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# A phase II trial of radiation therapy and weekly cisplatin chemotherapy for the treatment of locally-advanced squamous cell carcinoma of the vulva: A gynecologic oncology group study

David H. Moore [a,*], Shamshad Ali [b], Wui-Jin Koh [c], Helen Michael [d], Mack N. Barnes [e], Carolyn K. McCourt [f], Howard D. Homesley [g], Joan L. Walker [h]

[a] Gynecologic Oncology of Indiana, Indianapolis, IN, USA
[b] GOG Statistical & Data Center, Buffalo, NY, USA
[c] Fred Hutchinson Cancer Research Center, Seattle, WA, USA
[d] Indiana University School of Medicine, Indianapolis, IN, USA
[e] University of Alabama School of Medicine, Birmingham, AL, USA
[f] Women & Infants Hospital, Providence, RI, USA
[g] Wake Forest University School of Medicine, Winston-Salem, NC, USA
[h] University of Oklahoma, Oklahoma City, OK, USA

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ABSTRACT

*Objectives.* To determine the efficacy and toxicity of radiation therapy and concurrent weekly cisplatin chemotherapy in achieving a complete clinical and pathologic response when used for the primary treatment of locally-advanced vulvar carcinoma.

*Methods.* Patients with locally-advanced (T3 or T4 tumors not amenable to surgical resection via radical vulvectomy), previously untreated squamous cell carcinoma of the vulva were treated with radiation (1.8 Gy daily × 32 fractions = 57.6 Gy) plus weekly cisplatin (40 mg/m$^2$) followed by surgical resection of residual tumor (or biopsy to confirm complete clinical response). Management of the groin lymph nodes was standardized and was not a statistical endpoint. Primary endpoints were complete clinical and pathologic response rates of the primary vulvar tumor.

*Results.* A planned interim analysis indicated sufficient activity to reopen the study to a second stage of accrual. Among 58 evaluable patients, there were 40 (69%) who completed study treatment. Reasons for prematurely discontinuing treatment included: patient refusal ($N=4$), toxicity ($N=9$), death ($N=2$), other ($N=3$). There were 37 patients with a complete clinical response (37/58; 64%). Among these women there were 34 who underwent surgical biopsy and 29 (78%) who also had a complete pathological response. Common adverse effects included leukopenia, pain, radiation dermatitis, pain, or metabolic changes.

*Conclusions.* This combination of radiation therapy plus weekly cisplatin successfully yielded high complete clinical and pathologic response rates with acceptable toxicity.



## Objectives

The management of patients with locally advanced vulvar cancer presents a difficult therapeutic challenge. Historically, when the disease involves the anus, rectum, rectovaginal septum, proximal urethra, or bladder, primary exenterative surgery necessitating colostomy and/or urinary diversion has been required. Boronow [1] and Hacker [2] independently explored the efficacy of a radiation-surgical approach for advanced vulvar cancer as an alternative to pelvic exenteration. In Boronow's series, 37 women with extensive primary tumors received preoperative brachytherapy with or without external beam radiation therapy followed by radical vulvectomy. No residual tumor was present in 42% of surgical specimens and 59% of patients were alive and without recurrent cancer at the time of his report. In Hacker's series of 8 patients, there was no residual disease in the surgical specimen in 4 (50%) cases, 7 of 8 patient avoided exenterative surgery, and 5 (62%) patients were without evidence of recurrent cancer at last follow-up.

Based on these impressive results, the Gynecologic Oncology Group (GOG) studied cisplatin plus 5-fluorouracil chemoradiation therapy for the preoperative treatment of patients with locally-advanced squamous cell carcinoma of the vulva not amenable to surgical resection by standard radical vulvectomy (GOG protocol 101) to prospectively evaluate the efficacy of chemoradiation in reducing the scope of necessary surgery [3]. After chemoradiation, 48% of evaluable patients had no evident

* Corresponding author at: Gynecologic Oncology of Indiana, 5255 East Stop 11 Road, Suite 310, Indianapolis, IN 46237, USA. Fax: +1 317 851 2566.
*E-mail address:* David.Moore@ssfhs.org (D.H. Moore).

