RECIDIVE di CARCINOMA della VULVA

Quale trattamento oncologico?

Negrar ,17 giugno 2015

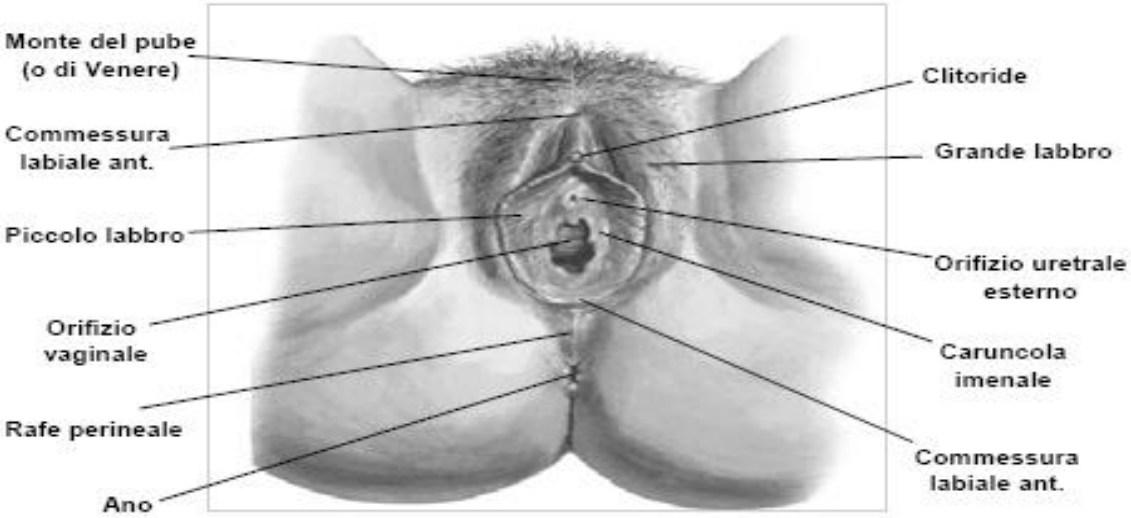
Paola Agnese Cassandrini

LA VULVA

E' costituita da diverse formazioni anatomiche:

- ***Monte di Venere***
- ***Grandi labbra***
- ***Piccole labbra***
- ***Clitoride***
- ***Vestibolo della vagina***

APPARATO GENITALE ESTERNO



Carcinoma of the vulva.

Stage I	Tumor confined to the vulva
IA	Lesions ≤2 cm in size, confined to the vulva or perineum and with stromal invasion ≤1.0 mm*, no nodal metastasis
IB	Lesions >2 cm in size or with stromal invasion >1.0 mm*, confined to the vulva or perineum, with negative nodes
Stage II	Tumor of any size with extension to adjacent perineal structures (1/3 lower urethra, 1/3 lower vagina, anus) with negative nodes
Stage III	Tumor of any size with or without extension to adjacent perineal structures (1/3 lower urethra, 1/3 lower vagina, anus) with positive inguino-femoral lymph nodes
IIIA	(i) With 1 lymph node metastasis (≥5 mm), or (ii) 1–2 lymph node metastasis(es) (<5 mm)
IIIB	(i) With 2 or more lymph node metastases (≥5 mm), or (ii) 3 or more lymph node metastases (<5 mm)
IIIC	With positive nodes with extracapsular spread
Stage IV	Tumor invades other regional (2/3 upper urethra, 2/3 upper vagina), or distant structures
IVA	Tumor invades any of the following: (i) upper urethral and/or vaginal mucosa, bladder mucosa, rectal mucosa, or fixed to pelvic bone, or (ii) fixed or ulcerated inguino-femoral lymph nodes
IVB	Any distant metastasis including pelvic lymph nodes

