Review

Systemic therapy in squamous cell carcinoma of the vulva: Current status and future directions

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HIGHLIGHTS

- Current treatment strategies have not led to improved survival in women with advanced-stage vulvar carcinoma.
- Knowledge of the pathogenesis and mutational profile of vulvar carcinoma may allow for the development of new treatment strategies.
- Future trials should use innovative designs, focus on quality of life, include elderly patients, collect biomarkers and incorporate targeted agents.

ARTICLE INFO

ABSTRACT

Objective. The advances achieved in the surgical management of vulvar squamous cell carcinoma (SCC) have not been mirrored in systemic therapy options. The objective of this paper is to summarize current evidence regarding systemic therapy in vulvar cancer, review the latest research on the biology of this disease, and identify future strategies to improve patient management.

Methods. MEDLINE and EMBASE were searched for all relevant English-language articles from inception to December 10, 2012. Existing evidence regarding systemic therapy in vulvar SCC was synthesized descriptively, with an emphasis on prospective studies when available. Single-patient case-reports were excluded.

Results. We identified 12 studies of neoadjuvant chemoradiation, 8 studies of neoadjuvant chemotherapy alone, 18 studies of chemoradiation as primary therapy, 4 studies of chemotherapy in the adjuvant setting, and 8 studies of chemotherapy for recurrent or metastatic disease. Review of the biology of vulvar cancer was performed, and promising targets for the future were identified based on the two biologic pathways of disease development. New therapeutic strategies such as immune-therapy and targeted agents hold promise for the future.

Conclusions. Advances in systemic therapy for vulvar SCC are urgently needed, especially in the setting of recurrent and metastatic disease. A focus on the investigation of new targeted agents is encouraged and consideration of quality of life and sexual health issues is essential. International cooperation and adaptive trial designs are required to improve outcomes for this group of traditionally under-served women.

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Introduction

The incidence of vulvar cancer has been increasing over the past 20 years [1]. Vulvar cancer is diagnosed in an estimated 4,490 US women, and leads to 950 deaths annually [1]. One third of these women will be diagnosed with FIGO stage III and IV disease [2]. There has been no improvement in survival for those diagnosed with advanced or recurrent disease in the last 2 decades [2]. New approaches are therefore required to improve outcomes in patients with advanced disease.

Significant progress has been made in the surgical management of vulvar cancer over the past 20 years. Wide local excision has largely replaced radical vulvectomy for early-stage disease [3]. Assessment of groin lymph nodes has transitioned from en-bloc resection to separate inguinal incisions [4], and finally to sentinel lymph node biopsy in appropriately selected patients [5]. These modifications have maintained oncologic outcomes while significantly reducing morbidity. The development of effective systemic therapy options for patients with vulvar cancer, however, has not kept pace with these surgical advances.

Trials of systemic therapy for patients with vulvar cancer are difficult to perform. The rare nature of this disease makes randomized controlled trials (RCT) virtually impossible for single institutions, and even multicentre trials have difficulty meeting accrual targets. The patient population is predominantly elderly, and often suffering from medical comorbidities, making enrolment into phase I/II trials difficult. Significant improvements in systemic therapy for vulvar cancer will require new ways of thinking about, and investigating, therapeutic options, especially for those with advanced-stage disease. This review summarizes the current evidence for systemic therapy in vulvar cancer, highlighting the latest research on the biology of this disease and seeks to act as a catalyst for new initiatives in the gynecologic oncology community to facilitate the development of better strategies for patient management.

Methods

MEDLINE and EMBASE were searched from inception to December 10, 2012 to identify English-language publications of systemic therapy for squamous cell carcinoma (SCC) of the vulva. The search strategy was created in conjunction with a research librarian experienced in systematic reviews. Search terms included appropriate controlled vocabulary for each database and keyword searches including various terms for vulvar cancer in combination with terms such as "chemoradiation", "chemotherapy", "systemic therapy", "targeted therapy", and "biologic agents". In addition, the PubMed related articles feature was used and reference lists of eligible articles were searched to ensure all relevant articles were identified. Articles describing treatment for melanoma or non-SCC histologies were excluded. Given the rarity of vulvar cancer, no limits were placed on study methodology, however, single-patient case series were excluded as were studies not providing clinical outcomes for patients given systemic therapy.