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vulva tumor and 31% had no residual tumor in the pathologic specimen. Only 3% of patients had residual unresectable disease. With a median follow-up of 50 months, one patient required pelvic exenteration, two patients required colostomy to resect persistent disease, and five patients underwent pelvic exenteration to resect recurrent cancer. The vulva was the initial site of recurrence in eight patients, and three additional patients had a vulvar recurrence along with recurrent cancer in the groin ($N=2$) or pelvis ($N=1$) [3].

Neither the optimal radiation dose-fractionation scheme, nor the optimal combination of chemoradiation therapy (total dose) and surgical excision has been determined. In GOG protocol 101, the total radiation dose was purposefully less than what is used when radiation is the sole planned treatment, and a split course regimen was adopted to diminish the potential for severe acute toxicity. Others have achieved excellent response and local control rates with higher doses of chemoradiation alone [4,5]. Furthermore, there is emerging evidence that prolongation of overall treatment time may be counterproductive and should be avoided whenever possible [6].

The present protocol specified cisplatin 40 mg/m$^2$ (to maximum dose 70 mg) weekly concurrent to radiation therapy (adopting the standard for squamous cell carcinoma of the cervix), eliminated a planned treatment break, and delivered a higher total dose of radiation (20% escalation in dose over GOG protocol 101) to the primary tumor in hopes of achieving higher complete clinical and pathologic response rates, and improved local control rates, with acceptable treatment-related toxicity.

## Methods

The study was limited to patients with locally-advanced, previously untreated squamous cell carcinoma of the vulva with T3 or T4 primary tumors (N0-3, M0) [7] not amenable to surgical resection by standard radical vulvectomy. Patients had GOG Performance Status of 0–3, adequate bone marrow function, renal and hepatic function, and were judged capable of tolerating a radical course of chemoradiation therapy. Patients with vulvar melanomas or sarcomas, septicemia or severe infection, gastrointestinal bleeding or severe gastrointestinal symptoms, or who had received prior pelvic radiation or cytotoxic chemotherapy were ineligible. Women with other invasive malignancies, with the exception of non-melanoma skin cancer, who had any evidence of the other cancer present within the previous 5 years were also ineligible. All study participants signed an IRB-approved informed consent statement and authorization permitting release of personal health information.

### *Radiation therapy*

Patients received radiation therapy to the vulva, inguinal-femoral, and lower pelvic lymph nodes by AP–PA fields: superior border–inferior sacroiliac joint; inferior border—2 cm below the most inferior portion of the primary vulva tumor (unless the primary tumor could be entirely encompassed with an *en-face* technique; lateral border—to include groin nodes medial to vertical planes through the anterior superior iliac crest bilaterally. Women with clinically negative or resectable groin nodes underwent pretreatment inguinal-femoral lymph node dissection. Patients who had negative groin lymph nodes were allowed to receive radiation therapy to only the primary tumor (with or without groin radiation) at the discretion of the treating physician. For highly selected patients with relatively small primary tumors that were considered T3/T4 by virtue of involvement of midline structures, a separate *en face* electron or low energy photon perineal port could be used to address the primary lesion, while the groin/pelvic lymph nodes were still treated with AP-PA fields. Intensity modulated radiation therapy (IMRT) was not allowed.

Treatment consisted of 1.8 Gy/daily fraction × 5 days, repeated weekly to a total dose of 57.6 Gy in 32 fractions to gross disease. At 45 Gy, radiation fields were reduced from initial wide coverage, to encompass only the primary vulvar tumor site and any other sites of gross residual disease with 2 cm margins. Every attempt was made to avoid radiation treatment interruptions. There was no scheduled radiation break. Treatment breaks if needed for confluent moist desquamation (cutaneous ulceration) or severe acute gastrointestinal or genitourinary toxicity were kept to an absolute minimum. Radiation was withheld for a granulocyte count $<1000/\mu L$ or a platelet count $<40{,}000/\mu L$. Patients received transfusions as needed to keep weekly hemoglobin levels $>10$ g/L.

### *Chemotherapy*

Patients received concurrent cisplatin (40 mg/m$^2$ to maximum dose 70 mg) chemotherapy administered weekly throughout radiation therapy with antiemetic premedication and vigorous hydration. Patients could receive up to a maximum of 7 weekly cycles of cisplatin. The use of amifostine was allowed but not required. If used, amifostine was administered 200 mg/m$^2$ IV bolus 30 minutes prior to each radiation dose with appropriate hydration and antiemetic premedication. No chemotherapy cycle was to begin until the granulocyte count was $\geq 1500$/mcL and the platelet count was $\geq 100{,}000$/mcL. The protocol also specified chemotherapy dose modifications for experienced gastrointestinal (nausea and vomiting; diarrhea), renal, and other toxicities.

