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● *Clinical Investigation*

PREOPERATIVE CHEMORADIATION FOR ADVANCED VULVAR CANCER: A PHASE II STUDY OF THE GYNECOLOGIC ONCOLOGY GROUP

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Purpose: To determine the feasibility of using preoperative chemoradiotherapy to avert the need for more radical surgery for patients with T_3 primary tumors, or the need for pelvic exenteration for patients with T_4 primary tumors, not amenable to resection by standard radical vulvectomy.

Methods and Materials: Seventy-three evaluable patients with clinical Stage III–IV squamous cell vulvar carcinoma were enrolled in this prospective, multi-institutional trial. Treatment consisted of a planned split course of concurrent cisplatin/5-fluorouracil and radiation therapy followed by surgical excision of the residual primary tumor plus bilateral inguinal–femoral lymph node dissection. Radiation therapy was delivered to the primary tumor volume via anterior-posterior–posterior-anterior (AP–PA) fields in 170-cGy fractions to a dose of 4760 cGy. Patients with inoperable groin nodes received chemoradiation to the primary vulvar tumor, inguinal–femoral and lower pelvic lymph nodes.

Results: Seven patients did not undergo a post-treatment surgical procedure: deteriorating medical condition (2 patients); other medical condition (1 patient); unresectable residual tumor (2 patients); patient refusal (2 patients). Following chemoradiotherapy, 33/71 (46.5%) patients had no visible vulvar cancer at the time of planned surgery and 38/71 (53.5%) had gross residual cancer at the time of operation. Five of the latter 38 patients had positive resection margins and underwent: further radiation therapy to the vulva (3 patients); wide local excision and vaginectomy necessitating colostomy (1 patient); no further therapy (1 patient). Using this strategy of preoperative, split-course, twice-daily radiation combined with cisplatin plus 5-fluorouracil chemotherapy, only 2/71 (2.8%) had residual unresectable disease. In only three patients was it not possible to preserve urinary and/or gastrointestinal continence. Toxicity was acceptable, with acute cutaneous reactions to chemoradiotherapy and surgical wound complications being the most common adverse effects.

Conclusion: Preoperative chemoradiotherapy in advanced squamous cell carcinoma of the vulva is feasible, and may reduce the need for more radical surgery including primary pelvic exenteration. © 1998 Elsevier Science Inc.

Chemoradiation, Advanced vulvar cancer, 5-Fluorouracil, Cisplatin.

INTRODUCTION

Since the turn of the century, deep resection of the entire vulva and dissection of the groin lymph nodes has been standard therapy for invasive carcinoma of the vulva. *En bloc* excision of the primary tumor and draining lymphatics was first used by Pringle in the management of vulvar melanoma, and later adapted by Basset for the treatment of cancers of the clitoris (1, 2). Further refinements of this surgical technique were made by Taussig in the United States, and Way in the United Kingdom (3, 4).

When the disease involves the anus, rectum, rectovaginal septum, proximal urethra, or bladder, adequate surgical resection is possible only by pelvic exenteration combined with radical vulvectomy. In selected patients the 5-year survival for patients with advanced vulvar cancer treated with pelvic exenteration is about 50% (5–7). However, operative mortality is about 10% and postoperative physical and psychological morbidity are substantial (8).

Radiation therapy has traditionally been considered to have a limited role in the primary management of vulvar cancer. Survival rates for patients treated with radiotherapy were poor (9, 10). Furthermore, severe acute skin reactions were common, perpetuating the belief that vulvar and perianal tissues were intolerant of radiation therapy. Better understanding of radiobiological principles has led to refinements in clinical techniques, resulting in improved efficacy and decreased toxicity of vulvar cancer radiotherapy.

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Late complications may be lessened by the use of smaller fraction sizes, limiting radiation field size, and the selective use of electrons or interstitial brachytherapy (11–14).