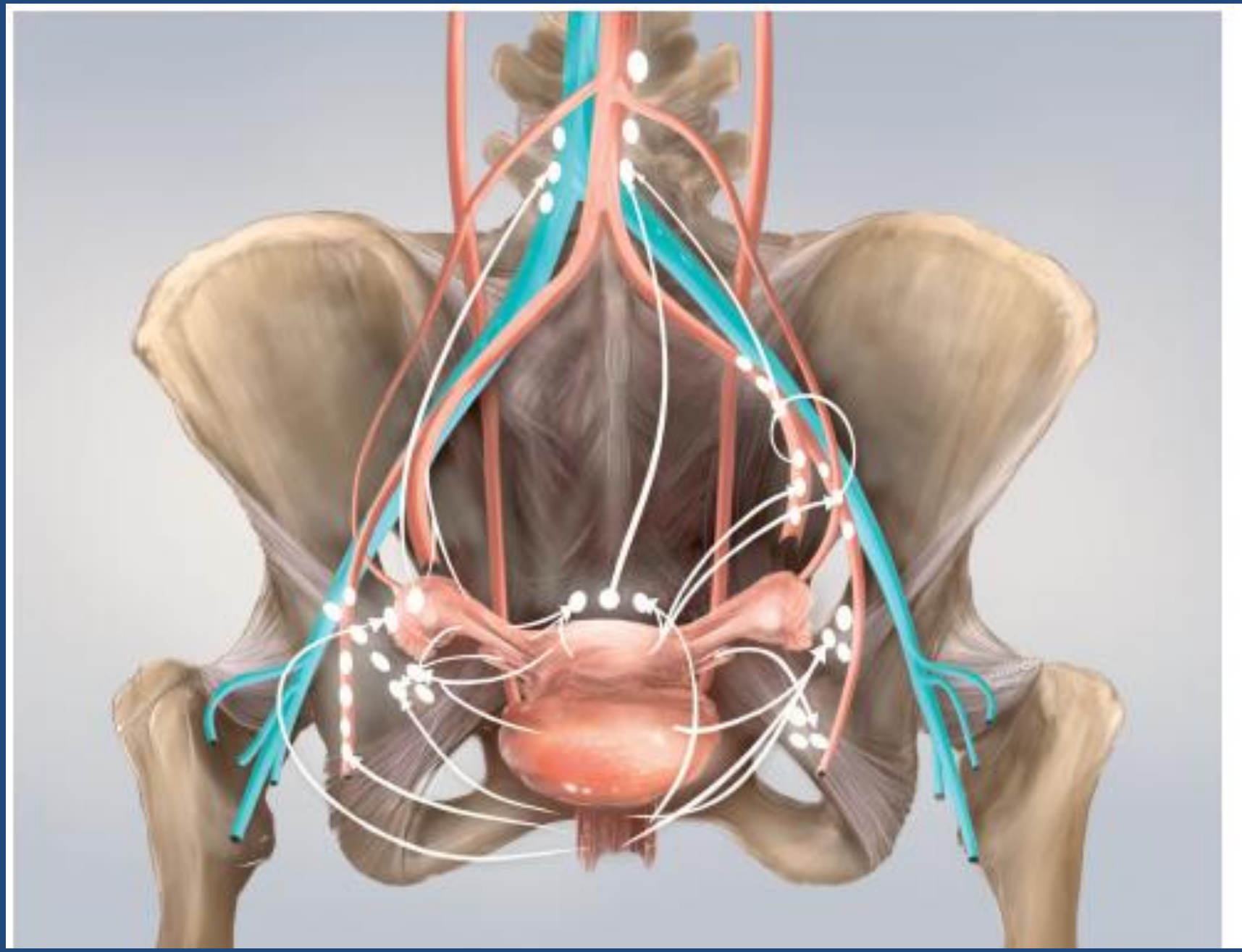


Table 2
Studies of neoadjuvant chemotherapy for vulvar cancer.