Current approaches to systemic therapy

Neoadjuvant chemoradiation

Chemoradiation has been evaluated as a strategy to allow for surgical resection in patients presenting with unresectable locally advanced vulvar cancer (LAVC) or to allow for more limited, and less morbid surgery, in patients who would otherwise require exenteration. Studies of neoadjuvant chemoradiation are summarized in Table 1. According to a survey of members of the Gynecologic Cancer Intergroup (GCIG), there is significant heterogeneity in the chemotherapy regimens used in the neoadjuvant setting along with radiation therapy (RT) [6]. The most commonly used chemotherapy regimen was weekly cisplatin (in 60% of GCIG groups) followed by cisplatin and 5-FU (in 31% of groups) [6]. No study has compared various chemotherapy agents in conjunction with standardized RT for the treatment of LAVC.

Maneo et.al. presented the results of an RCT comparing neoadjuvant chemoradiation to primary surgery in abstract form only; it is therefore not included in Table 1 [7]. Sixty-eight women with operable LAVC were randomized to either primary radical surgery followed by RT if more than one groin lymph node contained metastatic disease, or to neoadjuvant chemoradiation followed by surgery. Chemoradiation comprised 50 Gy neoadjuvant RT with concurrent infusional 5-FU 750 mg/m^2 days 1–5 and Mitomycin-C 15 mg/m^2 IV day 1, with two courses given three weeks apart. They found no difference in rates of morbidity or wound separation, and also no difference in recurrence or survival between groups at a mean follow-up of 42 months. Details regarding the extent of primary tumor and the complexity of surgical procedures required in each group are not provided, and quality of life (QOL) was not reported.

GOG 101 was a two-part prospective study by the Gynecologic Oncology Group (GOG) investigating the use of neoadjuvant chemoradiation for LAVC. The study separately investigated the role of concurrent RT and cisplatin/infusional 5-FU chemotherapy in patients with unresectable disease due to local tumor extent [8] or fixed or ulcerated inguinal lymph nodes [9]. RT was given in two courses separated by a 2 week break.

The first component of GOG 101 evaluated 71 patients with unresectable vulvar disease, or disease requiring exenteration [8]. Clinical CR occurred in 47% (34/71) of patients. Of the patients with clinical CR who had surgery, 70% (22/31) had a pathologic CR. Two of 71 patients (3%) had unresectable disease after chemoradiation, and three patients (4%) required exenteration. Although postoperative wound complications were frequent, morbidity related to surgery in the irradiated vulva was not excessive. Toxicity from chemoradiation was acceptable, although acute vulvar cutaneous reactions were almost universal. Four treatment-related deaths (5%) were reported. At a median follow-up of 50 months, recurrence was reported in 34% (24/69) of patients, while 56% of patients (40/71) were alive without evidence of disease.

The second component of GOG 101 evaluated 46 patients with unresectable nodal disease [9]. After chemoradiation, 38 patients (83%) were able to undergo surgery (37 with resectable nodal disease).

Table 1

Studies of neoadjuvant chemoradiation for vulvar cancer.

Study	N	Indication	CT regimen	RT regimen	Response	Survival	Achieved resectability without exenteration
Levin [54]	6	LAVC n = 6	5-FU 1000 mg/m² infusion d1–4 + MMC 10 mg/m² 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)
Carson[a] [55]	8	LAVC n = 6 Recurrence n = 2	5-FU 750 mg/m² infusion d1–5 + MMC 7.5 mg/m² IV d4 + CisP 10 mg/m² 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)
Whitaker [56]	12	LAVC n = 9 Recurrence n = 2	5-FU 750–1000 mg/m² infusion d1– 4 + MMC 10–12 mg/m² 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)
Scheistroen [57]	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)
Eifel [58]	12	LAVC n = 12	CisP 4 mg/m²/d infusion d1–4 + 5-FU 250 mg/m²/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)
Landoni[a] [59]	58	LAVC n = 41 Recurrent n = 17	5-FU 750 mg/m² infusion d1–5 + MMC 15 mg/m² 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
Lupi[a] [60]	31	LAVC n = 24 Recurrent n = 7	5-FU 750 mg/m² infusion d1–5 + MMC 15 mg/m² 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)
Moore[a] GOG 101 [8]	71	LAVC n = 71	5-FU 1000 mg/m² infusion d1–4 + CisP 50 mg/m² 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)
Montana[a] GOG 101 [9]	46	LAVC n = 46	5-FU 1000 mg/m² infusion d1–4 + CisP 50 mg/m² 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)
Gerszten [61]	18	LAVC n = 18	5-FU 1000 mg/m² infusion d1–4 + CisP 50 mg/m² 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)
Beriwal [62]	18	LAVC n = 18	CisP 40 mg/m² d 1 and 5-FU 1000 mg/m² 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, then1.8 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)
Gaudineau [63]	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)

