GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries

CANCER SITE	NO. OF NEW CASES (% OF ALL SITES)	NO. OF DEATHS (% OF ALL SITES)
Breast	2,088,849 (11.6)	626,679 (6.6)
Cervix uteri	569,847 (3.2)	311,365 (3.3)
Corpus uteri	382,069 (2.1)	89,929 (0.9)
Ovary	295,414 (1.6)	184,799 (1.9)
Vulva	44,235 (0.2)	15,222 (0.2)
Vagina	17,600 (0.1)	8,062 (0.1)

- ✓ Incidence: 1–2/100,000 women/year (0.4:100,000 <40 years to 20:100,000 >70 years)
- ✓ 3–5% of all gynaecological malignancies
- ✓ SCC = 85–90% , melanoma= 2.4–5%, Bartholin gland carcinoma for 1–3%

Bray F et al. Cancer Journal for Clinicians 2018; 0:1-31

Squamous cell vulvar cancer (SCVC) : Treatment

- ✓ Surgery is the cornerstone of treatment and includes radical local excision or tailored radical vulvectomy with inguinal LDN .
- ✓ SNB is a safe alternative to LDN in pts with tumor size <4 cm, without clinically suspicious groin N
- ✓ Adjuvant inguinal and pelvic RT warranted in pts with more than one intranodal metastasis or with extra-nodal tumor growth

Locally advanced SCVC: definition

- At presentation, approximately 1/3 of pts with SCVC have locally advanced disease
- For these pts there is little consensus for both the definition and the treatment modality
- Current approaches include ultra-radical surgery, exclusive RT , CCRT and a combination of treatment modalities, but a recommended therapeutic strategy is lacking
  i. Large primary tumors extending beyond the vulva or presenting with bulky positive groin nodes *(Hacker 2015)*
  ii. Tumors either close or involving the neighboring organs: vagina, urethra, bladder, anus and/or rectum. These tumors may also be fixed to the pelvic bones *(Aragona 2014)*

Locally advanced SCVC: definition

iii. Tumors which encroach upon or cross the borders with surrounding structures such as the urethra or anus *(O'Donnel 2017)*

iv. Primary or recurring tumors that cannot be locally managed with a radical vulvar resection *(Hoffman 2003)*

Most definitions support the concept that the standard surgical approach is not feasible for:

i. The impossibility to remove the primary tumor with adequate surgical margins

ii. The presence of groin nodes fixed to the fascia, muscle, or vascular structures

"Resectability" depends on both the surgeon skills and philosophy and the risks acceptable for each patient (multidisciplinary setting).

Locally advanced SCVC: primary surgery

When the disease involves the anus, rectum, recto-vaginal septum, proximal urethra or bladder, pelvic exenteration (colonstomy, urinary diversions and reconstructive procedures) should be considered only in carefully selected pts

>5-year OS: 20-70% (mainly dependent on nodal and surgical margin status)

>Hopkins and Morley (1992)

5-year OS: 71.4% for N- vs 0% for N+

>Post-surgical complication rates: 52.6- 100%

>Perioperative mortality rates: 0 - 20% (in most series <4%)

Collected data from the literature

Locally advanced SCVC: primary RT

- ✓ RT may downsize the tumor in 70–85% of cases, thus reducing the need for exenteration, although a temporary bowel diversion may be sometimes required to better tolerate RT and to avoid the clinical sequelae of bowel fistulas that may occur during RT
- ✓ The surgical approach after neoadjuvant RT can be extremely complex, because of necrotic areas that need to be removed with the tumor. Plastic reconstruction is often needed to fill areas with loss of substance

