

**American College of Radiology
ACR Appropriateness Criteria®**

**MANAGEMENT OF LOCOREGIONALLY ADVANCED SQUAMOUS CELL CARCINOMA
OF THE VULVA**

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Summary of Literature Review

Definition of Locoregionally Advanced Vulvar Cancer

Vulvar cancer is a rare disease, with an estimated incidence of 4,490 new cases and 950 deaths in the United States in 2012 [1]. Vulvar cancer predominantly involves older women, with 68 years as the median age of diagnosis. Over the past 25 years the incidence has slightly increased [2].

Vulvar cancer prognosis is intricately related to the extent of the primary and most importantly lymph node involvement as reflected in the recently revised 2009 staging system of the International Federation of Gynecology and Obstetrics (FIGO) staging [3,4].

Although there is not a formal definition of locoregionally advanced vulvar cancer (LRAVC), it has been addressed in the context of several clinical trials as vulvar disease without distant metastasis that is beyond surgical resection with standard radical vulvectomy, irrespective of groin lymph node involvement. Included in this category are patients with FIGO clinical stage III or IVA carcinoma of the vulva, tumor extension to the adjacent genitourinary system and anorectum, or fixation to bones. Approximately 30% of vulvar patients present with stage III-IV disease or lymph node involvement [2]. In the revised FIGO staging, stage II disease includes tumor of any size with extension to adjacent perineal structures (one-third lower urethra, one-third lower vagina, anus, with negative nodes) [4]. These patients should also be included in this category since they are generally beyond curative resection with radical vulvectomy alone, and definitive curative surgery would be associated with acceptable survival, at the cost of considerable morbidity. Management of LRAVC requires considerable pretreatment assessment and planning to determine the best course of therapy for individual patients.

Initial Workup and Evaluation of LRAVC

The staging workup for patients with LRAVC prior to neoadjuvant therapy or surgical resection is not standardized. The extent of the primary tumor can generally be assessed clinically, although imaging may aid in determining the extent of involvement or invasion into surrounding normal organs. While inguinal-femoral lymph node involvement is a significant determinant of prognosis, clinical palpation is unreliable for determining the presence of groin lymph node metastasis [5], and imaging may assist with this assessment. Additionally, for LRAVC, imaging can help identify inguinal lymph node depth and the presence of distant metastatic disease, both of which can impact treatment planning.

Potential imaging modalities for LRAVC include ultrasound (US), computed tomography (CT), positron emission tomography (PET)/CT, and magnetic resonance imaging (MRI). US along with fine-needle aspiration has shown

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a high level of sensitivity and specificity for identifying involved inguinal lymph nodes for vulvar cancer [6,7]. While CT can be used to assess pelvic anatomy or depth of groin lymph nodes, some studies suggest that other imaging modalities, if available, are more useful. Given the rarity of vulvar cancer, many of the diagnostic and treatment approaches are extrapolated from cervical and anal cancer. The clinical value of fluorine-18-2-fluoro-2-deoxy-D-glucose (FDG)-PET/CT in cervical cancer for primary staging and surveillance has been extensively evaluated [8-11]. A more limited number of studies have also evaluated the utility of FDG-PET for anal cancer [12,13].

Scant studies have been reported concerning the management of vulvar cancer using FDG-PET. Cohn et al [14] in a prospective study, evaluated the role of FDG-PET in staging disease with respect to groin nodal metastasis, prior to nodal dissection. These investigators registered 67% sensitivity, 95% specificity, 86% positive predictive value (PPV), and 86% negative predictive value (NPV) for detecting nodal metastasis, while for detection of extranodal disease, FDG-PET demonstrated high specificity and accuracy. Significantly, PET was better at detecting extranodal metastases than groin metastases in this small study of vulvar cancer patients.