Study	N	Indication	CT regimen	No of cycles	Response	Survival	Achieved resectability without exenteration
Durrant[a] EORTC [12]	28	LAVC n = 18 Recurrence n = 10	Bleo 5 mg IM d1–5 + MTX 15 mg PO d 1and 4 + CCNU 40 mg PO d5–7 week 1, then Bleo 5 mg IM d1 and 4 + MTX 15 mg PO d1 and 4 weeks 2–5	Up to 4	CR in 11% (3/28) PR in 53% (15/28)	N/A	28% (8/28)
Benedetti-Panici[a] [64]	21	LAVC n = 21	CisP 100 mg/m^2 day 1 + bleo 15 mg days 1 and 8 + MTX 300 mg/m^2 day 8 every 21 days	Up to 3	PR in 14% (3/21) SD in 81% (17/21)	Median F/U: 33 months 3-yr OS 24% with median OS 18.5 mos	38% (8/21)
Wagenaar[a] EORTC [13]	25	LAVC n = 13 Recurrence n = 12	Wk 1: bleo 5 mg IM d1–5 + CCNU 40 mg PO d5–7 + MTX 10 mg PO d1 + 4 Wks 2–6: bleo 5 mg IM d1 + 4 + MTX 15 mg PO d1. Cycle repeated after 1 wk break	Up to 3	CR 8% (2/25) PR 48% (12/25)	Mean F/U: 12 months Status: 12% (3/25) alive NED Median OS 7.8 mos	40% (10/25)
Bafna [65]	9	LAVC n = 9	Cyclo 500 mg + MTX 50 mg + 5-FU 500 mg days 1, 8 every 14 d	3	pCR in 11% (1/9) PR in 89% (8/9)	NS	100% (9/9)
Geisler [11]	13	LAVC n = 13 A) n = 10 B) n = 3	A) 5-FU 1000 mg/m^2/24 h infusion d1–5 + CisP 50 mg/m^2 IV d1, q3wks B) CisP 50 mg/m^2 IV q3wks	3–4	A) PR in 60% (6/10), pCR in 40% (4/10) B) 0% response	Median F/U: 49 months A) 90% (9/10) alive NED, mean OS 79 mos B) 0% alive NED, mean OS 9 mos	64% (9/14)
Domingues [66]	25	LAVC n = 25 A) n = 10 B) n = 5 C) n = 10	A) Bleo 20 mg/m^2 IV d1–10 continuous infusion B) Tax 100 mg/m^2 IV weekly C) 5-FU 750 mg/m^2 d1–4 continuous infusion + CisP 60–80 mg/m^2 IV d1, weekly	3	A) CR in 10% (1/10), PR in 50% (5/10) B)PR in 40% (2/5) C) PR in 20% (2/10)	Mean F/U: 22 months A) 30% (3/10) alive NED, mean OS 46 mos B) 20% (1/5) alive NED, mean OS 17 mos C) 10% (1/10) alive NED, mean OS 7 mos	40% (10/25)
Aragona [14][a]	35	LAVC n = 35	CisP + 5-FU (n = 12) or CisP + Tax (n = 6) or CisP + 5-FU + Tax (n = 6) or VinC + bleo + CisP (n = 6) or bleo alone (n = 5)	3	PR in 86% (30/35)	Median F/U: 49 months Status: 68% (24/35) alive NED Recurrence in 14% (4/29) of pts undergoing surgery	77% (27/35)
Han[a] [10]	6	LAVC n = 4 Recurrence n = 2	Tax 60 mg/m^2 IV + Carbo AUC 2.7 IV weekly	9	ORR = 0%	Median F/U: 4.2 months Status: 33% (2/6) alive NED	0% (0/6)

[a] Prospective trial; LAVC: locally-advanced vulvar cancer, ORR: overall response rate, PFS: progression-free survival, CR: complete response, pCR: pathologic complete response, PR: partial response, mos: months, CisP: cisplatin, 5-FU: 5-fluorouracil, Tax: paclitaxel, bleo: bleomycin, VinC: vincristine, Cyclo: cyclophosphamide, Carbo: Carboplatin, AUC: Area under the curve, N/A: not available, MTX: methotrexate, SD: stable disease, PD: progressive disease, CCNU: lomustine, N/A: not available, NED: no evidence of disease and no recurrence.

juvant chemoradiation for vulvar cancer.