### *Surgery*

Six to eight weeks following the completion of chemoradiation, patients underwent surgical excision of gross residual disease in the vulva and/or inguinal-femoral lymph nodes (if the groin nodes were considered unresectable prior to chemoradiation). If there was a complete clinical response, women were required to undergo at least an incisional biopsy of the primary tumor site. If the primary vulvar tumor involved the anal canal, rectovaginal septum or proximal urethra (where incisional biopsy of the original tumor site might compromise bowel or bladder function), fine needle aspiration was allowed. If the incisional biopsy was positive for residual microscopic disease, or if there was gross residual tumor following primary chemoradiation, radical surgical resection of the primary tumor site was performed.

Tumor specimens were submitted for GOG Pathology Committee review. Required specimens for quality control included: 1) stained slide to demonstrate positive initial biopsy; 2) stained slide to demonstrate any positive lymph node biopsy; 3) stained slide of post chemoradiation biopsy; and 4) stained slides of the post-irradiation lymph nodes and vulvectomy to demonstrate the deepest tumor penetration.

### *Statistical considerations*

This was a phase II study enrolling a single cohort of patients with vulvar cancer to evaluate chemoradiation. The intent-to-treat principle was not strictly adhered to in that patients who refused all radiation therapy without any medical contraindication were considered inevaluable for response. The hypothesis was based on the primary endpoint: complete pathologic response (pCR). The null hypothesis provided the range of CR probability (pCR) associated with an insufficiently active regimen and the alternative hypothesis provided the probability range associated with an active regimen: Ho: pCR $\leq 0.30$ versus Ha: pCR $\geq 0.45$. During the first stage of accrual, with a sample size of 25 patients, protocol treatment would be considered inactive if there were 7 or fewer complete pathologic responses. If there were 8 or more complete pathologic responses the study would re-open to a second stage of accrual and an additional 33 patients would be entered. Protocol treatment would be considered inactive if there

were 22 or fewer complete pathologic responses among the total study population of 58 patients). These decision rules have the following operating characteristics: Pr (Reject Ho|Ho) = 0.07 and Pr (Reject Ho|Ha) = 0.81 [8].

It was estimated that the first stage of accrual would take 1 2/3 years and the second stage of accrual, if necessary, would take 2 1/4 years.

## Results

The study was opened to initial patient accrual 1/19/05. After the planned interim analysis indicated sufficient activity, the study was reopened to a second stage of accrual 7/16/07 and closed 9/21/09. There were 61 women entered into the study and three were later deemed ineligible: improper pre-protocol therapy ($N=1$); inadequate pathology ($N=2$). Characteristics of the 58 patients evaluable for response and toxicity are listed in Table 1. All study participants had previously untreated squamous cell carcinoma of the vulva. The primary tumor size (mean, range) was $6.15 \pm 3.9$ cm.

All patients completed at least two cycles of weekly cisplatin chemotherapy concurrent with radiation therapy. Completion of planned treatment was defined as having received > 97% of specified radiation dose (at least 55.8 Gy or 1.8 Gy/fraction × 31 fractions) plus at least five cycles of chemotherapy. There were 40 (69%) women who completed the planned study treatment plus 6 (10%) women who completed planned radiation therapy but fewer than five cycles of chemotherapy. The distribution of chemotherapy cycles administered was: 2–3 cycles (5 patients); 4 cycles (4 patients); ≥5 cycles (49 patients). Reasons for prematurely discontinuing treatment included: patient refusal ($N=4$), treatment-related toxicity ($N=9$), death ($N=2$), other ($N=3$). In general, the specified protocol therapy was tolerable with the more common toxicities being hematologic, radiation dermatitis, pain, and metabolic (Table 2).

