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CLINICAL INVESTIGATION **Vulva**

PREOPERATIVE CHEMO-RADIATION FOR CARCINOMA OF THE VULVA WITH N2/N3 NODES: A GYNECOLOGIC ONCOLOGY GROUP STUDY

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Purpose: To determine if patients with carcinoma of the vulva, with N2/N3 lymph nodes, could undergo resection of the lymph nodes and primary tumor following preoperative chemo-radiation.

Methods and Materials: Fifty-two patients were entered in the study, but six patients did not meet the criteria of the protocol and were excluded. The remaining 46 patients are the subject of this report. Patients underwent a split course of radiation, 4760 cGy to the primary and lymph nodes, with concurrent chemotherapy, cisplatin/5-FU, followed by surgery.

Results: Four patients did not complete the chemo-radiation, because three expired and one refused to complete the treatment. Four patients who completed chemo-radiation did not undergo surgery, because two of them died of non-cancer-related causes, and in the other two patients, the nodes remained unresectable. Following chemo-radiation, the disease in the lymph nodes became resectable in 38/40 patients. Two patients who completed the course of chemo-radiation did not undergo surgery as per protocol because of pulmonary metastasis. One underwent radical vulvectomy and unilateral node dissection and the other radical vulvectomy only. The specimen of the lymph nodes was histologically negative in 15/37 patients. Nineteen patients developed recurrent and/or metastatic disease. The sites of failure were as follows: primary area only, 9; lymph node area only, 1; primary area and distant metastasis, 1; distant metastasis only, 8. Local control of the disease in the lymph nodes was achieved in 36/37 and in the primary area in 29/38 of the patients. Twenty patients are alive and disease-free, and five have expired without evidence of recurrence or metastasis. Two patients died of treatment-related complications.

Conclusion: High resectability and local control rates of the lymph nodes were obtained in patients with carcinoma of the vulva with N2/N3 nodes treated preoperatively with chemo-radiation. © 2000 Elsevier Science Inc.

Chemo-radiation, Vulvar cancer, N2/N3 nodes.

INTRODUCTION

Carcinoma of the vulva represents 3% to 5% of all gynecological malignancies, with a reported incidence of 0.5 to 2 cases per 100,000 women (1) and with a higher incidence (20 per 100,000) in women 70 years of age or older (2).

The standard treatment for advanced carcinoma of the vulva has been en-block resection of the primary tumor and regional lymph nodes (3). The magnitude of the surgery depends upon the extent of the disease at the primary site, involvement of adjacent organs, and the status of the lymph nodes. Both spread of the disease to the lymph nodes and extracapsular invasion have a negative impact on prognosis, irrespective of the stage of the primary (4–6).

Surgery for unresectable lymph nodes, fixed or ulcerated, is not recommended. Attempts to remove fixed, unresectable nodes have yielded very poor results with no long-term survivors reported by Taussig (7). If resection of the lymph nodes is not possible, disease progression ensues. Making unresectable nodes resectable allows patients to undergo potentially curative surgery. Preoperative radiation has been used in an attempt to decrease the magnitude of the surgery

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for the primary tumor (8–10). In his preliminary report, Boronow (8) used brachytherapy, with or without external beam radiation, to reduce the extent of the primary tumor before radical vulvectomy and bilateral inguino-femoral lymphadenectomy. There are no reports, however, describing the use of preoperative radiation for the purpose of making unresectable nodes resectable.

In recent years the concept of combined modality treatment (chemotherapy/radiation/surgery) for a variety of tumors has been explored extensively. With this approach, organ preservation and function have been achieved for several disease sites with comparable or improved local control and survival rates (11–14). Combined modality therapy has been used for advanced carcinoma of the vulva to reduce the magnitude or avoid surgery for the primary, but these studies do not address the issue of the management of advanced nodal disease (15–23).

The specific goal of this study was to determine if patients with carcinoma of the vulva with unresectable lymph nodes could tolerate a preoperative course of chemo-radiation, could undergo resection of the lymph nodes and the primary tumor and to determine the impact this treatment would have on outcome.

