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NEOADJUVANT THERAPY IN LOCALLY ADVANCED VULVAR CANCER : A SINGLE INSTITUTIONAL EXPERIENCE

Oncology

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ABSTRACT

Purpose : Therapeutic outcomes of patients with advanced vulvar cancer are generally poor and multimodality treatment is now considered the treatment of choice.We report a pilot study on neoadjuvant therapy followed by radical surgery for patients with locally advanced squamous cell carcinoma of the vulva.

Method : 16 patients of squamous cell carcinoma of the vulva, stage II-IVA were treated with neoadjuvant therapy.10 patients out of 16 received neoadjuvant chemoradiotherapy upfront,2 patients received hypofractionated radiotherapy and 4 patients received initial neoadjuvant chemotherapy followed by evaluation for preoperative chemoradiotherapy.After a period of 4-6 weeks,patients were evaluated for surgery.Out of 16 patients, 13 patients showed response amenable for surgery.1 patient refused for surgery and 12 patients underwent surgery. The remaining 3 patients completed the chemoradiotherapy course to the total dose.

Results : An objective response was observed in 81.25% (10 out of 12 patients). One patient refused for surgey and the pathologic complete response rate (pCR) was seen in 4/12(33.33%), pathologic microscopic foci in 2/12 (16.66%) and pathological macroscopic partial response was in 6/12 patients(50%).5 of 9 patients (55.55%) with biopsy proven inguinal lymph node metastases showed no residual lymph node in the specimen.

Conclusions : Neoadjuvant chemoradiotherapy followed by radical surgery seems to be effective and promising strategy for locoregionally advanced squamous cell carcinoma of vulva.The present article details a single institution study aimed to evaluate the efficacy of these approaches in reducing the need for more radical surgery in locally advanced vulvar cancer.

KEYWORDS

Empowerment Education, Development

Introduction

Vulvar carcinoma is an uncommon gynecological cancer. In early stage vulvar carcinoma, surgical resection with curative intent is the preferred treatment. In squamous cell carcinoma of vulva, patients with locally advanced disease with close proximity to the urethra, vagina, rectovaginal septum or anal margin are treated primarily with surgery which include exenteration with colostomy or urinary diversion.Thses patients generally experience high recurrence rates, operative mortality and a poor 5-year survival. There is significant physical and psychological morbidity resulting from these procedures due to extensive nature of the surgery (1).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 and severe acute skin reactions were common (2).Combined approaches, including preoperative radiation with or without chemotherapy is an accepted way to treat these patients to shrink tumors and minimize the extent of surgery.This potentially reduces morbidities and has shown good results and thus is considered the treatment of choice for locoregionally advanced diseases (3-5).Better understanding of radiobiological principles has led to refinement in radiotherapeutic techniques, resulting in improved efficacy and decreased toxicity of vulvar cancer radiotherapy. Late complications may be lessened by the use of smaller fraction size (5).

We report the results of a pilot study on concurrent chemoradiotherapy followed by radical surgery in a series of 16 patients with locally advanced squamous cell carcinoma of vulva.

Methods and Material

16 patients with a diagnosis of locally advanced squamous cell carcinoma of vulva were recruited for the pilot study during June 2014 through December 2016.Locally advanced tumors which were either bulky primary masses and/or clinically positive lymph nodes or those requiring extensive surgery that would have involved resection of urethra, vagina or anus with or without colostomy or urinary diversion were included.Exclusion criteria were previous history of chemotherapy or radiotherapy, pre-existing cardiac disease or diabetes, inoperability for poor medical conditions, presence of distant metastases and histology other than squamous cell carcinoma. The mean age of patients was 65 years (range:50-80 years). Karnofsky Performance status was above 70. Pretreatment work-up was done which included electrocardiogram, chest X-ray, liver and renal function tests and complete blood count.Prior to treatment, all patients underwent pelvic clinical examination under anaesthesia and transabdominal ultrasound, to exclude any other concurrent genital diseases.All lesions were biopsy proven and fine-needle aspiration biopsies were obtained whenever enlarged or hardened inguinal nodes were palpated. All patients were evaluated at regular intervals to assure the tolerability of radical course of chemoradiation therapy followed by surgical resection.