At the conclusion of chemoradiation there were 37 patients with a complete clinical response (37/58; 64%) at the vulvar primary. Among these women there were 29 who underwent surgical biopsy and had a complete pathological response. There were five patients with complete clinical responses who proved to have persistent vulva disease and underwent post-treatment surgical resection. Three patients had pathology specimens inadequate to determine response. The complete pathological response rate at the vulvar primary among all evaluable patients, and among patients experiencing a complete clinical response, was 50% (29/58) and 78% (29/37), respectively.

There were 34 women who underwent pre-treatment groin lymph node dissection. Of these patients there were 19 (56%) who had positive lymph nodes, 12 (35%) who had negative lymph nodes, and 3 (9%) with uncertain groin pathology. Pathologic complete response rates at the primary vulvar tumor were 8/19 (42%), 9/12 (75%), and 2/3 (66%), respectively. There were 12 women who underwent groin lymph node dissection after receiving chemo-radiation therapy. Of these patients there were 7 (58%) who had positive lymph nodes, 3 (25%) who had negative lymph nodes, and 2 (17%) with uncertain groin pathology. Pathologic complete response rates at the primary vulvar tumor were 4/7 (57%), 1/3 (33%), and 0/2

**Table 1**
Patient characteristics.

| Characteristics | No. patients |
|---|---|
| Age (years) | |
| < 40 | 4 |
| 40–49 | 9 |
| 50–59 | 18 |
| 60–69 | 13 |
| ≥ 70 | 14 |
| Ethnicity | |
| Hispanic | 1 |
| Non-Hispanic | 45 |
| Not specified | 12 |
| Race | |
| Black | 2 |
| Native American | 2 |
| White | 54 |
| Performance status | |
| 0 | 36 |
| 1 | 18 |
| 2 | 3 |
| 3 | 1 |
| FIGO stage | |
| III | 39 |
| IVA | 19 |
| Vulva tumor size (cm) | |
| ≤ 2.0 | 7 |
| 2.1–4.0 | 12 |
| 4.1–6.0 | 19 |
| 6.1–8.0 | 6 |
| 8.1–10.0 | 6 |
| > 10.0 | 8 |
| Tumor grade[a] | |
| 1 | 12 |
| 2 | 35 |
| 3 | 9 |
| Not graded | 2 |
| Clinical groin node status | |
| N0 | 26 |
| N1 | 13 |
| N2 | 19 |

[a] Central pathology review pending for 1 patient.

**Table 2**
Adverse events.

| Adverse event[a] | Grade | | | | |
|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 |
| Leukopenia | 16 | 11 | 13 | 18 | 0 |
| Anemia[b] | 7 | 22 | 25 | 3 | 1 |
| Thrombocytopenia | 28 | 22 | 5 | 3 | 0 |
| Neutropenia | 30 | 7 | 10 | 8 | 3 |
| Other hematologic | 45 | 0 | 0 | 12 | 1 |
| Allergy/immunology | 54 | 1 | 3 | 0 | 0 |
| Auditory/hearing | 55 | 0 | 3 | 0 | 0 |
| Cardiovascular | 48 | 3 | 3 | 3 | 1 |
| Fatigue | 13 | 20 | 20 | 5 | 0 |
| Other constitutional symptoms | 45 | 7 | 6 | 0 | 0 |
| Alopecia | 45 | 8 | 3 | 2 | 0 |
| Radiation dermatitis | 47 | 1 | 4 | 6 | 0 |
| Rash desquamation | 29 | 7 | 12 | 8 | 2 |
| Other dermatologic/skin | 46 | 6 | 4 | 2 | 0 |
| Endocrine | 50 | 7 | 1 | 0 | 0 |
| Nausea | 15 | 25 | 17 | 1 | 0 |
| Vomiting | 30 | 19 | 8 | 1 | 0 |
| Diarrhea | 20 | 22 | 10 | 6 | 0 |
| Other gastrointestinal | 24 | 14 | 11 | 9 | 0 |
| Creatinine | 47 | 7 | 4 | 0 | 0 |
| Other renal/genitourinary | 37 | 10 | 8 | 3 | 0 |
| Hemorrhage | 54 | 3 | 0 | 1 | 0 |
| Hepatic | 52 | 4 | 2 | 0 | 0 |
| Infection | 44 | 1 | 5 | 7 | 1 |
| Lymphatics | 56 | 2 | 0 | 0 | 0 |
| Metabolic/laboratory | 33 | 12 | 3 | 6 | 4 |
| Musculoskeletal | 54 | 2 | 2 | 0 | 0 |
| Neuropathy, motor | 56 | 0 | 2 | 0 | 0 |
| Neuropathy, sensory | 48 | 7 | 3 | 0 | 0 |
| Other neurologic | 45 | 7 | 4 | 1 | 1 |
| Ocular/visual | 57 | 1 | 0 | 0 | 0 |
| Pain | 23 | 10 | 15 | 10 | 0 |
| Pulmonary | 53 | 0 | 4 | 1 | 0 |
| Sexual/reproductive | 52 | 4 | 1 | 1 | 0 |