[a] Prospective. 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; PR: partial response; 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: patients; MMC: mitomycin 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.

The lymph nodes demonstrated a pathologic CR in 15 of 37 patients (40%), and the vulvar tumor bed had a pathologic CR in 20 of 38 patients (52%). Of those undergoing surgery, 19 of 38 patients (50%) developed recurrent disease, 5 (13%) died of unrelated causes, and 2 (5%) died of treatment-related complications. However, 12 of 38 patients (32%) were alive with no evidence of disease at a median follow-up of 78 months. This was viewed as a very positive result in a poor-prognosis population.

Overall, chemoradiation as a neoadjuvant strategy has been reported to produce high rates of surgical resectability without exenteration, regardless of chemotherapy regimen used. Studies generally report high but manageable rates of vulvar cutaneous toxicity, with the morbidity of surgical excision not significantly increased compared to primary surgery. Whether resectable LAVC is better treated by exenterative primary surgery or by chemoradiation with or without limited surgery requires investigation in an RCT incorporating QOL and sexual health outcomes. Patients who are elderly and with multiple medical comorbidities may not tolerate extensive surgery, and therefore, chemoradiation provides promise in such patients. Future studies should compare two or more chemotherapy regimens while providing standardized RT to identify the optimal chemotherapeutic or biologic radiosensitizer. Incorporation of novel agents in combination with radiation (and/or chemotherapy) in the frontline setting should be considered. Reporting on such studies should describe the extent of disease and patient comorbidities, include biomarker evaluation, and provide data on QOL and sexual function.

Neoadjuvant chemotherapy

Chemotherapy alone as a neoadjuvant strategy to allow for less morbid surgery has several proposed advantages over neoadjuvant chemoradiation. Radiation to the vulva causes cutaneous toxicity in most patients, and rates of post-operative wound complications in the radiated field are high [10]. In an effort to avoid primary exenteration, studies of neoadjuvant chemotherapy have been published by several authors over the last 20 years, although this remains an under-investigated strategy. Vulvar cancer has proven responsive in the neoadjuvant setting in chemo-naive patients. Although studies are small, agents showing response include cisplatin, bleomycin, and most notably, infusional 5-FU [11]. Table 2 provides details of these studies.

The European Organisation for Research and Treatment of Cancer (EORTC) has published two phase II trials of neoadjuvant chemotherapy [12,13]. Both used a combination regimen including bleomycin, methotrexate and lomustine (CCNU). They enrolled patients with primary or recurrent LAVC who had not received any prior RT or chemotherapy. Although response rates in both studies were quite high (overall response rate (ORR) = 64% (18/28) [12] and ORR = 56% (14/25) [13]) toxicity was a significant issue. There were 4 (7.5%) treatment-related deaths and patient withdrawal due to toxicity was common.

More recently, Aragona et.al. published a prospective multi-center trial of neoadjuvant chemotherapy followed by radical surgery [14]. Thirty-five previously untreated patients with LAVC were given cisplatin-based chemotherapy. Surgical resection was undertaken if the clinical response was at least 50%. Thirty-three patients (94%) completed chemotherapy, and 27 (77%) underwent radical vulvectomy or local excision and bilateral inguino-femoral lymphadenectomy. The remaining two patients required posterior exenteration for persistent disease. Twenty-four patients (69%) remain disease-free at a median follow-up of 49 months and the authors reported a 92% 5-year overall survival. High rates of response and disease-free survival in this trial suggest cisplatin-based chemotherapy may demonstrate both improved clinical efficacy and reduced toxicity compared to bleomycin-based chemotherapy.

