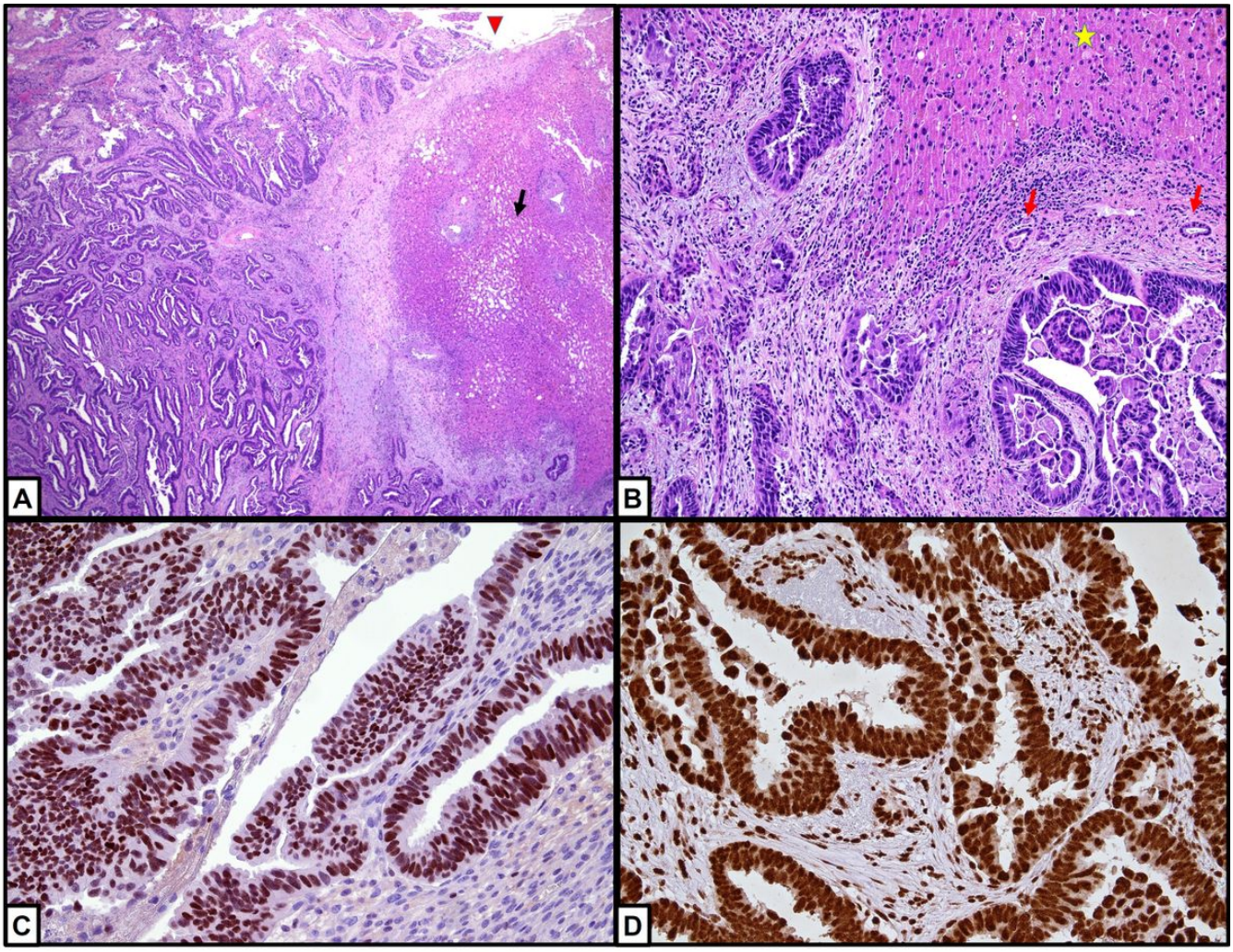

Figure 5

Hepatic metastasis of endometrioid carcinoma. A) The metastasis (on the left) involved the hepatic capsule (red arrowhead) and showed intraparenchymal gowth. The hepatic parenchyma (on the right, black arrow) showed mild steatosis and reactive chronic inflammation (Hematoxylin and Eosin, HE, 4x). B) Detail of the tumor glands (bottom) (yellow star: hepatic parenchyma; red arrows: normal biliary ducts) (HE, 20x). C) Immunohistochemical nuclear positivity of tumor cells for Estrogen receptors (10x). D) Tumor cells showed retained immunohistochemical nuclear expression of mismatch repair proteins (MLH1, 10x).

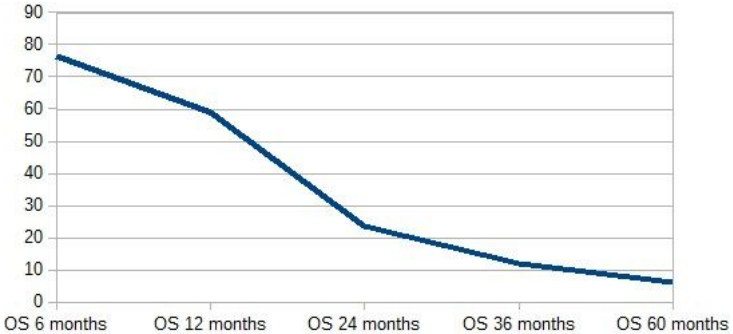

Figure 6

Overall survival of 18 patients with vulvar metastasis reported in literature.