[a] Adverse events were graded according to the worst toxicity experienced for each patient using CTCAE version 2. There was one treatment-related death, per Scientific Review Committee (patient expired during treatment).

[b] There were four patients who experienced grade 3–4 anemia and one of these patients received a blood transfusion.

(0%), respectively. There were 12 women who did not undergo groin lymph node dissection. Of these patients there were 5 (42%) who had a complete pathologic response for the vulva primary tumor.

With median follow-up time of 24.8 months, there are 35 women who are alive (4 with evidence of recurrent/persistent vulva cancer) and 23 who have died as a result of: cancer ($N=18$); treatment-related complications ($N=1$), other causes ($N=3$), undetermined ($N=1$) (Fig. 1). At the time of data analysis, there were 29 patients with complete pathological responses. Of these 29 patients there were 22 without evidence of recurrent vulvar carcinoma and seven (2 vulva, 2 loco-regional, 1 regional, 2 distant) with documented treatment failure. There were eight patients with complete clinical responses but documented persistent microscopic disease at the primary tumor site). Of these eight patients there were five who underwent surgery to resect persistent disease; three are alive with no evidence of recurrent vulvar carcinoma and two have died (one from cancer, one from neither cancer or treatment-related complications). Of these eight patients there were three who did not have surgery; two are alive and one patient has died (from neither cancer nor treatment related complications). Among 21 patients with persistent disease at the primary tumor site, eight underwent surgery to resect persistent disease. Of these eight patients, three are alive and without evidence of recurrent vulvar carcinoma, two have recurred (one vulva, one loco-regional) and three have died (two from cancer, one neither from cancer or treatment-related complications). Of the 13 patients who did not undergo surgery to resect persistent disease, four are alive (1 with loco-regional failure) and 9 have died (seven from cancer, one from treatment-related complications, one from other causes).

## Discussion

The current phase II study (GOG protocol 205) specified cisplatin 40 mg/m$^2$/week concurrent to radiation therapy. It also eliminated a planned treatment break and twice-daily radiation, and delivered a 20% higher dose of radiation (57.6 Gy) to the primary tumor than what was specified in GOG protocol 101 in hopes of achieving higher complete clinical and pathologic response rates, and improved local control rates, with acceptable treatment-related toxicity. In this regard, the results are superior to that of GOG 101, and promising (Table 3). The study was conducted in a multi-center, multi-disciplinary setting and quality of control reviews by Pathology and Radiation Oncology committees were performed to ensure adherence to protocol requirements. Strengths of the study also include: 1) rates of accrual approaching initial projections; 2) determination of cancer resectability by experienced gynecologic oncology surgeons; 3) the low frequency of inevaluable patients (< 5%); and 4) the fact that no patients were lost to follow-up.

**Table 3**
GOG studies of preoperative chemo-radiation: locally-advanced vulva carcinoma.

| | GOG 101 | GOG 205 |
|---|---|---|
| Evaluable | 71 | 58 |
| CCR | 34 (48%) | 37 (64%) |
| PCR | 22 (31%) | 29 (50%) |
| PCR/CCR | 22/34 (65%) | 29/37 (78%) |

CCR = Clinical Complete Response.
PCR = Pathological Complete Response.