Neoadjuvant chemotherapy has been less extensively studied than neoadjuvant chemoradiation. Trials to date have evaluated older chemotherapy agents, and have not included targeted agents.

Bleomycin, although effective, produces unacceptable toxicity in this population of patients [13]. Platinum and 5-FU based combinations appear to offer efficacy with a tolerable toxicity profile. Neoadjuvant systemic therapy warrants further investigation, and the inclusion of targeted agents selected on the basis of tumor biology and high quality pre-clinical data is over-due in this disease.

Primary chemoradiation

Chemoradiation as a stand-alone treatment for LAVC has become more common over the past several years. While in some instances neoadjuvant strategies allow for the option of surgical excision, the morbidity of surgery can be significant. Berek et.al [15] published an early study of primary chemoradiation and reported long-term disease-free survival in 83% (10/12) of patients, indicating chemoradiation was a promising strategy. As in other disease sites, the concurrent use of chemotherapy with RT appears to improve response rates compared with RT alone [16].

The most effective chemotherapy regimen for use with RT for the primary treatment of LAVC has not yet been elucidated. Multiple regimens are currently in use. Studies reporting primary chemoradiation are summarized in Table 3. One retrospective study compared outcomes for patients receiving weekly platinum-based chemotherapy versus infusional-5-FU-based regimens and found no difference in survival or local recurrence rates [17].

GOG 205 was a phase II trial of primary chemoradiation, which used a different radiation protocol and chemotherapy regimen than GOG 101 [18]. RT in GOG 205 was given daily, five days per week in 1.8 Gy fractions to a total dose of 57.6 Gy. This is a 20% dose increase compared to GOG 101, which had purposefully used a lower dose because all patients in that study subsequently underwent surgery. Treatment breaks were eliminated because studies of SCC in the head-and-neck found decreased effectiveness of split-course RT compared to continuous RT [19]. Chemotherapy was modeled after treatment of cervical cancer, with weekly cisplatin given at a dose of 40 mg/m^2 IV during RT. Patients only underwent radical surgical resection after chemoradiation if they had residual disease present on biopsy.

Fifty-eight eligible patients with LAVC requiring exenteration or with unresectable disease were evaluated [18]. All patients completed at least two weekly cycles of chemoradiation, and 40 of 58 women (69%) completed the entire protocol. One treatment-related death occurred and nine patients (15%) discontinued treatment due to excessive toxicity. Although acute toxicity was significant, the protocol was considered tolerable. Thirty-seven patients (64%) achieved a clinical CR and 29 (50%) a pathologic CR in GOG 205. After 24-months median follow-up, 22 of these 29 women (75%) continued to have no evidence of disease, while seven patients experienced recurrence. Of the 29 patients who had persistent disease after chemoradiation and who underwent surgical resection, eight (27%) were alive at last follow-up with no evidence of disease recurrence.

GOG 205 demonstrated primary chemoradiation is an effective strategy for the treatment of LAVC which would otherwise be unresectable or require exenteration. We now need comparative studies to identify the best chemotherapy and RT regimens in these patients in order to improve outcomes while minimizing toxicity and morbidity. QOL is an essential outcome for future trials of primary chemoradiation.

Adjuvant chemotherapy or chemoradiation

Adjuvant therapy, consisting of chemotherapy, radiation, or both, has been recommended in cases where surgical staging reveals inguinal lymph node metastases or close or involved margins. Only four studies of chemotherapy with or without RT in the adjuvant setting have been published to date. Three of these studies retrospectively evaluated

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.