The stage of the disease for the 16 patients, stage II-IVA (stage II, n=5, stage III, n=9, stage IV, n=2) according to the UICC TNM

classification is shown in table 1. The parameter used to assess clinical response was the maximal diameter of the primary tumor and involvement of (or proximity to) adjacent pelvic structures. The median pre-treatment tumor size was 5.0 cm in its largest dimension, ranging from 3.0 cm to 10.0 cm.6 patients had urethral involvement, 6 patients had involvement of lower vagina and 4 patients had involvement of anal verge at the time of presentation.Inguinal lymph nodes were palpable in 9 out of 16 (56%) patients.

Table 1- Staging distribution of recruited patients

TNM	STAGING	No.
T2N0	II	5
T2N1	IIIA	4
T3N1	IVA	3
T3N2	IVA	2
T3N0	IVA	2

Preoperative treatment

The treatment protocol included a preoperative phase in which radiation therapy and chemotherapy were given concurrently.All patients were judged eligible for surgery 3 weeks after the conclusion of neoadjuvant therapy.The chemoradiotherapy schedule was the following: chemotherapy cisplatin 40 mg/m2 was given intravenously weekly with radiotherapy. In patients with renal impairment, carboplatin (AUC 2 or flat dose 150 mg/m2 was given.The target of irradiation was the vulvar region with perineum and the lower and middle pelvis, including inguinal and external iliac lymph node chains. Two anteroposterior and posteroanterior opposed fields were used, and a daily dose of 1.8 Gy was given upto a total dose of 45 Gy in 25 fraction, calculated at midplane, in 5 weeks, with a 6 MV linear accelerator. Field shaping was permitted to spare uninvolved normal tissues. 10 patients received concurrent chemoradiotherapy upto 45 Gy in 25 fraction, 2 patient received only radiotherapy to the dose of 30 Gy in 10 fractions and 4 patients received neoadjuvant chemotherapy. All 4 patients showed suboptimal response to chemotherapy Out of these, 3 patients received concurrent chemoradiotherapy upto 45 Gy in 25 fractions and one patient refused for further treatment.All patients completed the planned course of preoperative chemoradiation treatment. The treatment was well tolerated and the expected acute desquamative skin reactions in the vulva and perineum were seen in all patients.

After 3 weeks of preoperative treatment, patients were assessed for surgery.They were reexamined clinically and if judged to be eligible for surgery, a complete preoperative laboratory check-up was performed.Deep venous thrombosis and pulmonary embolism were prevented by means of subcutaneous heparin administration in cases of leg varicosities. Heparin (5,000 IU) was given subcutaneously beginning 24 hours before surgery until the seventh postoperative day.

Surgery

Patients in clinical complete remission and those in partial remission were deemed eligible for surgery.Out of the 16 patients, 13 patients had complete response and partial response >50%. 12 patients underwent surgery after neoadjuvant treatment and 1 patient refused to continue the further treatment after neoadjuvant chemo-radiotherapy. The remaining 3 patients out of 16 patients who showed <50% partial clinical remission completed the radiotherapy dose upto 60Gy.This was administered through reduced anteroposterior, posteroanterior and/or a direct perineal portal with low energy photon beam calculated at the midplane of the residual primary tumor. The status of patients at last follow-up was studied.

Evaluation

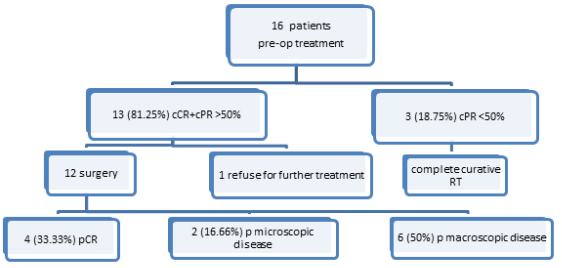
Clinical complete response (cCR) was defined as no visible or palpable tumor, while clinical partial response (cPR) was defined as residual tumor comprising less than 50% of the original tumor volume. Pathological complete response (pCR) was defined as no invasive tumor within the post-treatment pathology specimen, while pathological partial response (pPR) was defined as residual disease in the pathological specimen. Toxicity was graded using the RTOG morbidity-scoring criteria and evaluated weekly by physician.

Results

There were 16 eligible patients evaluable for toxicity and therapeutic efficacy after neoadjuvant treatment.