METHODS AND MATERIALS

This study was conducted by the Gynecologic Oncology Group (GOG), member institutions, and their affiliates between August 1989 and February 1994. Study participation was limited to patients with previously untreated squamous cell carcinoma of the vulva with unresectable, N2/N3 groin lymph nodes according to the FIGO staging system in use when this study was designed (24). The staging system currently in use differs from the one used for this study in what pertains to the lymph nodes. All patients were judged capable of tolerating a preoperative course of chemo-radiation therapy to be followed by surgical resection of primary tumor and bilateral inguinal-femoral lymphadenectomy. Patients were ineligible if: GOG performance status >2, serum creatinine >2.0 mg/dL, liver transaminases or total bilirubin more than two times upper limits of normal for reference laboratory, or inadequate bone marrow function (white blood count [WBC] $<3{,}000/\mu$L, granulocytes $<1{,}500/\mu$L, platelets $<100{,}000/\mu$L). Excluded from the study were women with prior malignancies, vulvar melanomas, or sarcomas; women who had previously received chemotherapy or pelvic radiation therapy, or women who had medical contraindications to the planned therapy. Participating institutions were required to have approval of the protocol by their respective institutional review board or its equivalent. All patients were required to give written consent in compliance with institutional, state, and federal guidelines.

The treatment schema, shown in Table 1, consisted of a split course of chemotherapy and radiation followed by surgery for the primary tumor and bilateral inguino-femoral lymph node dissection. The external beam radiation therapy fields shown in Fig. 1 included the area of the primary tumor and the inguino-femoral and low pelvic lymph nodes. The radiation therapy consisted of 170 cGy delivered through AP and PA portals, twice per day (BID) on days 1–4 and 170 cGy per fraction daily on Day 5 and Days 8 through 12 for a total dose of 2380 cGy.

Table 1. Treatment schema—preoperative chemo-radiation

	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/2^{2†}	X	X	X	X						
	Rest period 1-1/2 to 2-1/2 weeks									
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						

* Radiation therapy delivered 170 cGy twice daily, fractions six hours apart, days 1–4 and once daily for the remainder of the treatment.

† 5-fluorouracil, 1000 mg/m^2, 24-hour infusion.

Following this initial two-week cycle of treatment and a two to three weeks rest period for healing of the vulvoperineal reaction, a repeat two-week cycle of radiation was given using the same fields and radiation dose fractionation schema. The total dose to the primary tumor and the lymph nodes was 4760 cGy. The chemotherapy consisted of cisplatin, 50 mg/m^2 on Day 1 and 5-fluorouracil (5-FU), 1,000 mg/m^2 24-h infusion on Days 1–4 of the first week of each of the two-week cycles of radiation therapy. Following the second cycle of chemo-radiation, patients were evaluated for surgery. To allow for tumor regression and healing of the reaction, the surgery was carried out within three to eight weeks (median: 6 weeks) after the completion of the chemo-radiation treatment. The recommended surgery, per protocol, consisted of resection of the residual vulvar lesion and bilateral inguino-femoral lymph node dissection. In the event of complete regression of the primary tumor following the chemo-radiation treatment, the protocol required biopsy of the primary tumor site to rule out residual disease. If the biopsy was negative, resection of the primary was not required, but the inguino-femoral lymph node dissection was required. If at the completion of the course of chemo-radiation there was still unresectable disease in the primary or lymph nodes sites, additional radiation was recommended. Likewise, for patients with microscopically positive margins at the primary site or nodes, either further surgery or additional radiation was also recommended.