Table 3
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) alive NED
Kalra[a] [68]	3	LAVC n = 2 Recurrence n = 1	MMC 10 mg/m² IV d1 + 5-FU 1000 mg/m² 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) alive NED
Evans[a] [69]	4	LAVC n = 4	5-FU 1000 mg/m² continuous infusion d1–4 + MMC 10 mg/m² 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) alive NED
Thomas [20]	24	LAVC n = 9 Recurrence n = 15	5-FU 1000 mg/m² infusion d1–4 + MMC 6 mg/m² 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/m² infusion d1–4 + CisP 100 mg/m² 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) alive NED
Russell [70]	25	LAVC n = 18 Recurrence n = 7	5-FU 750–1000 mg/m² infusion d1–4 + CisP 100 mg/m² 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) alive NED
Koh [71]	20	LAVC n = 17 Recurrence n = 3	5-FU 750–1000 mg/m² 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) alive NED 5-yr DSS 49%
Sebag-Montefiore [72]	37	LAVC n = 19 Recurrence n = 18	5-FU 750 mg/m² infusion d1–5 + MMC 10 mg/m² 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/m² infusion d1–4 given weeks 1 + 5 of RT. Six patients also given MMC 10 mg/m² 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) alive NED 5-yr DSS 89%
Cunningham [74]	14	LAVC n = 14	5-FU 1000 mg/m² infusion d1–4 + CisP 50 mg/m² 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) alive NED
Leiserowitz [75]	23	LAVC n = 23	5-FU 1000 mg/m² infusion d1–4 + CisP 100 mg/m² 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) alive NED
Akl [76]	12	T1 in 3 pts, T2 in 5 pts, T3 in 4 pts	5-FU 1000 mg/m²/24 h as continuous infusion days 1–4 and 29–32 plus MMC 15 mg/m² 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) alive NED 3-yr DFS = 84%
Han [16]	14	LAVC n = 10 Recurrence n = 4	5-FU 1000 mg/m² infusion d 1–4 + MMC 10 mg/m² 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) alive NED 5-yr OS 54%
Mulayim [21]	7	LAVC n = 7	5-FU 1000 mg/m² infusion d1–4 + MMC 10 mg/m² 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) alive NED Median OS 31 months
Landrum [77]	33	LAVC n = 33	Either weekly CisP 40 mg/m² or two cycles of CisP 50 mg/m² IV d1 + 5-FU 1000 mg/m² 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-yr DFS 51.8%
Tans [78]	28	LAVC n = 20 Recurrence n = 8	5-FU 1000 mg/m² infusion d1–4 + MMC 10 mg/m² 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) alive NED 4-yr OS 65%
Moore[a] GOG 205 [18]	58	LAVC n = 58	Weekly CisP 40 mg/m² 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) alive NED

[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: pathologic complete 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: twice daily, f/u: follow-up, NED: no evidence of disease and no recurrence.

fewer than 10 patients respectively, and treated patients with a combination of 5-FU, Mitomycin-C and RT [16,20,21]. Conclusions from these studies are limited by their small numbers, by the heterogeneity of patients evaluated, and by the use of non-standardized RT.

One prospective study evaluating the use of chemotherapy alone in the adjuvant setting was published by Bellati et.al. [22]. They enrolled 14 patients with inguinal node metastases after primary surgery. Cisplatin 100 mg/m^2 was administered every 21 days for four cycles [22]. Four of 14 patients recurred (29%) at a median of 57 months of follow-up, including two recurrences in the groin. Three-year OS and PFS were 86% and 71% respectively.

Few studies evaluating chemotherapy with or without RT in the adjuvant setting have been published. Despite limited data, the use of chemotherapy concurrently with RT has been justified by extrapolation of results of chemoradiation in the neoadjuvant or primary settings. However, the incremental benefit from chemotherapy in addition to RT has yet to be fully evaluated, and deserves further study.

Chemotherapy alone for metastatic disease

Several studies have evaluated chemotherapy alone for patients with metastatic disease at diagnosis or at the time of recurrence. Table 4 includes studies enrolling at least 10 patients. Although initial reports were disappointing [23,24], some agents do show activity. Unlike in the neoadjuvant setting, however, these patients are often pre-treated, and recurrent disease in a previously radiated field is common, a factor which may limit chemotherapy effectiveness. Response rates in and out of field have not previously been reported in vulvar cancer studies but should be included in future clinical trials.