N	Indication	CT regimen	RT regimen	Response	Survival	Achieved resectability without exenteration
6	LAVC n = 6	5-FU 1000 mg/m^2 infusion d1–4 + MMC 10 mg/m^2 IV d1. 1–2 cycles	20–40 Gy in 2 Gy daily fractions	NS	Mean F/U: 11 months Status: 66% (4/6) alive NED	66% (4/6)
8	LAVC n = 6 Recurrence n = 2	5-FU 750 mg/m^2 infusion d1–5 + MMC 7.5 mg/m^2 IV d4 + CisP 10 mg/m^2 IV d 1, given weekly during RT.	45–50 Gy in 1.75 Gy daily fractions	pCR in 75% (6/8)	Mean F/U: 10 months Status: 25% (2/8) alive NED Recurrence or progression in 50% (4/8)	88% (7/8)
12	LAVC n = 9 Recurrence n = 2	5-FU 750–1000 mg/m^2 infusion d1–4 + MMC 10–12 mg/m^2 IV d1, week 1 of each course of RT	Split-course. 25 Gy in 2 Gy daily fractions, 2 courses with 1 month break	CR in 41% (5/12) PR in 33% (4/12)	F/U: 6–9 months Status: 25% (3/12) alive NED Recurrence in 60% (3/5) of pts with CR	58% (7/12)
42	LAVC n = 20 Recurrence n = 22	Bleo 30 mg IV d1, 3, 5 during weeks 1 + 3 of RT	30–45 Gy in 3 Gy daily fractions	CR in 16% (7/42) PR in 50% (21/42)	Mean F/U: 12 months Status: 2% (1/42) alive NED Recurrence in 85% (6/7) of pts with CR	16% (7/42)
12	LAVC n = 12	CisP 4 mg/m^2/d infusion d1–4 + 5-FU 250 mg/m^2/d infusion d1–4, given weekly for 4 wks	40 Gy in 2 Gy daily fractions	CR in 50% (6/12) PR in 41% (5/12)	Mean F/U: 18 months Status: 50% (6/12) alive NED Recurrence in 16% (1/6) pts w CR and 83% (5/6) of pts w PR	75% (9/12)
58	LAVC n = 41 Recurrent n = 17	5-FU 750 mg/m^2 infusion d1–5 + MMC 15 mg/m^2 IV d1 given week 1 of each course of RT	54 Gy in 2 courses (36 Gy + 18 Gy) with 14 d treatment break	ORR 77% (45/58) pCR in 31% (13/42)	Median F/U: 22 months Status: 48% (28/58) alive NED Recurrence in 27% (16/58)	N/A
31	LAVC n = 24 Recurrent n = 7	5-FU 750 mg/m^2 infusion d1–5 + MMC 15 mg/m^2 IV d1. Given for 2 cycles	54 Gy in 2 courses with 14 d treatment break	CR in 48% (15/31) PR in 41% (13/31)	Median F/U: 34 months Status: 61% (19/31) alive NED Recurrence in 25% (8/31)	93% (29/31)
71	LAVC n = 71	5-FU 1000 mg/m^2 infusion d1–4 + CisP 50 mg/m^2 IV d1, given week 1 of each course of RT	2 courses of 23.8 Gy, given as 1.7 Gy BID for 4 days and daily for 6 days with 2 wk break	CR 47% (34/71)	Median F/U: 50 months Status: 56% (40/71) alive NED Recurrence in 34% (24/69)	95% (68/71)
46	LAVC n = 46	5-FU 1000 mg/m^2 infusion d1–4 + CisP 50 mg/m^2 IV d1, given week 1 of each course of RT	2 courses of 23.8 Gy, given as 1.7 Gy BID for 4 days and daily for 6 days with planned 2wk break	pCR (nodes) 40% (15/37) pCR (vulva) 52% (20/38)	Median F/U: 78 months Status: 26% (12/46) alive NED Recurrence in 51% (19/37)	80% (37/46)
18	LAVC n = 18	5-FU 1000 mg/m^2 infusion d1–4 + CisP 50 mg/m^2 IV d1 given first and last week of RT	44.6 Gy, in 1.6 Gy BID fractions for 5 d, then 1.8 Gy daily for 7 d, with 1–2 wk break, then 1.6 Gy BID for 5 d	cCR in 72% (13/18) pCR in 39% (7/18)	Mean F/U: 24 months Status: 83% (15/18) alive NED Recurrence in 17% (3/18)	78% (14/18)
18	LAVC n = 18	CisP 40 mg/m^2 d 1 and 5-FU 1000 mg/m^2 infusion, d 1–5. Two cycles, given the first and last week of RT	IMRT 46 Gy in 1.6 Gy BID fractions for 5 d, then 1.8 Gy daily for 7–8 d then a break of 10–14 d, then 1.6 Gy BID for 5 d	cCR in 13/18 (72%) cPR in 5/18 (28%) pCR in 9/13 having surgery (64%)	Median F/U: 22 months Status: 55% (10/18) alive NED Recurrence in 28% (5/18)	100% (18/18)
22	LAVC n = 22	Carbo AUC 2 weekly during RT	50 Gy in 2 Gy daily fractions	pCR 27% (6/22) ORR 95% (21/22)	Median F/U 28 months Status: 54% (12/22) alive NED Recurrence in 32% (7/22)	100% (22/22)