There were two categories of patients eligible for this clinical trial: a) patients who were deemed to have unresectable primary tumor unsuitable for radical vulvectomy and, b) patients who were deemed to have unresectable lymph nodes. Patients with both disease characteristics were to be evaluated for groin node response as well as primary tumor response. The group of patients in the first category is the subject of a separate report by Moore (25). The sample size for each category was based on a two-stage sampling design with 15

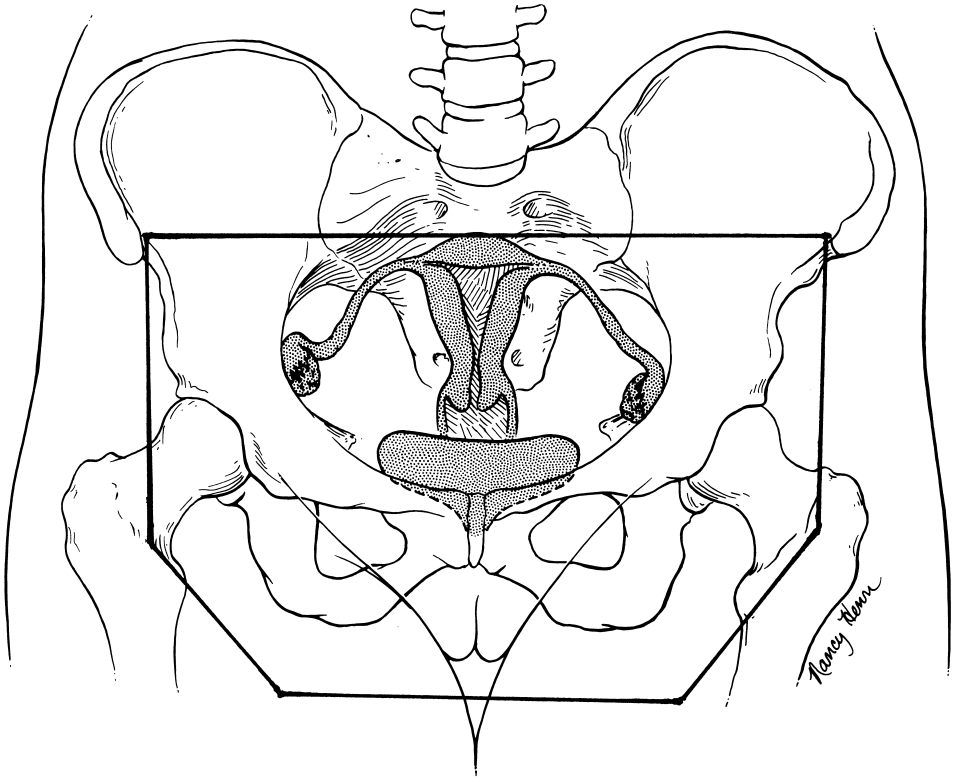


Fig. 1. Radiation therapy field.

patients to be accrued during the first stage and 25 patients to be accrued during the second stage (i.e., total of 40 patients). The decision rule for beginning the second stage of accrual was solely based on the patients with unresectable primary tumors; specifically, the number that required no more than a radical vulvectomy (less surgery) after the chemo-radiation. If at least 12 of the first 15 patients were converted to "less surgery," the study was to begin the second stage of accrual. The chemo-radiation would be deemed "effective" if at least 30 of the 40 patients converted to "less surgery." If the actual probability of conversion (Pc) is 0.85, this trial design would correctly conclude that chemo-radiation is effective 80% of the time. Conversely, if the actual probability of conversion is only 0.70, this trial design would incorrectly conclude "effective" 13% of the time. In hypothesis terminology, Ho: $Pc \leq 0.70$ and Ha: $Pc \geq 0.85$ with a Type I Error of 13% and power of 80%.

Outcome variables to assess therapeutic effectiveness were:

Conversion of the groin lymph nodes from unresectable to resectable, Control of the disease in the groin, Evaluation of the morbidity of combined modality treatment.

RESULTS

From August 1989 through February 1994, 52 women with carcinoma of the vulva and unresectable, N2/N3 (24) groin nodes were entered in the study. Six patients were excluded from the study for the following reasons: noncompliance with the treatment 1, inadequate data 1, resectable nodes 3, and previous surgery for the primary 1. The remaining 46 patients are the subject of this report.