Cormio et.al. [25] published a small phase II trial evaluating cisplatin plus the vinca alkaloid vinorelbine, which has activity against SCC at other disease sites. They enrolled 15 evaluable patients with recurrent disease after initial therapy with surgery and RT, and found an overall response rate of 40% (6/15 patients). Four patients (27%) achieved a complete response and 2 (13%) achieved a partial response, with a median duration of response of 5 months. Median PFS was 10 months (range 3–17) and median OS was 19 months (range 1–30). One patient experienced a treatment-related death.

Although these results appear promising, comparisons between individual studies are confounded by small patient numbers and potential patient selection bias. Results in pre-treated patients have generally been disappointing [26]. Currently there have been no studies of systemic treatment either in the front-line or second-line setting compared to best supportive care. A low-toxicity systemic therapy with the potential to improve QOL, produce a prolonged progression-free interval or increase survival after recurrence is urgently needed for patients with metastatic vulvar SCC, and new approaches using targeted agents may help to address this clinical problem. Intergroup participation could allow for comparative studies using newer agents to better define a standard approach to the treatment of metastatic vulvar SCC. The patient demographic of this disease means that it is imperative that future studies include patients over age 70, a group who have, historically, been under-represented in clinical trials, and response rates should be reported both inside and outside previously radiated fields.

Biology of vulvar squamous cell carcinoma

Vulvar SCC is thought to arise from two separate etiologic pathways. The first is HPV-related and is preceded by 'usual-type' vulvar intraepithelial neoplasia (VIN). HPV-related vulvar cancer classically has a 'warty' or 'basaloid' histologic appearance [27]. This pathway is thought to account for a large proportion of vulvar cancer in younger women, and may also be responsible for the increased incidence of vulvar neoplasia seen in the last two decades [28]. HPV-associated vulvar SCC may arise in patients with other HPV-related diseases of the lower genital tract, and risk is increased in smokers [27]. Similar to cervical SCC, in HPV-related vulvar SCC the E6 and E7 viral oncoproteins lead to inactivation of tumor-suppressors p53 and pRb (retinoblastoma); pRb inactivation results in overexpression of p16 [29]. P16 immunostaining has a sensitivity of 100% and specificity of 98% in the detection of HPV-associated vulvar SCC [27].

Many studies have evaluated the prevalence of HPV infection in vulvar SCC, and rates appear to vary significantly geographically. A population-based study in the US found that 68% of vulvar SCC was HPV-associated, while a population-based study in Denmark found 50% of cases to be HPV-related [30,31]. A recent meta-analysis of 93 studies worldwide found that 40% of vulvar SCC is HPV-related globally [32]. HPV-16 is the most common viral subtype identified, accounting for more than 75% of HPV-positive cases [32], and is present in up to 48% of all cases of vulvar SCC [31]. The currently available preventative HPV vaccines, all of which prevent infection with HPV-16, would therefore be expected to protect against a significant proportion of vulvar neoplasia, depending on the duration of the immune response. Whether HPV positivity affects prognosis is currently unclear, as studies have reported conflicting results [33].

The second etiologic pathway begins with either a benign vulvar dystrophy (lichen sclerosis or epithelial hyperplasia), or following 'differentiated' VIN [27]. The diagnosis of differentiated VIN is uncommon, and therefore SCC lesions developing along this second pathway, termed keratizing or well-differentiated, are usually not diagnosed in a pre-invasive state [34]. This pathway is believed to

Table 4
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 6.8 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.

be responsible for most vulvar SCC in elderly patients. P53 immuno-staining is most often seen in tumors arising along this non-HPV re-lated pathway, and has been reported to have a 64% sensitivity and 98% specificity for non-HPV-related vulvar SCC [27].

Potential therapeutic strategies for vulvar cancer

HPV-related vulvar cancer

Vulvar cancer is rare, however HPV-related tumors including those in other disease sites may share similar "druggable" characteristics. Exploiting data generated in other HPV-related tumor types or inclusion of vulvar cancer in novel HPV-related tumor trials have the potential to improve outcomes for women with HPV-related vulvar tumors. HPV vi-ruses exert their oncogenic effects primarily through E6 and E7 oncoproteins. E6 binds the ubiquitin ligase E6AP and also p53, leading to ubiquitin-mediated degradation of the p53 tumor suppressor. E6 binds to E6AP and other proteins at a Leucine-rich LxxLL motif [35]. The crystal structure of the E6 protein on its own, and when bound at the LxxLL motif, is now better understood, and inactivation of the E6 LxxLL binding pocket disrupts the ongogenic activity of E6 [35]. This may be an important therapeutic target for future drug development.