For LRAVC, MRI can determine the degree of involvement of normal organs and assist in identifying lymph node metastasis. The sensitivity and specificity of MRI for detecting abnormal lymph nodes in vulvar cancer critically depend on the size threshold used for distinguishing normal and abnormal lymph nodes. For a group of 22 vulvar patients, using ≥ 10 mm in the short axis as the threshold for superficial inguinal nodes, MRI has a 40% sensitivity and 97% specificity for detecting nodal metastasis [15]. In evaluating 39 vulvar cancer patients who had undergone MRI and inguinofemoral lymphadenectomy, MRI had a sensitivity of 86% (64%-97%), specificity of 82% (70%-91%), PPV of 64% (44%-81%), and NPV of 94% (83%-99%). Clinical examination had a specificity of 94% (84%-99%), PPV of 70% (35%-93%), and NPV of 80% (67%-89%) [16]. Based on these small studies, MRI may be useful for assessing inguinal-femoral lymph node involvement, but given the significant implications of groin lymph node involvement, imaging is not a substitute for pathologic assessment.

Role of Sentinel Lymph Node Biopsy

It is important to emphasize that the clinical investigations in sentinel lymph node (SLN) biopsy procedures have involved study populations primarily with early-stage disease. There are no data regarding SLN procedures for patients with locally advanced vulvar cancers who will of course have a higher risk of lymph node metastasis in general and bulky lymph nodal disease in particular.

It has been well recognized that the presence of lymph node metastasis is the most important prognostic factor in vulvar carcinoma [17,18]. Currently there is no noninvasive imaging technique that can exclude the presence of lymph node metastasis with a sufficiently high NPV [19,20]. Therefore, surgical evaluation — inguinal-femoral groin lymph node dissection — is the standard method to assess for the presence of groin lymph node metastasis and the need for postoperative treatment. Unfortunately, significant morbidity is common with inguinal-femoral lymphadenectomy with the short-term risks of wound breakdown, infection, and lymphocele and the long-term risks of lymphedema and cellulitis.

The SLN procedure is perceived as a means to adequately assess for groin lymph node metastasis and minimize the risk for surgical complications. Although false-negative results have been reported [21,22], they are infrequent and reduced with pathological ultrastaging of excised SLNs. Comparative studies provide evidence that there is reduced morbidity with the SLN procedure [23].

The Gynecologic Oncology Group (GOG) has reported the results of a phase II multi-institutional study of SLN biopsy. Eligibility was limited to women with vulvar squamous cell carcinoma, ≥ 1 mm invasion, primary tumor size 2-6 cm, and clinically negative groin lymph nodes. All women underwent intraoperative lymphatic mapping and SLN biopsy followed by inguinal femoral lymphadenectomy. Among the 452 women who underwent specified SLN procedures there were 418 (92%) who had at least one SLN identified. There were 132 node-positive women, including 11 (8.3%) with false-negative nodes. The sensitivity was 91.7% and the false-negative predictive value (1-negative predictive value) was 3.7%. In women with tumors < 4 cm the false-negative predictive value was 2% [24].

Two large prospective observational studies to evaluate SLN procedures have involved early-stage disease. In the Groningen International Study on Sentinel nodes in Vulvar cancer (GROINSS)-V trial, patients with T1-T2 (primary < 4 cm) squamous cell carcinoma of the vulva underwent SLN detection. For patients with a negative SLN as determined by pathological ultrastaging, inguinal-femoral lymphadenectomy was omitted. Among 259

patients with median follow-up of 35 months, there were six groin recurrences (2.3%; 95% confidence interval [CI]: 0.6%-5%), and the 3-year survival rate was 97% (95% CI: 91%-99%) [25]. Patients with metastatic disease in the SLN(s) — either by routine examination or by pathological ultrastaging — underwent inguinal-femoral lymphadenectomy. In investigating the relationship of SLN metastasis size and risk of non-SLN metastasis and disease-specific survival, it was found that no size cutoff seemed to exist below which chances of non-SLN metastases were close to zero, and it was concluded that all patients with SLN metastases should have additional groin treatment. The prognosis for patients with SLN metastasis >2 mm was poor, and novel treatment regimens should be explored for these patients [26].

A second observational study (GROINSS-V II) has been initiated whereby groin lymphadenectomy is omitted and patients with positive SLNs will proceed with postoperative chemoradiation therapy. Eligibility criteria are those of the first GROINSS-V study plus pretreatment CT/MRI is required to exclude the presence of bulky groin lymph nodes. The study has reached approximately 30% of planned accrual and is expected to close in 2014. (See [Variant 1](#).)