There are several potential shortcomings to this protocol and results interpretation. Multiple differences exist between the protocol therapies administered to patients participating in GOG 101 and in GOG 205; therefore, it is difficult to determine which change(s) contributed to the higher clinical and pathological response rates in the current study. Parallels between the higher absolute pathological complete response rate achieved (19%), and the increase in tumor dose delivered (20%) in the current study are perhaps not coincidental. Neither of these phase II studies focused on survival as a primary endpoint. Although it is tempting to state that long-term survival is irrelevant if the primary vulva tumor cannot be controlled, it is also true that local control is largely a palliative care issue for the patient who presents with unresectable groin lymph nodes or distant metastasis. A highly-effective treatment for these patients remains elusive. Neither of these phase II studies focused on patient-reported quality of life. Future studies should address quality of life in a manner that might determine what combination of chemotherapy, radiation dose, and surgical procedure not only effectively controls the primary

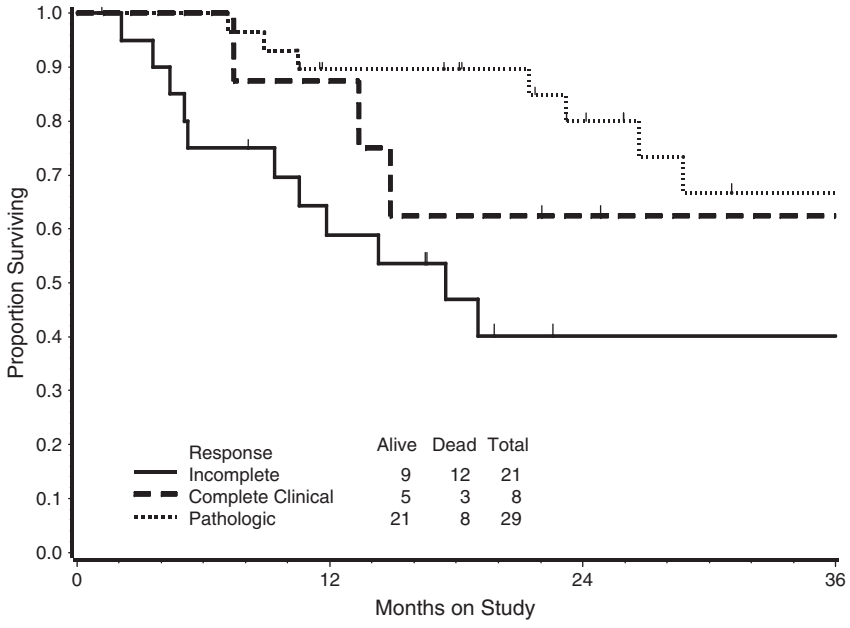


**Fig. 1.** Overall survival according to best response for the primary vulvar tumor to preoperative chemo-radiation therapy.

vulvar tumor but also leads to the best functional and cosmetic result to the patient.

It is important to maintain some caution in exercising chemoradiation strategies for women with locally-advanced vulva cancer. These patients are frequently elderly with significant coexisting medical problems. In addition to intestinal or urologic complications, radiation therapy can cause pelvic bone osteonecrosis or hip fracture. Conditions resulting in impaired microvasculature, such as diabetes mellitus, smoking, and atherosclerotic disease are associated with increased frequency and severity of complications after radiation treatment [9,10]. Even among carefully selected patients with a good baseline performance status, who were considered able to complete planned chemoradiation and surgery, there have been treatment-related deaths [3,11].

On the basis of GOG and many other phase II studies, but no randomized controlled trials in the disease, chemoradiation therapy is now inherent to the clinical management of locally-advanced vulvar cancer. In this context, the conclusions of van Doorn et al. are relevant: 1) Patients with an inoperable primary tumor or lymph nodes benefit from chemoradiation if an operation of lesser scope can ultimately be performed; 2) Preoperative chemoradiation is not justified in patients with tumors that can be adequately treated with radical vulvectomy and bilateral groin node dissection [12].

In order to encompass the target volume, conventional radiation therapy may treat a large amount of normal tissue, with resulting toxicity and limitations on tumor dose. Intensity-modulated radiation therapy (IMRT) may have potential benefits by reducing the dose to normal tissue while delivering a higher dose to the tumor [13]. Preliminary results of IMRT in combination with chemotherapy show promise for the treatment of vulvar carcinoma, apparently with a low incidence of severe toxicity [14,15].

A dose–response curve for squamous cell carcinoma of the vulva to radiation therapy is confirmed by the current study, but where 57.6 Gy sits on the curve is unknown. Future studies should assess response and local control rates to higher radiation doses than what was specified in this protocol. Furthermore, future trials of sequential chemo-radiation and surgery for the treatment of locally-advanced carcinoma of the vulva should include patient-reported quality of life as an outcomes measure to better define what combination of radiation (dose) and surgery (extent) leads to optimal local control and functional results.