In 1973, Boronow advocated a combined radiation–surgical approach to advanced vulvar cancer as an alternative to pelvic exenteration. In this preliminary report he suggested brachytherapy, with or without external radiation, and subsequent surgery (usually radical vulvectomy and bilateral inguinal–femoral lymphadenectomy) (15). In 1982, Boronow reported the first 26 primary cases treated in this manner. There was only one case of local recurrence, and no patient required a pelvic exenteration. Seventeen (65%) patients were alive and without recurrent cancer from 1 to 11 years post-therapy (16). Hacker and colleagues described the use of preoperative external beam therapy in patients with advanced vulvar cancer, followed by limited surgical resection. Rather than performing radical vulvectomy in all patients, they advocated that only the tumor bed should be removed. Five (62.5%) patients were without evidence of recurrent cancer with 15 months to 10 years of follow-up (17).

Impressive results have been achieved in the treatment of squamous cell carcinoma of the anus, a cancer heretofore treated with surgical resection necessitating colostomy. Cummings and colleagues treated 55 patients with radiation therapy, with or without concomitant 5-fluorouracil plus mitomycin-C chemotherapy. Surgical resections and colostomies were performed only for treatment failures or toxicity, and required in only 27% of cases (18). Others have reported local control rates of 85–90% with chemoradiation alone (19, 20).

In view of these promising results, it seemed desirable to further investigate preoperative chemoradiotherapy in patients with advanced vulvar cancer. The purpose of this study was to determine the feasibility of using preoperative chemoradiotherapy to obviate the need for pelvic exenteration for patients with T_4 primary tumors involving the proximal urethra, bladder, anal canal, or rectum. For patients with T_3 primary tumors not amenable to resection by standard radical vulvectomy, the study objective was to determine the feasibility of using preoperative chemoradiotherapy to allow for a less extensive surgical resection.

METHODS AND MATERIALS

The study was conducted by Gynecologic Oncology Group (GOG) member institutions and their affiliates between 8/89 and 2/94. Study participation was limited to patients with locally advanced, previously untreated squamous cell carcinoma of the vulva. Patients with T_3 or T_4 primary tumors, irrespective of groin node status, were eligible for the study. Patients with T_3 tumors had primary cancers which could not be resected by standard radical vulvectomy. All patients were judged capable of tolerating a radical course of chemoradiation therapy followed by surgical resection of any residual tumor in combination with bilateral inguinal–femoral lymphadenectomy. Patients were ineligible if: GOG performance status > 2, serum creatinine > 2.0 mg/dl, liver transaminases or total bilirubin > 2 times upper limits of normal for reference laboratory, or bone marrow function inadequate (WBC $< 3000/\mu$l, granulocytes $< 1500/\mu$l, platelets $< 100{,}000/\mu$l). Excluded from the study were women with: prior malignancies, vulvar melanomas or sarcomas, septicemia or severe infections, gastrointestinal bleeding, severe gastrointestinal symptoms, or women who had previously received chemotherapy or pelvic radiation therapy. Before each institution could enter patients, the protocol was approved by the respective institutional review board or its equivalent. All patients were required to give written informed consent meeting institutional, state, and federal guidelines.

Table 1. Treatment schema of preoperative chemoradiotherapy for locally advanced squamous cell vulvar carcinoma

	Day of treatment									
Treatment regimen	1	2	3	4	5	8	9	10	11	12
Radiation therapy*	XX	XX	XX	XX	X	X	X	X	X	X
Cisplatin, 50 mg/m^2	X									
5-FU, 1000 mg/m^2	X	X	X	X						
$1\frac{1}{2}$ to $2\frac{1}{2}$ weeks split course	29	30	31	32	33	36	37	38	39	40
Radiation therapy*	XX	XX	XX	XX	X	X	X	X	X	X
Cisplatin, 50 mg/m^2	X									
5-FU, 1000 mg/m^2	X	X	X	X						

5-FU = 5-fluorouracil.

*Radiation therapy delivered 170 cGy twice daily (fractions separated by 6 hours) during 5-FU infusion and 170 cGy once daily for remainder of treatment course. Each split course delivered 2380 cGy.