Rationale for Neoadjuvant Therapy in the Management of LRAVC

In women presenting with LRAVC, surgical treatment options range from radical vulvectomy and bilateral inguinofemoral lymphadenectomy with or without partial resection of the urethra, vagina, or anus to pelvic exenteration. This can be followed by adjuvant radiotherapy (RT) or chemoradiotherapy depending on the residual disease or risk of recurrence. Plastic reconstruction procedures are considered following excision of large vulvar tumors. When the disease involves the anus, rectum, recto-vaginal septum, proximal urethra, or bladder, in order to obtain adequate surgical margin, some form of pelvic exenteration is the only surgical option. Such radical surgery is often undesirable or inappropriate, since this treatment results in a 10% operative mortality and high complication rates, and may require a permanent colostomy and/or urinary diversion, with the subsequent severe implications in terms of significant physical and psychological morbidity. In addition, patients presenting with fixed or ulcerated groin nodes are often not amenable to surgery. Given the morbidity associated with up-front surgery in LRAVC, the use of neoadjuvant chemotherapy and radiation emerged.

Neoadjuvant Radiotherapy Alone

Boronow et al [27,28] first reported on the efficacy of neoadjuvant RT followed by surgical resection as an alternative approach to pelvic exenteration in patients with LRAVC. In this series of 48 patients, including primary and recurrent disease, 77% of patients received preoperative RT or brachytherapy with or without external beam radiation therapy (EBRT) followed by radical vulvectomy. No residual disease was identified in 42.5% of surgical specimens. Exenteration was performed in only 5% of the cases. The 5-year survival rates were 75.6% for the primary cases, 62.6% for the recurrent cases and an overall 72% for all 48 cases treated.

In a subsequent publication, Hacker et al [29] published similar findings in 8 patients treated with moderate doses of preoperative RT. In 87.5% of them satisfactory shrinkage of tumor occurred, thus allowing conservative surgical excision. In 50% of the cases there was no viable tumor in the surgical specimen, and 62.5% of patients were without evidence of recurrent cancer. Although the data are limited, it seems that moderate doses of preoperative radiation alone (45-54 Gy EBRT +/- 24 Gy brachytherapy) allows downsizing of the tumor in 70%-85% of patients, obviating the need for pelvic exenteration and resulting in significantly less morbidity without apparently compromising survival.

Neoadjuvant Chemotherapy Alone

Neoadjuvant chemotherapy alone has also been investigated as a potential means of downstaging advanced vulvar cancer to allow for a less extensive surgery. Different chemotherapy regimens have been used to avoid primary pelvic exenteration with varying degrees of success ([Appendix 1](#)). One of the initial reports of using neoadjuvant chemotherapy for advanced vulvar cancer was a case report out of Tokyo where a woman with stage IV (T3N3 + M1B) vulvar cancer was treated with 3 cycles of bleomycin, vincristine, mitomycin C, and cisplatin. She showed a clinically complete response and was able to undergo a radical vulvectomy with bilateral inguinal and pelvic lymphadenectomy which showed a partial pathologic response [30].

Around this same time, a phase II study of bleomycin, methotrexate, and lomustine (CCNU) for advanced inoperable vulvar cancer from the European Organisation for Research and Treatment of Cancer (EORTC) Gynaecological Cancer Cooperative Group (GCCG) was published. This study included 28 evaluable patients (18 primaries, 10 recurrent) and showed an overall response rate of 64% with 3 complete responses and 15 partial

responses. Although the response rates were favorable, only 8 patients were found to have resectable disease and only 7 patients subsequently underwent surgery [31]. As a follow-up to this study, the EORTC initiated another phase II study that ran from September 1987 through December 1993. Twenty-five patients (12 with local advanced cancer, 13 with locoregional recurrences) received a lower dose of methotrexate that was given only on day 1 of weeks 2-6, with a 1-week gap between consecutive cycles. An overall response rate of 56% was observed, with little difference between patients with primary cancers and those with recurrent cancers [32].