(Hacker 1984;; Boronow 1987; Rotmensch 1990; O'Donnell 2017; Mazumder 2019

Locally advanced SCVC: primary CCRT

Authors [ref.]	Chemotherapy	Total RT dose	Response
Thomas [35]	5-FU 1000 mg/m² /day c.i. for 4 or 5 days ± MMC 6 mg/m² day 1	45 -51 Gy	cCR: 6/9 (66.7%)
Berek [36]	CDDP 50 mg/m²/day 1-2 or CDDP 100 mg/m² day 1 or 2 + 5-FU 1000 mg/m²/day c.i. for 4 or 5 days	44-54 Gy	cCR: n 8/12 (66.7%)
Scheistroen [37]	BLEO 30 mg day 1, 3, 5 on week 1 and 3	30-45 Gy[a]	cCR: 5/20 (25%)
Koh [38]	5-FU 750-1000 mg/m² /day. for 3-4 days + CDDP 50-100 mg/m² day 1 (added in 5 cases) or MMC 10 mg/m² (added in 1 case)	40-54 Gy	cCR: 10/20[b] (50%)
Eifel [39]	CDDP 4 mg/m²/days 1-4 (total dose: 64 mg/m²) + 5FU 250 mg/m²/day c.i. days 1-4 (total dose: 4 mg/m²) over 4 weeks	40-50 Gy	cOR: 7/12[c] (58.3%)
Lupi [40]	5-FU 750 mg/m²/day c.i. days 1-5 + MMC 15 mg/m² day 1	54 Gy[d]	cOR: 22/24 (91.6%)
Landoni [41]	5-FU 750 mg/m²/day c.i. days 1-5 + MMC 15 mg/m² day 1	54 Gy[e]	cCR: 14/52[f] (26.9%)
Leiserowitz [42]	5-FU 1000 mg/m²/day c.i. days 1-4 + CDDP 100 mg/m² day 2 (added in 17 cases)	36-54 Gy[g]	cCR: 14/23 (60.9%)[h]
Cunnigham [43]	5-FU 1000 mg/m²/day c.i. days 1-4 + CDDP 50 mg/m² day 1	45-65 Gy[i]	cCR: 9/14 (64.3%)
Moore [44]	5-FU 1000 mg/m²/day c.i. days 1-4 + CDDP 50 mg/m² day 1	47.6 Gy[l]	cCR: 33/71: (46.5%)
Alk [45]	5-FU 1000 mg/m²/day c.i. days 1-4 + MMC 15 mg/m² day 1	30-36 Gy[m]	cCR: 12/12 (100%)
Han [46]	5-FU 1000 mg/m²/day c.i. days 1-4 + MMC 10 mg/m² or CDDP 100 mg/m² day 1	40-62 Gy	cCR: 10/14 (71.4%)[n]
Gerszten [47]	5-FU 1000 mg/m²/day c.i days 1-4 + CDDP 50 mg/m² day 1	44.6 Gy[o]	cCR: 1113/18 (72.2%)
Montana [48]	5-FU 1000 mg/m²/day c.i days 1-4 + CDDP 50 mg/m² day 1	47.6 Gy[p]	Nodes resectable in 37/46 (80.4%)[q] pCR on nodes: 15/37 (40.5%)
Gaudinieau [49]	Weekly CBDCA AUC2 (n.11) Weekly CBDCA AUC2 + PTX 60 mg/m² (n.2) CBDCA AUC5 + 5-FU 1000 mg/m²/day c.i. days 1-4 (n.2) RT alone (n.7)	50 Gy	pCR on vulva 16/22 (72.7%) pCR on nodes 6/22 (27.7%)
Moore [50]	Weekly CDDP 40 mg/m²	57.6 Gy	cCR: 37/58 (64%) on vulva

Locally advanced SCVC: primary CCRT

- ✓ CCRT as primary treatment followed by tailored surgery or as definitive therapy has been widely used in the last years
- ✓ Clinical complete response rates: 46.5 - 72.2%
- ✓ Tumor recurrence rate: up to 30% in complete responders
  40-100% in partial responders

Collected data from the literature

Locally advanced SCVC: primary CCRT

- Pts with grossly involved groin N may be treated with either LDN followed by RT or definitive CCRT or CCRT followed by surgery
- According to *Stecklein* (2018), the decision making should be based on several factors (size, number,location of involved N, and patient habitus)
- The pts with enlarged N close to the skin surface are more likely candidates for surgery, although the morbidity and potential for adjuvant treatment delays following extensive LDN must be taken into account
- Definitive CCRT should be preferred in pts with concomitant massive unresectable vulvar tumors, since the ability to control local disease usually dominates patient prognosis