The treatment schema consisted of a split course of chemoradiation therapy followed by surgical excision of the residual primary tumor plus bilateral inguinal–femoral lymph node dissection (Table 1). External beam radiation therapy was delivered to the primary vulvar tumor only through AP-PA fields to a dose of 4760 cGy, calculated at the midplane of the treatment volume. For patients with clinical N_2/N_3 groin nodes the radiation field included the primary vulvar tumor, inguinal–femoral lymph nodes, and lower pelvic nodes (Fig. 1). Field shaping was permitted to spare uninvolved normal tissues. Treatment was given as a planned split course consisting of two separate courses of 2380 cGy each. During each split course of radiation, 5-fluorouracil 1000 mg/m^2/day was given as a continuous infusion over the first 4 days, and cisplatin 50 mg/m^2 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 each 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. Cisplatin and 5-fluorouracil were infused with adequate hydration and antiemetic premedication. No treatment

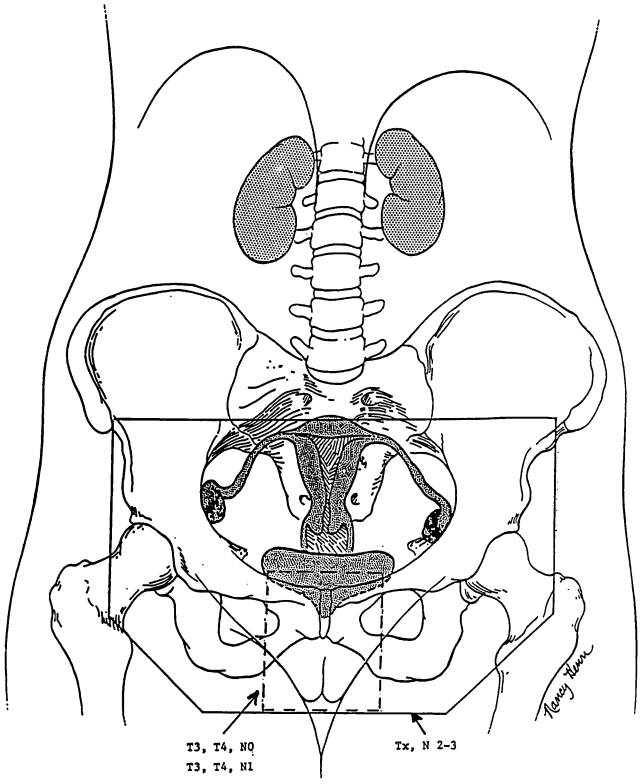

Fig. 1. Radiation fields. Patients with unresectable T_3/T_4 tumors and N_0/N_1 groin nodes received radiation therapy to the vulvar primary only (dotted line). For patients with N_2/N_3 groin nodes the field size was increased to include the groin and lower pelvic nodes (solid line).

course was initiated unless the granulocyte and platelet counts exceeded 1500/μl and 100,000/μl, respectively. Radiation therapy was withheld until chemotherapy could be restarted. Courses were separated by 1-1/2 to 2-1/2 weeks as determined by the severity of the acute vulvoperineal reaction. The Radiologic Physics Center, under the sponsorship of the American Association of Physicists in Medicine, supervised the dosimetry control for this clinical trial. Each institution must have demonstrated the ability to achieve an accuracy of $\pm$ 3% in measuring source output and $\pm$ 5% in delivering the prescribed dose.