Other groups have looked at the utility of cisplatin-based neoadjuvant regimens. Benedetti-Panici et al treated a group of 21 locally advanced vulvar patients with a combination of cisplatin, bleomycin, and methotrexate. Ninety percent of patients were operable, although 79% underwent radical surgery, with 33% showing pathological downstaging [33]. Another study compared cisplatin (50 mg/m²) alone (n=3) and in combination with 5-fluorouracil (5-FU) (n=10) for 13 vulvar cancer patients with disease involving the anal sphincter and/or urethra. While one cisplatin-alone patient showed progression, the cisplatin-5-FU patients all showed at least a clinical partial response and were able to avoid exenteration, and 4 patients had a complete pathologic response [34].

Domingues et al [35] retrospectively evaluated three different neoadjuvant chemotherapy regimens for their response rate: 1) 20 mg/m² bleomycin continuous infusion days 1-10 (n=10), 2) 100 mg/m² paclitaxel (n=5), and 3) 60-80 mg/m² cisplatin (day 1) plus 750 mg/m² 5-FU days 1-4 (n=10) and found response rates of 60%, 40%, and 20%, respectively. In countries where radiation therapy is not available, neoadjuvant chemotherapy could be considered as a potential neoadjuvant option.

Neoadjuvant Chemotherapy and Radiation

The addition of chemotherapy concurrent with RT for treating vulvar carcinoma was heavily influenced by advances in the treatment of squamous cell carcinoma of the anal canal, which showed improved local control and colostomy-free survival with concurrent chemotherapy, specifically 5-FU plus mitomycin C [36-40].

There have been a number of retrospective reports published in the literature that demonstrated the feasibility and potential therapeutic benefit of concurrent chemoradiation in patients with vulvar cancer [41-51]. Despite the fact that these studies included different patient populations, LRAVC and patients with recurrent disease, various chemotherapy regimens, and radiation fractionation schemes, most of them reported high response rates and impressive local control ([Appendix 2](#)). A recent survey from the Gynecologic Cancer Intergroup (GCIG) study on patterns of care for RT and chemotherapy in vulvar cancer confirms that there is a difference in the indications for treatment, treatment fields and use of chemotherapy among various members of the GCIG, even though the doses of radiation were similar among the members [52].

The GOG completed a Phase II trial to determine the feasibility of using preoperative chemoradiotherapy to treat T3 or T4 primary tumors that were unresectable or to avert the need for more radical surgery (GOG 101) [53]. A total of 73 evaluable patients with unresectable T3/T4 primary vulvar tumors with either N0/N1 groin nodes (50 patients) or N2/N3 groin nodes (23 patients) were included in this analysis. The treatment schema consisted of a split course of chemoradiation therapy delivered with anterior-posterior/posterior-anterior (AP/PA) fields to a total dose of 4760 cGy using a split course followed by surgical excision of the residual primary tumor plus bilateral inguinal–femoral lymph node dissection. For patients with clinical N2/N3 groin nodes the radiation field included inguinal–femoral lymph nodes and lower pelvic nodes, in addition to the primary vulvar tumor. During each split course of radiation, 5-FU 1000 mg/m²/day was given as a continuous infusion over the first 4 days, and cisplatin 50 mg/m² was given as a single brief infusion on the first day. During the 4 days of chemotherapy administration, the radiation was administered in two daily fractions of 170 cGy given at least 6 hours apart. For the remainder of each half of the split course, radiation was given as a single daily fraction of 170 cGy, thus bringing the total dose per course to 2380 cGy. Courses were separated by 1-1/2 to 2-1/2 weeks as determined by the severity of the acute vulvoperineal skin reaction.

This concurrent chemoradiation regimen yielded encouraging results, with an overall response rate of 33/71 (46.5%). Only 2/71 patients (2.8%) had residual unresectable disease, and among the 50 patients initially requiring exenterative surgery, only one patient required exenterative surgery and two patients required colostomy to resect residual disease. At a median follow-up of 50 months, 24 women (32.9%) developed recurrent vulvar cancer and 40 patients (54.9%) were alive and without evidence for recurrent disease. Toxicity was acceptable, with acute cutaneous reactions to chemoradiotherapy and surgical wound complications being the most common

adverse effects. This trial demonstrated that preoperative chemoradiotherapy is feasible in patients with LRAVC and may reduce the need for more radical surgery, including pelvic exenteration [53].