The search for the ideal “radiation sensitizer” continues for many disease sites. The rarity of vulvar cancer precludes prospective randomized clinical trials in the absence of international collaboration. Whether such trials will ever be conducted is doubtful. Consideration could be given to combining patients with squamous cell carcinomas of the vulva, vagina, and cervix into common trials provided study endpoints are not compromised. At the very least, patients with locally-advanced vulvar cancer have already derived considerable benefit based on strategies from chemoradiation studies in primary squamous cancers of the cervix and other disease sites.

**Conflict of interest statement**

The authors wish to report that there are no conflicts of interest with the exception of Dr. Walker who reports a financial relationship with Abbott Laboratories.

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## References

[1] Boronow RC, Hickman BT, Reagan MT, Smith RA, Steadham RE. Combined therapy as an alternative to exenteration for locally advanced vulvovaginal cancer. II. Results, complications, and dosimetric and surgical considerations. Am J Clin Oncol 1987;10:171–81.
[2] Hacker NF, Berek JS, Juillard JF, Lagasse LD. Preoperative radiation therapy for locally advanced vulvar cancer. Cancer 1984;54:2056–61.
[3] Moore DH, Thomas GM, Montana GS, Saxer A, Gallup DG, Olt G. Preoperative chemoradiation for advanced vulvar cancer: a Phase II study of the Gynecologic Oncology Group. Int J Radiat Oncol Biol Phys 1998;42:79–85.
[4] Wahlen SA, Slater JD, Wagner RJ, et al. Concurrent radiation therapy and chemotherapy in the treatment of primary squamous cell carcinoma of the vulva. Cancer 1995;75:2289–94.
[5] Russell AH, Mesic JB, Scudder SA, et al. Synchronous radiation and cytotoxic chemotherapy for locally advanced or recurrent squamous cell cancer of the vulva. Gynecol Oncol 1992;47:14–20.
[6] Parsons JT, Bova FJ, Million RR. The reevaluation of split-course technique for squamous cell carcinoma of the head and neck. Int J Radiat Oncol Biol Phys 1980;6:1645–52.
[7] Vulva. American Joint Committee on Cancer. AJCC Cancer Staging Manual. 6th ed. New York: Springer; 2002. p. 243–9.
[8] J.R. Schultz, F.R. Nichol, G.L. Elfring, S.D. Weed. Multiple-Stage Procedures for Drug Screening. Biometrics 6/73:29, 293–300.
[9] Micha JP, Goldstein BH, Rettenmaier MA, Caillouette JT, Fee MJ, Brown JV. Pelvic radiation necrosis and osteomyelitis following chemoradiation for advanced stage vulvar and cervical carcinoma. Gynecol Oncol 2006;101:349–52.
[10] Hoffman KE, Horowitz NS, Russell AH. Healing of vulvo-vaginal radionecrosis following revascularization. Gynecol Oncol 2007;106:262–4.
[11] Montana GS, Thomas GM, Moore DH, Saxer A, Mangan CE, Lentz SS, et al. Preoperative chemo-radiation for carcinoma of the vulva with N2/N3 nodes: a Gynecologic Oncology Group study. Int J Radiat Oncol Biol Phys 2000;48:1007–13.
[12] Van Doorn HC, Ansink A, Verhaar-Langereis M, Stalpers L. Neoadjuvant chemoradiation for advanced primary vulvar cancer. Cochrane Database Syst Rev 2006;3:CD003752.
[13] Jhingran A. Potential advantages of intensity-modulated radiation therapy in gynecologic malignancies. Semin Radiat Oncol 2006;16:144–51.
[14] Beriwal S, Heron DE, Kim H, et al. Intensity-modulated radiotherapy for the treatment of vulvar carcinoma: a comparative dosimetric study with early clinical outcome. Int J Radiat Oncol Biol Phys 2006;64:1395–400.
[15] Beriwal S, Coon D, Heron DE, et al. Preoperative intensity-modulated radiotherapy and chemotherapy for locally advanced vulvar carcinoma. Gynecol Oncol 2008;109:291–5.