Surgery to remove the residual primary vulvar lesion, plus inguinal–femoral lymph node dissection, was carried out 4 to 8 weeks from the completion of chemoradiotherapy. In the event of a complete response to chemoradiotherapy, the protocol mandated incisional biopsy of the primary tumor site plus inguinal–femoral lymph node dissection. In the event of no response to chemoradiotherapy with a still unresectable primary tumor, additional radiation therapy, 2000 cGy, was administered through reduced A-P, P-A and/or a direct perineal portal with either low-energy photon beam or with electrons, interstitial, or intracavitary therapy. If photons were used, the daily dose was 170–200 cGy calculated at the midplane of the residual primary tumor. If electrons were used, the energy was chosen according to the thickness of the tumor volume treated. The dose at the deepest point within the tumor volume was at least 80% of the dose at the surface of the tumor. For patients with resected primary tumors but with microscopically positive margins, either further surgery or additional radiation, 1000–1500 cGy, to the primary tumor volume was recommended. Outcome variables to assess therapeutic effectiveness were: 1) the conversion from exenterative to nonexenterative surgery with preoperative chemoradiotherapy (or for patients with T_3 lesions, the conversion to a less radical operation than performed usually); and 2) the morbidity of preoperative chemoradiotherapy. Adverse effects were graded using standard Gynecologic Oncology Group toxicity scales.

The sample size was based on a two-stage sampling design. The principal outcome variable was the conversion of a patient's surgical management to a less radical procedure. If at least 12 of the first 15 patients were converted to less radical operations, the study was continued. If the actual rate of conversion is 0.85, this study design would correctly conclude that chemoradiotherapy is effective 80% of the time, and if the actual rate of conversion was 0.70 incorrectly conclude "effective" 13% of the time.

RESULTS

A total of 104 patients were entered in this GOG study of preoperative chemoradiation. Eight patients were later declared ineligible: three had prior or concomitant malignancy (vulva, breast, lung); three had tumors that could have been resected by radical vulvectomy prior to chemoradiotherapy; one was noncompliant with completing assigned treatment and removed from the study; one lacked adequate radiotherapy information. Among the remaining 96 women, 23 had T_1/T_2 resectable primary tumors and N_2/N_3 unresectional groin nodes and were excluded from this analysis. A total of 73 patients with unresectable T_3/T_4 primary vulvar tumors with either N_0/N_1 groin nodes (50 patients) or N_2/N_3 groin nodes (23 patients) were included in this analysis. Two of these patients were inevaluable for therapeutic efficacy: one patient did not complete prescribed treatment due to medical condition and one patient refused to continue after the first treatment course. Therefore, there were 73 eligible patients evaluable for toxicity and 71 patients evaluable for therapeutic efficacy.

Demographic characteristics included age over 50 years (80.8%), white race (82.2%), and GOG performance status 0–1 (87.7%). Primary tumors involved the labium in 94.5%, and exceeded 6 cm in diameter in almost half of the patients (46.6%). Clinical status of the groin lymph nodes was described as N_2/N_3 in 36 (49.3%) patients, but for 13 of these women the attending physician felt the nodes were surgically resectable prior to the initiation of chemoradiotherapy.

Four patients had unresectable vulvar cancers fixed to bone. For the remainder, tumor resection was deemed possible, but because of tumor distribution, surgical procedures

Table 2. Extension of disease*

Sites involved	No. of cases	%
Vagina	50	68.5
Anus	33	45.2
Urethra	22	30.1
Rectum	18	24.7
Bladder	4	5.5
Bone	4	5.5

*Each patient is included in every site that is applicable.

beyond standard radical vulvectomy were considered (Table 2). Toxicity was acceptable, with acute cutaneous reactions to chemoradiotherapy the most common adverse effect (Table 3). Moist desquamation occurred in 20 patients: for 10 patients, no skin reactions to chemoradiotherapy were reported. Early postoperative complications in surgical wounds were frequent and included: necrosis (7 patients); abscess (3 patients); hematoma (1 patient); and wound evisceration (1 patient). Severe myelosuppression during treatment was absent. Two patients developed sepsis: one patient developed moist desquamation and sepsis during chemoradiation therapy; one patient developed a surgical wound infection on postoperative day 10 and died of treatment; one patient developed a hip fracture 20 months after completing therapy; the femoral heads were included in the radiation field. There were two treatment-related fistulas: one patient had a rectovaginal fistula at the conclusion of chemoradiation therapy and underwent posterior exenteration; one patient developed a post-treatment rectovaginal fistula managed by diverting colostomy.