GOG 101 also included 46 women with unresectable N2/N3 groin lymph nodes who underwent preoperative chemoradiation. Among patients who completed chemoradiation and were considered for surgery, the nodes became resectable in 38/40 patients (95%). One of these patients underwent radical vulvectomy without groin lymphadenectomy. The lymph node specimens were histologically negative in 15/37 patients (41%). Only one patient experienced a groin failure. Overall, 20 patients were alive and without evidence of recurrent cancer, and five patients expired without evidence of recurrence [54].

In an attempt to further improve complete clinical/pathological response rates — and ultimately improve local control — the GOG conducted a prospective phase II trial (GOG 205), using a combination of weekly cisplatin with daily fractionated RT to a total dose of 57.6 Gy. This dose was a 20% increase over that used in GOG 101, and the previously used planned break was eliminated, since there was evidence that prolongation of overall treatment time may be counterproductive and should be avoided whenever possible [55]. The primary objective of the study was to assess the efficacy and toxicity of the combination in achieving a complete clinical and pathologic response at the primary site. Among 58 evaluable patients, there were 40 (69%) who completed study treatment; 37 patients (64%) achieved a complete clinical response. Of them, 34 underwent biopsy and 29 (78%) had a complete pathological response (50% of the entire series). The authors concluded that this combination of radiation therapy plus weekly cisplatin successfully yielded high, complete clinical and pathologic response rates with acceptable toxicity [56].

Neoadjuvant Chemotherapy and Radiation vs Definitive Chemoradiation

Shylasree et al [57] published a systematic review of the role of definitive chemoradiotherapy in LRAVC. The review included two retrospective studies [48,58] and a one randomized controlled trial [59]. The authors concluded based on the published evidence that there was no significant difference in overall survival or treatment-related adverse events when primary chemoradiation or neoadjuvant chemoradiation were compared with primary surgery. In addition, none of these studies include data on quality of life [57]. (See [Variant 2.](#))

Radiation Therapy Techniques in LRAVC

Target Volume

The target volumes for advanced vulvar cancers include the vulva and generally the bilateral external iliac, internal iliac, and inguinofemoral nodal areas, depending on nodal stage and involvement. Patients are set up supine and often in a frog-leg position to minimize skin folds. With 2D and 3D planning, vulvar cancer treatment has used an AP/PA field setup. Often, a wide AP and narrow PA field are used, with electrons supplementing the dose to the inguinal region (provided that the nodal depth is within electron range) to limit the dose to the femoral heads [43,47]. The use of CT or MRI planning helps ensure adequate dosing of the target volumes, in particular for the inguinal lymph node regions [60]. GOG 205 recommended a superior field border of the sacroiliac joints, an inferior border 2 cm below the primary vulvar tumor, and a lateral border to include groin nodes medial to the anterior superior iliac crest bilaterally [56]. A patterns of care study from 12 cooperative groups of GCIG reported that the majority of groups use a superior pelvic field border of L4/5 and that 16 of 18 groups use CT planning [52].

Intensity Modulated Radiation Therapy

Beriwal et al [61] evaluated using intensity-modulated radiation therapy (IMRT) along with chemotherapy for preoperative treatment of 18 stage II-IVa vulvar cancer patients and found that the technique was well-tolerated, with no patients experiencing grade 3 acute or late toxicity. Fourteen patients underwent surgery, nine patients had a pathologic complete response, and five patients had partial responses. In a small dosimetric study, IMRT was shown to be a feasible way to allow for dose escalation while adequately sparing organs at risk [62]. The Radiation Therapy Oncology Group (RTOG[®]) is creating an IMRT contouring atlas for vulvar cancer.

The next GOG phase II study (GOG 0279) is building on the success of GOG 0205 neoadjuvant chemoradiation therapy approach by improving the radiation technique approach using IMRT, increasing the radiation dose, and adding gemcitabine to cisplatin in achieving complete pathological response in the treatment of LRAVC.

Interstitial Brachytherapy

Some small institutional studies have suggested that interstitial brachytherapy might be useful for delivering a boost to bulky primary vulvar tumors, for treating recurrences, or for palliation [63,64]. The use of interstitial brachytherapy has not been assessed in a randomized controlled study.