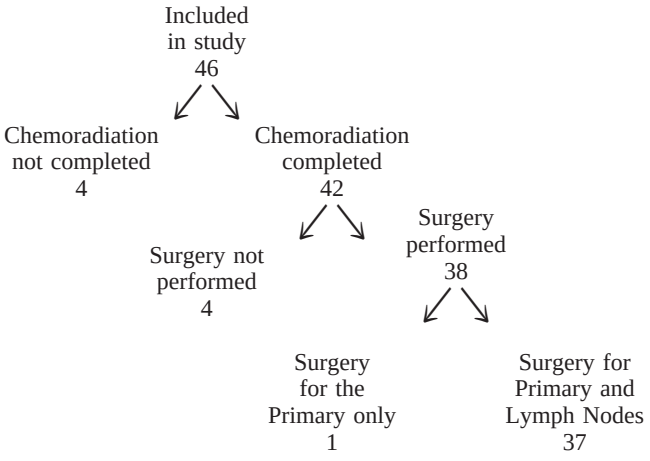
The age distribution of the patients ranged from 35 to 88 years with a median of 69. The race distribution was as follows: white = 37 patients; black = 5 patients, Hispanic = 2 patients, and other = 2 patients. The GOG performance status was as follows: 0 = 20 patients; 1 = 19 patients; 2 = 7 patients. The extent of the primary and nodal disease is presented in Table 2.

The breakdown of the treatment received by the 46 patients eligible for study is shown in Table 3. Four patients did not complete chemo-radiation for the following reasons:

Table 2. Extent of primary and nodal disease ($N = 46$)

Extent of disease	No. (%)
Primary	
Labium minus	2 (4)
Labium majus	1 (2)
Labium majus and minus	12 (26)
Clitoris and labium	5 (11)
Perineum and labium	17 (37)
Clitoris and perineum	9 (20)
Nodes	
N2	19 (41)
N3	27 (59)
Unilateral	27 (59)
Bilateral	19 (41)

Table 3. Protocol summary



one patient developed a malignant pleural effusion, one patient died of congestive heart failure, another patient expired due to worsening general condition, and one patient refused to complete the treatment. The remaining 42 patients completed the chemo-radiation as per protocol. The treatment was well tolerated except for the anticipated muco-cutaneous reaction in the vulvo-perineal region, which resulted in a lower dose in one patient (3910 cGy). The reaction healed to some degree during the planned treatment break after the first two-week cycle of chemo-radiation. Four of the 42 patients who completed chemo-radiation did not undergo surgery. In two of these four patients, the nodal disease remained unresectable, and they died with uncontrolled disease. One patient died of congestive heart failure, and one died of a pulmonary emboli. As shown in Table 3, 38 patients completed the pre-operative course of chemo-radiation and subsequently underwent surgery. Two of these patients were diagnosed with pulmonary metastases after having completed the course of chemo-radiation and did not undergo surgery as per protocol. One patient underwent resection of the primary tumor only, and the other underwent radical vulvectomy and unilateral lymph node dissection. Therefore, 37 patients underwent node dissection, and the surgical specimen of the lymph nodes was histologically negative in 15/37 patients.

The extent of the surgery for the primary tumor was determined by the response to the preoperative treatment. The surgery consisted of simple biopsies in four patients who had complete regression of the primary disease. All the other patients underwent resection of the primary tumor. The surgical specimen of the primary was negative in 20/38 patients.

The untoward effects of the treatment, classified according to the GOG standard criteria (26), are presented in Table 4. As can be seen in this table, the most common side effects of the treatment were related to the muco-cutaneous reaction. Seven patients developed wound breakdown following the surgery, which ultimately healed with conservative measures. One patient sustained a hip fracture about two years after having completed the treatment. Two patients developed fatal treatment-related complications. One patient suffered femoral artery necrosis one month after surgery, and the other patient developed persistent leukopenia and died of septicemia two months post treatment. Therefore, a total of three patients died as a consequence of the therapy: the patient mentioned earlier who died of a pulmonary emboli while undergoing chemo-radiation and two other patients who died in the postoperative period. The three patients who died before chemotherapy was completed, two of congestive heart failure and one of deteriorating general condition, were not considered to have died directly as a result of the treatment.