Overall, 71 patients completed the prescribed treatment plan and were evaluable for response (Table 4). The median dose of radiation delivered was 4760 cGy (range: 4090–4780 cGy). Toxicity was acceptable. Of these, seven patients did not undergo a post-treatment surgical procedure: deteriorating medical condition (congestive heart failure—1, diabetes mellitis—1); other medical condition (preoperative ECG changes and surgery canceled—1 patient); unresectable residual tumor (2 patients); patient refusal (2 patients). Two of these patients who did not undergo an operation were described as having a complete clinical response to chemoradiotherapy.

Table 3. Acute adverse effects

	Grade				
Acute adverse effect	0	1	2	3	4
Hematologic	47	16	7	3	0
Emesis	44	13	16	0	0
Diarrhea	57	8	6	1	1
Other gastrointestinal	49	8	14	0	2
Urinary	54	12	6	1	0
Hepatic	71	1	1	0	0
Pulmonary	67	5	1	0	0
Infection	64	1	5	1	2
Neurologic	66	3	2	2	0
Cutaneous	10	8	16	19	20
Cardiovascular	69	0	1	2	1
Lymphatics	47	9	13	4	0
Fever	63	3	6	1	0
Wound breakdown	64	3	2	2	2

Following chemoradiotherapy, 34/71 (48%) patients had no visible cancer. Three of these patients did not undergo surgery. Of the remainder, 22/31 (70%) had no residual microscopic disease. Five patients had residual microscopic disease and negative surgical margins. Four patients had residual microscopic disease involving surgical margins: two were salvaged with further surgery (wide local excision; wide local excision and partial vaginectomy); one patient died from pneumonia prior to receiving further radiation therapy; one patient refused additional treatment and 5 months later underwent total pelvic exenteration for recurrence.

Grossly evident residual tumor was present in 38/71 (53.5%) patients. Five of these patients did not undergo surgery. Of the remainder, 28/33 (84.8%) had negative pathologic margins. One of these patients required a posterior exenteration to resect residual clinical disease following chemoradiotherapy. The five patients with positive margins underwent: further radiation therapy to the vulva (3 patients); wide local excision and vaginectomy necessitating colostomy (1 patient); and no further therapy (1 patient). Among the 50 patients initially presenting with vulvar cancers requiring exenterative surgery, only one patient required exenterative surgery and two patients required colostomy to resect residual disease.

Using this strategy of preoperative, split course, twice-daily radiation combined with cisplatin plus 5-fluorouracil chemotherapy, only 2/71 (2.8%) patients had residual unresectable disease. In only three patients was it not possible to preserve urinary and/or gastrointestinal continence.

Among those patients who are alive, the median time of follow-up was 50 months (range: 22–72 months). Twenty-four (32.9%) women developed recurrent vulvar cancer. Five of these patients subsequently underwent exenterative surgery to resect recurrent disease: total pelvic exenteration (2 patients); anterior exenteration (2 patients); posterior exenteration (1 patient). 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 (2 patients) or pelvis (1 patient). Other sites of recurrence include: groin (1 patient); pelvis (2 patients); abdomen (1 patient); pelvis and abdomen (1 patient); distant (6 patients); unknown (2 patients). There have been 20 deaths from recurrent vulvar cancer, four deaths from treatment-related complications (one patient each: femoral artery hemorrhage, postoperative cerebrovascular accident, postoperative pneumonia and septicemia, wound necrosis and infection), four deaths from other causes, and one death for unknown reasons. Two patients are alive with recurrent vulvar cancer. Overall, 40 (54.9%) patients are alive and without evidence for recurrent disease.