Dose

Preoperative radiation dose has ranged from 30 Gy in 10 fractions of 3 Gy, 40 Gy in 20 fractions of 2 Gy, 47.6 Gy in 1.7 Gy fractions and split course to 57.6 Gy in 1.8 Gy fractions in the recent GOG 205 [43,53,54,56,65]. The GCIIG patterns of care study found that neoadjuvant radiation is generally used for unresectable disease or FIGO stage III or above, with most treating the vulva to a dose of 48.2 +/- 5 Gy, and that an average neoadjuvant inguinal dose was 49.9 +/- 5.5 Gy [52]. Increasing dose for neoadjuvant chemoradiotherapy studies has shown improved overall and pathologic complete response rates, and perhaps future studies will help identify subpopulations of patients who can forgo surgery and be treated with concurrent chemotherapy and radiation alone. (See [Variant 3](#) and [Variant 4](#).)

Follow-up

Although no established standard exists, the majority of the panel supports performing a physical examination every 3-6 months for the first 5 years and then annually. Any suspected recurrent or persistent disease should be biopsied. Extrapolating from cervical and anal cancer, PET/CT may be useful for assessing response and monitoring for new distant disease.

Summary

- Locoregionally advanced vulvar cancer (LRAVC) can have a variety of presentations, but generally would have significant morbidity if managed with upfront exenterative surgery.
- Whole-body FDG-PET/CT is a useful imaging modality for initial work-up and for assessing response to chemoradiotherapy.
- Standard treatment for LRAVC includes neoadjuvant chemoradiotherapy with weekly concurrent cisplatin, as in GOG 205.
- Radiation should involve CT planning, with treatment volumes including the vulva and the bilateral inguinal and pelvic lymph nodes, preferably with 3D or IMRT planning as well.
- In assessing response to neoadjuvant chemoradiotherapy, besides imaging, examination under anesthesia with directed biopsies can be helpful for determining if the patient requires surgery.
- Radiation can also be a useful palliative treatment option for patients with painful vulvar cancer and unable to tolerate more aggressive treatment.

Supporting Documents

- [ACR Appropriateness Criteria® Overview](#)
- [Evidence Table](#)

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The ACR Committee on Appropriateness Criteria and its expert panels have developed criteria for determining appropriate imaging examinations for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide radiologists, radiation oncologists and referring physicians in making decisions regarding radiologic imaging and treatment. Generally, the complexity and severity of a patient's clinical condition should dictate the selection of appropriate imaging procedures or treatments. Only those examinations generally used for evaluation of the patient's condition are ranked. Other imaging studies necessary to evaluate other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate imaging procedures or treatments. Imaging techniques classified as investigational by the FDA have not been considered in developing these criteria; however, study of new equipment and applications should be encouraged. The ultimate decision regarding the appropriateness of any specific radiologic examination or treatment must be made by the referring physician and radiologist in light of all the circumstances presented in an individual examination.