Radiotherapy given to the vulva, groin, and pelvis unless otherwise stated. AUC: area under the curve; N/A: not available; LAVC: locally advanced vulvar cancer; IMRT: intensity-modulated radiation therapy; CR: complete response nse; cCR: clinical complete response; cPR: clinical partial response; pCR: pathologic complete response; DSS: disease-specific survival; OS: overall survival; Carbo: carboplatin; NED: no evidence of disease and no recurrence; pts nitomycin C; 5-FU: 5-fluorouracil; f/u: follow-up; RT: radiation therapy; cisP: cisplatin; mos: months; wk: weeks; d: days; ORR: overall response rate; Gy: Gray; BID: twice a day.

Studies of chemoradiation for primary treatment of vulvar cancer with curative intent.

Study	N	Indication	CT Regimen	RT Regimen	Response	Recurrence	Survival
Iversen [67]	13	LAVC n = 9 Recurrence n = 4	Bleo 30 mg IM d1,3,5 repeated after 2 weeks	36–40 Gy in 3 Gy daily fractions	N/A	F/U: 12 months Recurrence NS	30% (4/13) a
Kalra[a] [68]	3	LAVC n = 2 Recurrence n = 1	MMC 10 mg/m^2 IV d1 + 5-FU 1000 mg/m^2 infusion d1–5 given weeks 1 and 4 of RT	50 Gy in 2 Gy daily fractions	CR in 100% (3/3)	Mean F/U: 33 months Recurrence in 0% (0/3)	100% (3/3) a
Evans[a] [69]	4	LAVC n = 4	5-FU 1000 mg/m^2 continuous infusion d1–4 + MMC 10 mg/m^2 IV d1	25–50 Gy in 2 Gy daily fractions	CR in 50% (2/4) PR in 50% (2/4)	Mean F/U: 18 months Recurrence 0% (0/2) with CR	50% (2/4) ali
Thomas [20]	24	LAVC n = 9 Recurrence n = 15	5-FU 1000 mg/m^2 infusion d1–4 + MMC 6 mg/m^2 IV d1, given weeks 1+ 4	36–59 Gy in 1.8 Gy fractions, most with a 2-wk break	CR in 58% (14/24)	Median F/U: 20 months Recurrence in 50% (7/14) with CR	N/A
Berek[a] [15]	12	LAVC n = 12	5-FU 1000 mg/m^2 infusion d1–4 + CisP 100 mg/m^2 d1 every 28 days for 2 cycles	40–52 Gy in 1.6–1.8 Gy daily fractions, with boost to vulva (up to 74 Gy)	CR in 67% (8/12) PR in 25% (3/12)	Median F/U: 37 months Recurrence in 17% (2/12)	83% (10/12)
Russell [70]	25	LAVC n = 18 Recurrence n = 7	5-FU 750–1000 mg/m^2 infusion d1–4 + CisP 100 mg/m^2 IV d1, 2–3 cycles given.	54 Gy for macro and 36 Gy for microscopic disease	CR in 80% (20/25)	Median F/U: 24 months Recurrence in 15% (3/20) with CR	56% (14/25)
Koh [71]	20	LAVC n = 17 Recurrence n = 3	5-FU 750–1000 mg/m^2 IV infusion d1–4, weekly for 3 cycles	54 Gy in either daily or BID fractions	CR in 50% (10/20) PR in 40% (8/20)	Median F/U: 37 months Recurrence in 30% (6/20)	35% (7/20) a 5-yr DSS 49%
Sebag-Montefiore [72]	37	LAVC n = 19 Recurrence n = 18	5-FU 750 mg/m^2 infusion d1–5 + MMC 10 mg/m^2 IV d1, given first 5 d and last 5 d of RT	45 Gy in 2 Gy daily fractions	CR in 40% (15/37) PR in 29% (11/37)	F/U: NS Recurrence in 33% (5/15) with CR	2-yr OS 37%