Locally advanced SCVC: NACT + surgery

Authors [ref]	Drug	patients	Clinical response	
Wagenaar [54]	BLEO 5 mg im d 1-5 week 1 CCNU 40 mg po d 5-7 week 1 MTX 15 mg po d 1, 4 week 1 BLEO 5 mg im d 1,4 weeks 2-6 MTX 15 mg po d 1 weeks 2-6 repeated at 49-day intervals up to 3 cycles	25*	CR=2 (8.0%)	PR=12 (48.0%)
BenedettiPanici [55]	CDDP 100 mg/m^2 d1 BLEO 15 mg d 1, 8 MTX 300 mg/m^2 d 8 repeated at 21-day intervals for 2-3 cycles	21	primary PR=2 (9.5%)	groins CR=11 (52.4%) PR=3 (14.3%)
Geisler [56]°	CDDP 50 mg/m^2 d1 + 5-FU 1000 mg/m^2 /die c.i d 1-5 CDDP 50 mg/m^2 d1 repeated at 21-day interval for 3-4 cycles	10 3	CR=1 (10%) 0	PR=9 (90%) 0
Raspagliesi [57]	PTX 175 mg/m^2 day 1 + CDDP 50 mg/m^2 day 1 + IFO 5 g/m^2 24-h c.i. day 2 PTX 175 mg/m^2 day 1 + CDDP 70 mg/m^2 day 1 repeated at 21-day intervals for 3 cycles	4 6 Overall 10	CR=1 (25.0%) CR=2 (33.3%) 3 (30%)	PR=3 (75.0%) PR=2 (33.3%) 5 (50.0%)

NACT followed by surgery should be still considered as an investigational approach in pts with locally advanced SCVC for both the limited results and the difficulties to deliver such aggressive drug regimens in old women often burdened with severe comorbidities.

Trattamento del carcinoma a cellule squamose localmente avanzato della vulva in Italia: studio osservazionale retrospettivo multicentrico

RAZIONALE

Le incertezza sulla esatta definizione del SCVC localmente avanzato e la bassa numerosità con la dispersione dei casi fanno sì che siano carenti le informazioni sulla sua reale incidenza e sulle strategie terapeutiche nel nostro Paese.

DISEGNO

Studio multicentrico osservazionale no profit che prevede di arruolare pazienti con diagnosi di SCVC localmente avanzato.

La raccolta dati è retrospettiva (periodo 2008-2017) e l'analisi degli stessi avrà una durata di 12 mesi con presunta data di inizio a Gennaio 2021

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CRITERI DI INCLUSIONE

1) Pazienti non pretrattate con SCVC localmente avanzato per diffusione uretrale, ano-rettale o vaginale

2) Pazienti non pretrattate con SCVC localmente avanzato per fissità dei linfonodi inguinali

3) Pazienti non pretrattate con SCVC per diffusione uretrale, ano-rettale o vaginale e per fissità dei linfonodi inguinali

CRITERI DI ESCLUSIONE

1) pazienti già sottoposte a trattamento per SCVC

2) pazienti con SCVC metastatico

3) pazienti con neoplasia della vulva non di istotipo squamoso

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OBIETTIVI

Primari

i. Valutare il numero dei casi di SCVC localmente avanzato (ossia non trattabile con vulvectomia radicale e LFD inguinale con margini chirurgici liberi senza danno sfinterico) giunti all' osservazione nel decennio 2008-2017 presso le U.O. di Ginecologia e le U.O. di Radioterapia nel nostro Paese

ii. Valutare le terapie utilizzate in queste pazienti

Secondari

i. Valutare le complicanze dei diversi trattamenti

ii. Valutare l' outcome clinico delle pazienti

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RACCOLTA DEI DATI

Di ciascuna paziente verranno raccolti e riportati nella CRF:

1) numero dei casi giunti alla osservazione nel periodo 2008-2017
2) età e comorbidità
3) precedenti neoplasie
4) n. casi definiti localmente avanzati per diffusione uretrale, ano-rettale o vaginale
5) n. casi definiti localmente avanzati per fissità dei linfonodi inguinali
6) n. casi definiti localmente avanzati per presenza contemporanea di diffusione uretrale, ano-rettale o vaginale e di fissità dei linfonodi inguinali

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7) n. casi trattati con chirurgia ultra-radicale (specificare quale, con eventuali procedure plastiche ricostruttive), complicanze, terapia post-operatoria (specificare quale), recidiva, status

8) n. casi trattati con RT definitiva (modalità e dosi della RT), risposta clinica, complicanze , recidiva , status

9) n. casi trattati con RT neo-adiuvante (modalità e dosi della RT), risposta clinica, tipo di chirurgia, risposta patologica, complicanze , recidiva , status

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10) n. casi trattati con CCRT definitiva (modalità e dosi della RT; dosi e schedula della CT), risposta clinica , complicanze , recidiva , status

11) n. casi trattati con CCRT neo-adiuvante (modalità e dosi della RT; dose e schedula della CT), risposta clinica, tipo di chirurgia , risposta patologica, complicanze, recidiva, status

12) n. casi trattati con NACT (dose e schedula), risposta clinica, tipo di chirurgia, risposta patologica, complicanze, recidiva , status

13) n. casi trattati con CT esclusiva (dose e schedula), risposta clinica, status

14) n. casi trattati con Best Supportive Care , status