Recent advances have exploited an ever-expanding knowledge of the immune system in the pathogenesis of cancer. VIN has been associ-ated with an increase in regulatory T-cells [36], while clearance of gen-ital HPV infection is thought to be influenced by local T-cell mediated immunity [37]. Imiquimod, an immune response modifier stimulating both innate and adaptive immune responses [38], has demonstrated ac-tivity in the treatment of VIN. Differential responses are noted, however, with non-responders exhibiting decreased local infiltration of T-cells compared to responders. Although this work has been done in pre-invasive disease, immune modulation holds promise for invasive dis-ease as well. Studies are currently underway in HPV-related cervical cancer investigating the CTLA-4 targeting agent ipilimumab, which may be relevant to HPV-related vulvar cancer in the future. Further-more, immune therapy using long peptides of the E6 and E7 proteins can induce a strong T-cell immune response in-vitro [39]. More recent-ly, Kenter et.al. reported the use of a synthetic long-peptide vaccine in 19 women with HPV-16 positive VIN3 in a phase II trial [40]. Women experienced only mild toxicity in the form of local swelling and fever. Vaccine-induced T-cell response was demonstrated in 85% of patients. After 12 months follow-up, 15 of 19 women (79%) experienced a clini-cal response, with CR in 47% (9/19). Complete responses were main-tained at the 24 month follow-up. Currently, these therapies appear to be significantly more effective in the treatment of pre-invasive disease, but the approach remains promising [41].

Although anti-angiogenic agents have not yet been evaluated in vulvar SCC, targeting angiogenesis is an attractive therapeutic strat-egy in HPV-related cancer. Recently data was presented from GOG-240, an RCT enrolling women with recurrent, metastatic cervical cancer [42]. Women were randomized in a 2 × 2 factorial design to chemotherapy with or without bevacizumab, a monoclonal antibody directed against vascular endothelial growth factor (VEGF). The study demonstrated a significant improvement in OS for women who received bevacizumab in addition to chemotherapy: hazard of death of 0.71 (97.6% CI 0.54–0.95, p = 0.0035) and median OS of 17 months compared to 13.3 months in the chemotherapy alone arms [42]. Angio-genesis is an attractive option in many cancers and is not restricted to those associated with HPV. There is a clear rationale for targeting angio-genesis in HPV-related vulvar cancer but anti-angiogenic agent data may be relevant to non HPV-related tumors as well.

Epidermal growth factor receptor (EGFR)

The epidermal growth factor receptor (EGFR) has emerged as one of the most promising targets for non HPV-related vulvar cancers where

EGFR gene amplification has been demonstrated [43]. EGFR may be targeted by monoclonal antibodies directed against the extracellular ligand-binding domain of the receptor or inhibitors that prevent ac-tivation of the tyrosine kinase domain [44]. Case reports have sug-gested effectiveness of EGFR receptor inhibitors in patients with LAVC [45], lending impetus to a phase II study demonstrating the ef-fectiveness of erlotinib, with a 67.5% clinical benefit rate and modest toxicity [43]. Combining conventional chemotherapy with EGFR ty-rosine kinase inhibitors (TKIs) (e.g. erlotinib, cetuximab) to improve response is particularly attractive [46]. Response to EGFR inhibitors in colorectal cancer is dependent on the presence of wild-type Kirsten *Ras* (*K-Ras*) and Harvey *Ras* (*H-Ras*) [47]. It is important, as with all targeted agents, that we take the opportunity to identify predictive bio-markers in future vulvar studies. This is particularly important in a rare tumor where clinical trials are infrequent.