Wahlen [73]	19	LAVC n = 19	5-FU 1000 mg/m^2 infusion d1–4 given weeks 1 + 5 of RT. Six patients also given MMC 10 mg/m^2 IV d1	45–50 Gy in 1.8 Gy daily fractions, plus implant or electron boost to vulva	CR in 52% (10/19) PR in 36% (7/19)	Median F/U: 34 months Recurrence in 10% (1/10) with CR	79% (15/19) 5-yr DSS 89%
Cunningham [74]	14	LAVC n = 14	5-FU 1000 mg/m^2 infusion d1–4 + CisP 50 mg/m^2 d1, given on first and last week of RT	45–50 Gy plus vulvar boost of 9–14 Gy	CR in 64% (9/14) PR in 29% (4/14)	Mean F/U: 26 months Recurrence in 11% (1/9) with CR	28% (4/14) a
Leiserowitz [75]	23	LAVC n = 23	5-FU 1000 mg/m^2 infusion d1–4 + CisP 100 mg/m^2 IV d2, given 2–3 times during RT	Vulvar and inguinal region. 54 Gy in 1.8 Gy BID fractions	CR in 78% (18/23)	Mean F/U: 45 months Recurrence in 17% (4/23)	60% (14/23)
Akl [76]	12	T1 in 3 pts, T2 in 5 pts, T3 in 4 pts	5-FU 1000 mg/m^2/24 h as continuous infusion days 1–4 and 29–32 plus MMC 15 mg/m^2 IV day 1	Vulva only (all pts node negative). 30–36 Gy in 2 Gy daily fractions	CR in 100% (12/12)	Mean F/U: 41 months Recurrence in 16% (2/12)	66% (8/12) a 3-yr DFS =
Han [16]	14	LAVC n = 10 Recurrence n = 4	5-FU 1000 mg/m^2 infusion d 1–4 + MMC 10 mg/m^2 IV d1; given week 1 and 5 of RT	40–62 Gy; 7 pts received customized brachy	CR in 71% (10/14) PR in 29% (4/14)	Median F/U: 26 months Recurrence in 20% (2/10) with CR	57% (8/14) a 5-yr OS 54%
Mulayim [21]	7	LAVC n = 7	5-FU 1000 mg/m^2 infusion d1–4 + MMC 10 mg/m^2 IV d1, given weeks 1 and 4 of RT	60 Gy for macro and 45 Gy for microscopic disease	CR in 85% (6/7)	Median F/U: 31 months Recurrence in 28% (2/7)	42% (3/7) ali Median OS 3
Landrum [77]	33	LAVC n = 33	Either weekly CisP 40 mg/m^2 or two cycles of CisP 50 mg/m^2 IV d1 + 5-FU 1000 mg/m^2 IV d1–4	47.6 Gy in 1.8 Gy daily fractions	CR in 87% (29/33)	Median F/U: 31 months Recurrence in 17% (5/29) with CR	N/A
Mak [17]	24	LAVC n = 24	Either weekly CisP or 3–4 week 5-FU based regimens	50 Gy, timing of fractions varied	CR in 58% (20/34)	Median F/U: 31.5 months Recurrence NS	Actuarial 2-y 51.8%
Tans [78]	28	LAVC n = 20 Recurrence n = 8	5-FU 1000 mg/m^2 infusion d1–4 + MMC 10 mg/m^2 IV d1, given first week of each course of RT	Split course 40 Gy + 20 Gy in 2 Gy fractions with 2-wk break	CR in 71% (20/28) PR in 14% (4/28)	Median F/U: 42 months NS	64% (18/28) 4-yr OS 65%
Moore[a] GOG 205 [18]	58	LAVC n = 58	Weekly CisP 40 mg/m^2 IV, up to 7 cycles	57.6 Gy in 1.8 Gy daily fractions	cCR in 63% (37/58) pCR in 50% (29/58)	Median F/U: 24 months Recurrence in 24% (7/29) with pCR	51% (30/58)