Table 4. Adverse effects

	Grade			
Adverse effect	1	2	3	4
Cardiovascular	–	1	1	–
Cutaneous	2	9	13	12
Diarrhea	7	7	1	–
Femoral artery necrosis	–	–	–	1
Femoral artery stenosis	–	–	1	–
Fever	4	1	–	–
Genitourinary	11	3	–	–
Hematologic	11	13	1	–
Hematoma	–	–	–	1
Hip fracture	–	–	1	–
Lymphatics	6	4	–	–
Nausea/vomiting	9	10	–	–
Neurologic	2	2	1	–
Other gastrointestinal	4	6	3	1
Pulmonary	2	1	–	1
Septicemia	–	–	–	1
Wound breakdown	1	2	7	–
Wound infection	–	2	1	2

The outcome of treatment in the group of 38 patients who underwent surgery is presented in Table 5. Twelve patients are alive and free of disease with follow-up ranging from 56–89 months (median 78 months). Five patients died of intercurrent disease, without evidence of cancer, from six to 73 months after entry into study. Two patients died of treatment-related complications. Nineteen patients developed recurrent and/or metastatic disease. Nine of these patients had local recurrence at the primary site only, one patient had local recurrence at the primary site and distant metastasis, and one patient recurred in the nodal area only.

Table 5. Treatment outcome after surgery ($n = 38$)

Outcome	Number
No evidence of disease	12
Dead of intercurrent disease	5
Dead with complications	2
Recurrence, primary only	9
Recurrence, primary only and distant metastasis	1
Recurrence, inguinal nodes only	1
Distant metastasis only	8

One of the patients with recurrence in the vulvar area died of a myocardial infarct two weeks after undergoing resection of the recurrence. Eight patients failed due to distant metastasis only. One of these patients recurred in the paraaortic nodes and was treated with chemotherapy and radiation. Subsequently, she developed metastasis in the supraclavicular nodes, was treated with chemotherapy, and died 42 months later in complete remission. Control of the disease in the lymph nodes was obtained in 36/37 patients and in volume of radiation, inguinal nodes and primary, in 27/38 patients.

DISCUSSION

In recent years significant advances have been made in the evaluation and treatment of neoplastic diseases. Perhaps the most important development has been the introduction of combined modality treatment to lessen the impact and morbidity of a single modality, such as surgery.

Combined radiation and surgery for carcinoma of the vulva was introduced with the studies of Boronow (8, 9) and Hacker (10). These authors showed that with preoperative radiation the extent and magnitude of surgery for carcinoma of the vulva could be reduced. These studies demonstrated that the vulvar region can be treated with radiation, with relative good tolerance, particularly in the pre-operative setting. Boronow (9) reported 65% disease-free survival in 26 patients with Stage III-IV disease treated preoperatively with external beam therapy and/or brachytherapy. Hacker (10) reported on eight patients with advanced vulvar cancer treated with preoperative radiation, with more conservative surgery having been performed in seven patients. Whereas radiation has been used to lessen the surgery for the primary, there are no studies reporting on the systematic use of preoperative radiation to make unresectable nodes resectable.

Hydroxyurea, cisplatin, and 5-fluorouracil have radiosensitizing properties that have been well documented in vivo studies (27–29). These agents used alone or in combination, with conventional or hyperfractionated external beam therapy, have been used for squamous cell carcinomas in various sites with good results and acceptable toxicity (30–34). The GOG studies have demonstrated an improvement in progression-free survival and overall survival with the addition of chemotherapy to radiation in locally advanced squamous cell carcinoma of the cervix (35–37).