Appendix 1. Neoadjuvant Chemotherapy in LRAVC

Author	Number of Patients	Chemotherapy Regimen	Number of cycles	Response	Years of Study
Shimizu 1990 [30]	1 (case study)	Bleomycin, vincristine, mitomycin C, cisplatin	3, surgery, then 2 additional chemo	cCR, pPR Underwent surgery	1990 case study
Durrant 1990 [31]	28 evaluable (18 primary, 10 recurrent)	Bleomycin 5 mg days 1-5, methotrexate 15 mg po days 1 and 4, CCNU 40 mg po days 5-7 Weeks 2-6: Bleomycin 5 mg IM and M 15 mg pg given Days 1 and 4 (6 week cycle of chemo)	3	18/28 (64%) response 3/28 CR 15/28 PR 12/18 RR for primary tumor, 6/10 RR recurrences 8 found to have resectable disease 7 had surgery	1/1983-8/1986 prospective
Wagenaar 2001 [32]	25 (12 locally advanced, 13 locoregional recurrence)	Bleomycin (B) 5mg IM day 1-5, methotrexate(M) 15mg po days 1 and 4, CCNU 40 mg po day 5-7. During weeks 2-6 B mg intramuscular days 1 and 4, M 15mg po on day 1 of week (6 week cycle repeated every 49 days)	3	Overall RR 56%, advanced 7/12 (58%), recurrent 7/13 (54%)	9/1987-12/1993 prospective
Benedetti-Panici 1993 [33]	21	Cisplatin 100mg/m ² (day 1), bleomycin 15mg (day 1, 8), methotrexate 300 mg/m ² (day 8)	2-3	90% operability (79% radical surgery), 33% pathological downstaging	1/1988-12/1989
Geisler 2006 [34]	10 Cisplatin/5-FU (3 patients received cisplatin only)	Cisplatin 50 mg/m ² IV over 1mg/min (day 1), 5-FU 1000 mg/m ² over 24 hours (Day 1-5)	2-4	9/10 cisplatin/5-FU underwent surgery Cisplatin alone no measurable response Cisplatin -5-FU – 9/10 CPR, 1/10 CCR; 4/13 PCR Anal and urethra spared in all cisplatin/5-FU	1997-2003
Domingues 2010 [35]	25 patients A) 10 patients, bleomicine B) 5 patients, paclitaxel C) 10 patients 5-FU/cisplatin	A. Days 1-10, bleomicine 20 mg /m ² continuous infusion B. Day 1 paclitaxel 100 mg/m ² , hydroxyzine 50 mg, ranitidine 50mg; dex 20 mg weekly C. Day 1: cisplatin 60-80 mg/m ² Days 1-4: 5-FU 750 mg/m ² , 3/3 weeks		A 60% RR B 40% RR C 20% RR	1996-2000 retrospective

cCR = complete clinical response; pCR = partial clinical response; pPR = pathological partial response; CR = complete response; PR = partial response; RR = relative risk; 5-FU = 5-fluorouracil; IV = intravenous; po = per os

Appendix 2. Neoadjuvant Radiation plus Chemotherapy in LRAVC

Authors	Vulvar patients (n)	Chemotherapy	Total radiation dose (Gy)	Response to chemoradiation
Wahlen 1995. [51]	19	5-FU, MitC	45-50	cCR =53%, cPR=37%
Landoni 1996 [47]	58	5-FU, MitC	54	pCR=31%
Koh 1993 [46]	20	5-FU + Cis (n=5) or +MitC (n=1)	40-54	cCR=50%, cPR=40%
Berek 1991 [41]	12	Cis + 5-FU	44-54	cCR=67%, OR=91.7%
Russell 1992 [49]	25	5-FU + Cis (n=11)	34-72	cCR = 80%, pCR=40%
Eifel 1995 [43]	12	5-FU + Cis	40-50	OR=91%, pCR=33%
Cunningham 1997 [42]	14	5-FU+Cis	45-65	cCR=64%, OR=92%
Gerszten 2005 [45]	18	Cis + 5-FU	44.6	cCR=72.2%, OR=100%
Moore 1998 [53]	71	Cis+5-FU	47.6	cCR=46.5%
Levin 1986 [66]	6	5-FU+MitC	20-25	OR =100%
Thomas 1989 [50]	24	5-FU+/-MitC	36-64	cCR=58.3%
Sebag-Montefiore 1994 [67]	32	5-FU+MitC	45-50	cCR=46.8%, OR=81.2%
Lupi 1996 [68]	31	5-FU+MitC	54	OR=93.5%
5-FU = 5-fluorouracil; MitC = mitomycin-C; Cis = cisplatin; cCR = complete clinical response; pCR = partial clinical response; OR = odds ratio				

Clinical Condition: Management of Locoregionally Advanced Squamous Cell Carcinoma of the Vulva

Variant 1: 63-year-old woman with a biopsy proven squamous cell carcinoma of the vulva involving the anterior vaginal wall to proximal 1/3 of the urethra with suspected bladder involvement and fixed right inguinal lymph nodes but no palpable lymph nodes on the left.