Combination studies of EGFR inhibitors are attractive because of their favorable toxicity profiles. EGFR inhibitors have been tested in combination with synthetic retinoids, a potentially useful class of agents for induction of apoptosis. Zanchi et.al. [44] identified a syner-gistic interaction when a novel atypical retinoid and EGFR inhibitor were used in concert in solid tumor cell lines including the vulvar carcinoma cell line A431. A significant improvement in apoptotic re-sponse was noted with the combined treatment with evidence sug-gesting that EGFR inhibition lowers cell survival signals, which enhances the pro-apoptotic effect of the atypical retinoid. Vega et.al. [48] demonstrated that an EGFR antibody (C225) can be conjugat-ed with a doxorubicin-bound copolymer (PEG–PG–Dox). Selective binding of C225–PEG–PG–Dox to A431 cells was noted, with increased receptor-mediated uptake compared to controls (5 min vs. 24 h). C225–PEG–PG–Dox demonstrated greater potency in A431 cell growth inhibition compared to free doxorubicin. HER2 over-expression has also been noted in vulvar carcinoma. Agents directed at HER2 receptors (e.g. trastuzumab) have been combined with EGFR inhibitors (e.g. gefitinib) leading to increased radiosensitization [49].

Novel targets

Novel systemic chemotherapeutics are under investigation in vulvar carcinoma cell lines. Hadj-Bouazza et.al. [50] describe a newly synthe-sized alkylating agent (N,N-Di-(2-chloroethyl)-2-(thymin-1-yl)acet-amide) with in-vitro activity in the A431 vulvar carcinoma cell line, with in-vivo data to follow. Kumar et.al. [51] describe the development of a riccardiphenol analog (2-[2,6-dimethyl-6-(4-methyl-penta-1,3-dienyl)-cyclohex-2-enylmethyl]-4-methoxy-phenol) with growth in-hibition in a number of cancer cell lines, including A431.

The tumor microenvironment is emerging as potential therapeutic target. Vulvar tumors are easily accessible for repeat biopsy and elevat-ed interstitial fluid pressure and hypoxia has been reported in vulvar tu-mors [52]. Kim et.al. [53] described a significant reduction in cell growth in a vulvar cancer cell line with cisplatin and celecoxib (a COX-2 inhibi-tor) compared to single-agent cisplatin, an investigation prompted by the increased expression of COX-2 in vulvar carcinoma tissue speci-mens, particularly among elderly patients.

Conclusion

The management of advanced stage and metastatic vulvar carcino-ma remains problematic for clinicians: in the last 2 decades there has been no improvement in outcome for women diagnosed with advanced disease. Vulvar cancer has commonly been considered relatively chemo-resistant, however, phase II trials of neoadjuvant chemotherapy demonstrate significant chemo-responsiveness in previously untreated patients [14]. Primary chemoradiation in patients with LAVC has also been successful in phase II trials [18]. A reduction in morbidity is a pri-mary objective of chemoradiation to avoid exenteration. Evaluation of QOL is therefore paramount in future comparative studies, in addition

to evaluation of the most effective chemotherapy regimen for use in conjunction with RT.

Inter-group international trials may be needed to provide the number of patients required for comparative studies. Innovative clinical trial designs, using Bayesian methods and adaptive trial designs may be useful for comparing multiple treatment options in a rare disease site. Additionally, extrapolation of study results from SCC at other disease sites (cervix, head-and-neck) holds promise, especially if tumors contain similar mutational profiles.

Many patients presenting with LAVC are elderly, and have multiple medical comorbidities. Although chemotherapy and chemoradiation protocols are often reported to be tolerable for patients enrolled in phase I/II trials, these trials often exclude elderly patients with lower performance status and other medical comorbidities. Future trials must include elderly patients in order to be generalizable to the majority of women with LAVC.

Targeted agents and differential treatment strategies for HPV-positive and negative SCCs will likely affect the future management of this disease. An understanding of specific mutations along important biological pathways in individual tumors may help guide treatment with targeted agents. Novel approaches to increase drug delivery to the tumor site and drug uptake within tumor cells are also important avenues of research. While an impressive array of research has been performed or is underway, it is clear that more work is needed to better define optimal treatment strategies for women with advanced vulvar cancers. International collaboration is essential in order to improve the outlook for women with this disease.

Conflict of interest statement

No conflicts of interest to declare.

Acknowledgments

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