Table 4. Surgical management of primary tumor versus anticipated surgical management prior to chemoradiotherapy

	Actual procedure							
Anticipated procedure	Biopsy	Wide local excision	Vulva	Other	Vagina	Anterior exenteration	Posterior exenteration	None
Vagina	3	7[1]	3	0	0	0	0	2[2,4]
Urethra	0	1	1	0	0	0	0	1[4]
Bone	0	1	2	0	0	0	0	0
Anterior exenteration	2[5]	1	2	3[6,6,6]	0	0	0	3[3,7,7]
Posterior exenteration	2	12	15[5,9]	1[1]	1	0	1	1[2]
Posterior exenteration + Urethra	0	0	1	0	0	0	0	0
Total exenteration	1	2	0	1[8]	0	0	1	0

Vagina = Radical vulvectomy + vaginectomy.
Urethra = Radical vulvectomy + distal urethral resection.
Bone = Tumor fixed to bone.
Key (each numeric symbol = one patient):
[1] Partial vaginectomy (1 patient).
[2] No surgery because of deteriorating condition (2 patients).
[3] No surgery because of other medical condition but complete response (1 patient).
[4] No surgery because of patient refusal (2 patients).
[5] Tumor completely regressed but received additional radiotherapy (2 patients).
[6] Plus distal urethral resection (3 patients).
[7] No surgery because tumor considered unresectable (2 patients).
[8] Posterior vaginal and anal resection plus colostomy (1 patient).
[9] One patient subsequently underwent wide local excision and descending colostomy.

DISCUSSION

Many early reports demonstrated that vulvar cancer is sensitive to radiation therapy (12, 19, 21, 22). Boronow (16) and Hacker (17) suggested the efficacy of a combined radiation–surgical approach for advanced vulvar cancer as an alternative to pelvic exenteration. In Boronow's series, 77% of primary cases received preoperative radiation followed uniformly by a radical vulvectomy. No residual tumor was present in 42.5% of surgical specimens. In Hacker's series, one patient remained inoperable because of groin disease, but only 2/8 patients required radical vulvectomy to resect residual tumor. In 50% of cases there was no residual disease in the surgical specimen. At the relatively low doses of radiation used (4400–5400 cGy), Hacker recommended local excision of the tumor bed in all patients even in the presence of a complete clinical response. Based on these promising results, it seemed desirable to further investigate preoperative radiation therapy in patients with locally advanced vulvar cancer.

Interest in adding concurrent chemotherapy to radiotherapy was stimulated by positive results reported in other tumor sites. Theoretically, if the net effects of radiation–drug interactions in tumors are synergistic, and if late normal tissue toxicity is independent of acute radiation–drug interactions, improved local control rates may be achieved. Alternatively, with concurrent chemotherapy it may be possible to obtain the same local control rate at lower toxicity compared to a treatment scheme employing higher total doses of radiation. The combination of cisplatin and 5-fluorouracil has definite activity against squamous cell carcinomas of the cervix (23). When used in the treatment of squamous cell carcinoma of the anus, cisplatin plus 5-fluorouracil chemoradiation yielded results superior to radiation therapy alone, and local control rates comparable to 5-fluorouracil and mitomycin-C (24). Cisplatin and 5-fluorouracil have known properties *in vitro* of radiosensitization (25, 26). Cisplatin and 5-fluorouracil chemoradiotherapy have been used extensively by the Gynecologic Oncology Group for locally advanced squamous cell carcinomas of the cervix and were chosen for this study.

Our data and the existing medical literature leave unresolved issues of whether concurrent chemotherapy improves treatment results in vulvar cancer, to what degree, and what is optimal chemotherapy in a chemoradiotherapy scheme (Table 5) (9, 27–33). There are data suggesting that chemoradiotherapy is more effective than radiation alone for local tumor control in patients with anal carcinoma (18, 19, 34). Results from a recently published Phase III cooperative group trial, in which patients were randomized to receive chemoradiotherapy with either mitomycin-C plus 5-fluorouracil versus 5-fluorouracil alone, demonstrated a significantly lower colostomy rate and higher disease-free survival in the mitomycin-C-containing arm, albeit with greater acute hematologic toxicity (35).