Treatment	Rating	Comments
Pretreatment Evaluation		
X-ray chest	5	
CT abdomen and pelvis	7	
US and biopsy right inguinal node	7	
CT chest	7	
MRI abdomen and pelvis	8	
FDG-PET/CT whole body	9	
Sentinel lymph node biopsy	3	
Cystoscopy	5	
Neoadjuvant Chemotherapy		
Cisplatin and 5-FU	3	
Bleomycin and methotrexate and CCNU	2	
Radiation Only (Definitive)		
30 Gy in 3 Gy fractions	3	
45-50.4 Gy in 1.8 Gy fractions + 14-24 Gy EBRT boost	7	
45-50.4 Gy in 1.8 Gy fractions + 14-24 Gy interstitial brachytherapy boost	6	
Neoadjuvant Chemoradiotherapy (to be followed by surgery)		
Concurrent weekly cisplatin	8	
Concurrent 5-FU and mitomycin C	6	
Concurrent 5-FU and cisplatin	7	
Neoadjuvant Chemoradiotherapy (radiation dose to the gross tumor volume [GTV])		
30 Gy in 3 Gy fractions	3	
47.6 Gy in 1.7 Gy fractions	6	
57.6 Gy in 1.8 Gy fractions	7	
60-70 Gy in 1.8 Gy fractions	3	
Radiation Fields (assuming pelvic nodes negative on imaging)		
Vulva only	1	
Vulva and right inguinal lymph nodes	1	
Vulva and bilateral inguinal lymph nodes	2	
Vulva, bilateral inguinal lymph nodes and low pelvic lymph nodes	9	

Radiation Superior Field Border (assuming pelvic nodes negative on imaging)		
L4/L5 (or bifurcation of the aorta)	6	
L5/S1(or bifurcation of the common iliacs)	8	
Below the bifurcation of the common iliacs into external and internal iliacs	3	
Treatment Technique		
2D RT	5	If 3D not available.
3D conformal RT	8	
CT planning	8	
IMRT	8	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: Management of Locoregionally Advanced Squamous Cell Carcinoma of the Vulva

Variant 2: 68-year-old woman with a 6 cm squamous cell vulvar cancer involving the clitoris and lower urethra and biopsy positive lymph nodes on the left side who is treated neoadjuvantly with non-split course radiation and concurrent cisplatin and 5-FU. After approximately 40 Gy, the lymph node metastases have shown a complete clinical response, while the vulvar primary shows little clinical response and possibly progression.

Treatment	Rating	Comments
Assess response with imaging	5	
Change concurrent chemotherapy regimen	3	
Continue radiation to planned 57.6 Gy	8	
Stop external radiation after 45-50 Gy and use interstitial brachytherapy boost to vulvar primary	3	
Increase planned radiation dose to 65 Gy	7	
Continue radiation and add adjuvant chemotherapy prior to surgery	3	
Stop radiation and go immediately to exenterative surgery	3	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: Management of Locoregionally Advanced Squamous Cell Carcinoma of the Vulva

Variant 3: 73-year-old woman who had a 4.5 cm squamous cell vulvar cancer involving the lower vagina and bilateral inguinal lymph nodes who was treated with neoadjuvant chemoradiation with 57.6 Gy and concurrent weekly cisplatin, as in GOG 205, who demonstrates a clinical complete response in the region of the primary and lymph nodes.

Treatment	Rating	Comments
Assessment of Response		
Clinical only	2	
MRI	6	
PET	7	
Examination under anesthesia/Biopsy of primary region	7	
Biopsy of primary and sentinel lymph node biopsy	3	
Biopsy of primary region and bilateral inguinal lymph node dissection	4	
Local excision and sentinel lymph node biopsy	3	
Local excision and bilateral inguinal lymph node dissection	3	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Variant 4: 81-year-old woman with a history of type 2 diabetes, coronary artery disease, a myocardial infarction 8 months ago, and a current KPS of 70 presents with a painful, 6 cm squamous cell vulvar cancer involving the rectovaginal septum. Clinical examination and imaging suggests no evidence of lymph node or metastatic disease. Patient currently has normal bowel movements and continence.

Treatment	Rating	Comments
Palliative radiation to vulvar tumor only with external beam radiation	7	
Palliative radiation with interstitial brachytherapy	3	
Radiation to vulva, groins, and pelvis	7	
Chemotherapy only with cisplatin and 5-FU	3	
Concurrent cisplatin and 5-FU and radiation to 57.6 Gy	5	
Definitive surgery with exenteration	1	
Supportive care only with wound care and pain management	3	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		