[a] Prospective. Radiotherapy given to the vulva, groin, and pelvis unless otherwise stated. LAVC: locally advanced vulvar cancer, RT: radiation therapy, ORR: overall response rate, CR: complete response, PR: partial response, pCR: pat plete response, cCR: clinical complete response, PFS: progression-free survival, 5-FU: 5-fluorouracil, MMC: mitomycin-C, brachy: brachytherapy, Bleo: bleomycin, CisP: cisplatin, N/A: not available, DSS: disease specific survival, BID: tw follow-up, NED: no evidence of disease and no recurrence.

Studies of chemotherapy for advanced or metastatic vulvar cancer.

Study	N	Indication	CT Regimen	Response	Survival
Thigpen[a] GOG [23]	22	Recurrent metastatic disease, 20/22 chemo naive patients, most had prior RT	Cisplatin 50 mg/m^2 IV q3wks	0% CR 0% PR	N/A
Thigpen[a] GOG [23]	13	Recurrent metastatic disease, chemo naive patients, most had prior RT	Piperazinedione 9 mg/m^2 IV q3wks	0% CR 0% PR	N/A
Muss[a] GOG [24]	11	Recurrent metastatic disease. 91% (10/11) had prior RT and 36% (4/11) had prior CT	Mitoxantrone 12 mg/m^2 IV q3wks	0% CR 0% PR	Median PFS 1.3 mos Median OS 3.2 mos
Cormio[a] [25]	16	Recurrent disease, chemo-naive patients All had prior RT	Cisplatin 80 mg/m^2 IV d1 + Vinorelbine 25 mg/m^2 IV d1 and d8, q21d for up to 6 cycles	40% ORR (6/15) 27% CR (4/15) and 13% PR (2/15)	Median PFS 10 months Median OS 19 months
Witteveen[a] EORTC [26]	29	Recurrent metastatic or LAVC not amenable to RT or surgery. 69% (20/29) had previous RT and 17% (5/29) had prior CT	Paclitaxel 175 mg/m^2 IV q3wks: up to 9 cycles	6% CR (2/29) 6% PR (2/29)	Median PFS 2.6 mos Median OS 6.3 mos 1-yr OS 30%

[a] Prospective. LAVC: locally advanced vulvar cancer; ORR: overall response rate; PFS: progression-free survival; CR: complete response; PR: partial response; RT: radiation therapy; CT: chemotherapy; N/A: not available.

Carcinoma della vulva recidivato

Spesso la recidiva è in una area precedentemente radiotrattata

Sono presenti pochi studi clinici in letteratura

Oncology. 2009;77(5):281-4. doi: 10.1159/000259259. Epub 2009 Nov 16.

Cisplatin and vinorelbine chemotherapy in recurrent vulvar carcinoma.

Cormio G[1], Loizzi V, Gissi F, Serrati G, Panzarino M, Carriero C, Selvaggi L.

16 pazienti con recidiva di carcinoma della vulva (9 con recidiva locale ,7 con recidiva linfonodale inguinale

CDDP g1 + vinorelbina gg1-8
4 pz con CR (27%) + 2 PR (13%)
4 pz SD (27%) 5 pz progressione
Median PFS 10 mesi OS 17 mesi

Ann Oncol. 2009 Sep;20(9):1511-6. doi: 10.1093/annonc/mdp043. Epub 2009 Jun 1.

Phase II study on paclitaxel in patients with recurrent, metastatic or locally advanced vulvar cancer not amenable to surgery or radiotherapy: a study of the EORTC-GCG (European Organisation for Research and Treatment of Cancer--Gynaecological Cancer Group).

Witteveen PO[1], van der Velden J, Verqote I, Guerra C, Scarabeli C, Coens C, Demonty G, Reed N.

31paz da 10 centri con malattia avanzata o recidivata
Paclitaxel 175 mg/mq ogni 21 gg

20 paz. Precedentemente radiotrattate
Neutropenia di grado 3 e 4 nel 27% delle paz
2 CR + 2 PR (13%)
PFS 2,6 mesi OS 6.8 mesi