Optimal radiation dose-fractionation has not been determined. This protocol examined the role of chemoradiation prior to a required surgical intervention and the total dose of radiation chosen was purposefully less than what is usually used when radiation is the sole planned method of treat-

Table 5. Chemoradiation as the primary treatment of vulvar carcinoma

Author	Chemo	RT Dose (cGy)	No. of patients	No. post-Tx surgery*	CR (%)	Outcome
Thomas[27]	5-FU ± MitC	4000–6100	9	6	67	DFS—77%, median F/U 20 mo
Koh[29]	5-FU ± MitC	3000–7040	20	13	50	DFS—49% at 5 yr
Iversen[9]	Bleomycin	3600–4000	15	2	0	Survival—26% at 12 mo
Scheistroen[30]	Bleomycin	3000–4500	42	4	25	Median survival—8 mo
Levin[32]	5-FU + MitC	1800–4500	6	4	0	Survival—66% at 9 mo
Wahlen[31]	5-FU + MitC	4500–5000	19	6	53	Local control—74%, median F/U 34 mo
Russell[33]	5-FU ± CDDP	4680–7200	25	1	80	DFS—56%, median F/U 24 mo
Sebag-Montefiore[28]	5-FU + MitC	4500–5000	37	8	47	Survival—37% at 2 yr
Moore (this study)	5-FU + CDDP	4760	71	64	47	DFS—67%, median F/U 45 mo

Abbreviations: 5-FU = 5-fluorouracil; MitC = mitomycin-C; CDDP = cisplatin; DFS = disease-free survival; F/U = follow-up.

* No. post-Tx surgery refers to the number of patients who underwent postchemoradiotherapy resection of persistent/recurrent vulvar cancer.

ment. Others have achieved excellent local control rates with radiation doses exceeding 50 Gy (24, 36). Multiple daily fraction radiation is undergoing clinical investigation for many tumor sites and has theoretical advantages over once-daily radiation schedules (37). Two randomized controlled trials in squamous cell head and neck cancers have demonstrated improved control rates with multiple daily fraction radiation therapy (38, 39). The purpose of giving two daily fractions in this protocol was to maximize the possibility of drug–radiation interaction during the cisplatin administration and 5-fluorouracil infusion. The planned split-course chemoradiation scheme was supported by the findings of Thomas and colleagues that acute toxicity was more severe in the chemotherapy arm, and could be diminished by a split-course regimen while still achieving a superior outcome (27). However, there is emerging evidence that prolongation of overall treatment time may be counterproductive (20, 36). Given the frequency of severe acute skin reactions with continuous vulvar radiation, future studies should consider eliminating a planned break, instead permitting a break only as necessary by the development and severity of acute cutaneous reactions, and only for as short a duration as possible.

Finally, the different treatment strategies and results reported to date in vulvar carcinoma are insufficient to resolve the question of whether surgery is necessary when there is a complete response to radiotherapy. At a median radiation dose of 5100 cGy, Thomas and colleagues reported complete responses in 6/9 (67%) patients; three women subsequently experienced vulvar relapses (27). Koh used higher radiation doses (median dose 5400 cGy) and 10/20 (50%) of patients achieved a complete response. Five of these women subsequently underwent surgery and pathologically none had residual cancer. In his series the overall 5-year local control rate was noticeably better at radiation doses $\geq$ 5000 cGy without a substantial increase in toxicity (29). The risk for persistent vulvar cancer at the primary site following radiotherapy is in part a function of initial tumor volume, cell proliferation rates, intrinsic radioresistance, total radiation dose and fractionation scheme, and treatment field selection. We selected moderate doses of preoperative radiation rather than higher doses which might control larger tumors at the cost of greater toxicity.

The results from this prospective, multi-institutional trial confirm those from other published series that preoperative chemoradiotherapy is feasible in advanced squamous cell carcinoma of the vulva, averting the need for exenterative surgery in the vast majority of patients. To date, follow-up is too brief and the number of patients too small to allow for an in-depth analysis of survival or patterns of failure. These data, further understanding of drug–radiation–tumor interactions, studies of vulvar cancer tumor biology, and objective quality-of-life assessments will contribute to the design of future clinical trials in this patient population.

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