The studies of concurrent chemotherapy and radiation for carcinoma of the vulva thus far reported usually include a small, heterogeneous group of patients, with or without nodal disease, treated with different chemotherapy and radiation schedules and doses (15–23). In the report by Thomas (16) seven of nine patients treated with definitive radiation and chemotherapy, 5-FU infusion ± Mitomycin C were disease-free, but three patients required local excision of residual or recurrent disease. Russell (18), reported a study of 18 patients, 14 with N0 and four with N2 disease, treated with concurrent radiation and chemotherapy, 5-FU ± cisplatin, using 180 cGy, BID radiation fractionation during the chemotherapy administration, as it was used in our study. Two of the four patients with N2 disease were disease-free at last follow-up (18). In Koh's study of 20 patients treated with cisplatin/5-FU and conventional radiation, three of five patients with involved nodes were disease free (19). Lupi (22) reported on 24 patients with advanced primaries and N1-N2 nodal disease, treated with Mitomycin C/5-FU and conventional fractionation. In Lupi's series, 15 patients were free of disease with follow-up ranging from 22 to 73 months. None of the aforementioned studies specifically describe the response of the lymph nodes to this type of therapy.

In our study of patients with advanced nodal disease, a very high resectability rate, 95%, was achieved after preoperative chemo-radiation, as there were only two patients whose nodal disease did not become resectable with the preoperative treatment. The specimen of the lymph nodes was negative in 15/37 (41%) of these patients who underwent lymph node dissection. This rate of negative lymph node surgical specimens is considered to be very high given that the patients received a protracted, low dose, preoperative, split course of radiation. The effectiveness of this combination therapy on the inguinal lymph nodes is reflected in ultimate control of the disease in this area in 36 of 37 patients who completed chemo-radiation and underwent inguinal node dissection.

The untoward effects of this combined chemo-radiation/surgery therapy were appreciable but were tolerated by the majority of the patients. The muco-cutaneous reaction in the vulvo-perineal area was severe and mandated the treatment break designed in the protocol. It is conceivable that these patients' heart disease and general condition were adversely affected by the treatment they received. One patient suffered a pulmonary emboli after she completed the chemo-radiation and before she underwent surgery. Two other patients died in the immediate postoperative period, one of femoral artery necrosis and the other of sepsis. These three patients are considered to have died directly as a consequence of the treatment. On the other hand, the three other deaths that occurred before the patients completed chemo-radiation are not attributed to the treatment, although the treatment might have precipitated these events.

This combination of chemo-radiation did not interfere with the lymphadenectomy or the surgery for the primary. With the combination of preoperative chemo-radiation and surgery, control of the disease in the area of the primary and lymph nodes was achieved in 27/38 of the patients and freedom from any recurrence (local or distant) in 20/38 patients. Nine patients developed distant metastasis. Eight of these patients had no evidence of disease elsewhere, and one patient had recurrence at the primary site also. This high failure rate due to distant metastasis underlines the need for better methods to identify and treat subclinical metastatic disease at presentation.

The most effective radiation dose/fractionation schema for carcinoma of the vulva is not known. The BID fractionation schedule was adopted based on the experience of

Thomas (16) with infusion 5-FU and Mitomycin C for advanced carcinoma of the cervix. This protocol was designed as a split course of chemo-radiation in anticipation of the degree of muco-cutaneous vulvo-perineal reaction expected with combined therapy. It is possible that this fractionation schema contributed to the relatively good tolerance of the chemo-radiation, the significant tumor regression, and the favorable outcome in this group of patients.

Conversely, a split course of radiation prolongs the overall radiation treatment time, and this may have lessened the effectiveness of the radiation as is the case for cervical carcinoma (38–39).

The goals set forth in this protocol were achieved. The course of preoperative chemo-radiation used in this protocol allowed these patients to undergo resection of unresectable lymph nodes, otherwise not possible. The pathologic complete response rate and control of the disease in the nodal area were excellent given the stage of the nodal disease at the outset. This suggests that patients with less advanced nodal disease could be treated initially with chemo-radiation, with surgery reserved for those patients who do not achieve a complete clinical and radiographic response. Further investigation is needed to determine the best chemotherapy/radiation/surgery combination to obtain the maximum benefit for patients with carcinoma of the vulva with unresectable nodes.

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