Pre-operative neoadjuvant treatment

CT scan and clinical examination were used for staging primary disease and lympy nodes. The responses to neo-adjuvant treatment were as follows: 5 patients (31.25%) showed complete clinical remission, 8 showed (50%) partial remission >50%, 3 (18.75%) had partial remission<50% and progression was not observed in any patient. Overall, preoperative treatment led to marked shrinkage of the primary tumor (complete responses and partial responses >50%) in 13 of 16 patients (81.25%)



Surgical Treatment & Node Dissection

12 of 13 patients underwent radical vulvectomy plus bilateral inguinal lymphadenectomy and 1 patient refused for surgery. Among the 5 patients with clinically complete response, histologic examination of the specimens revealed 4 patients with complete pathologic response and only microscopic neoplastic foci in 1 patient.Overall, the pathologic complete response rate was 4/12 (33.33%), pathologic microscopic foci in 2/12 (16.66%) and pathological macroscopic partial response was 6/12 (50%).

All Patients submitted to surgery underwent bilateral inguinal lymphadenectomy. The procedure included the dissection of superficial and deep inguinal lymph nodes. Mean number of lymph nodes removed per groin was 7 (range: 4-12). Inguinal lymph node involvement was bilateral in 1 patients and unilateral in 3 patients, so 4 of 9 patients with pathologically involved lymph node. It is noteworthy that inguinal lymph nodes were free of tumor in 5 of the 9 (55.55) patients with lymph node involvement previously ascertained by means of fine needle aspiration biopsy.

Toxicity Evaluation & Surgical Morbidity

In no patient did the preoperative treatment have to be interrupted, so all 16 patients were assessable for response and toxicities. The neoadjuvant treatment was completed within the expected 5 to 6 weeks in 14 patients, and treatment was delayed in 2 patients due to myelotoxicity.Radiation therapy was relatively well tolerated. The only acute toxic effects reported were moderate, transient perineal inflammatory reaction, proctitis and cystitis, which were observed in 15 patients.These were controlled with topical treatments, including corticosteroids and antimycotics. No patient had grade 3 chronic gastrointestinal and genitourinary toxicity.The radiation therapy was seen in postoperative morbidity in 10 out of 12 patients.

Mean hospitalization for patients undergoing surgery was 26 days (range: 15-45 days). There was no major intraoperative complications possibly related to the preoperative chemoradiotherapy treatment. The postoperative complication rate was 83.33% (10/12). There were 8 patients with necrosis and dehiscence of the inguinal (5 patients) and vulvar (3 patients) and 2 patients required colostomy.6 out of 10 patients had prolonged lymphorrhea.

Discussion

Locally advanced vulvar carcinoma poses a challenge in gynecologic oncology because in the radical surgery is hampered by the size and /or the site of the tumor. According to UICC TNM guidelines for clinical staging, most of these patients would be staged T3-4 N1-2. In the early stages, the involvement of the distal urethra, anal verge or the vagina guarantees adequate surgey with margins without undue morbidity. However,the involvement of the anus, rectum, rectovaginal septum or the proximal urethra, exenterative surgery is the treatment of choice.This entails the risk of severe post-surgical complications and poor quality of life..Many early reports demonstrated that vulvar cancer is sensitive to radiation therapy and numerous studies have shown the feasibility of preoperative chemoradiation therapy followed

by less extensive surgery in the locally advanced patients.(6,7).

For these reasons, alternative approaches including exclusive or preoperative radiation with or without chemotherapy have been investigated. In advanced vulvar cancer, exclusive radiotherapy with different doses has been used by several authors with controversial results.In 1982, Boronow et al reported 26 primary cases of advanced carcinoma vulva treated with a combined radiation surgical approach.There was only one case of local recurrence, and no patient required a pelvic exenteration. 17 (65%) patients were alive 1-11 years post therapy without recurrence(8).A follow-up of this study in 1987 showed good local control in 32 of 37 patients (86%) with stage III and IV disease, otherwise destined for exenterative procedures (9).Hacker and colleagues described the use of preoperative external beam therapy in patients with advanced vulvar cancer, followed by limited surgical resection and in 50% of cases, there was no residual disease in surgical specimen after preoperative treatment of 4400-5400 cGy .5 patients (62.5%) were without evidence of recurrent cancer with 15 months to 10 years of follow-up (10).Good results were also reported from a Gynecologic Oncology Group study in 1986 (11) but in contrast, some studies with poor results were those by Helgason et al in 1972 and Pirtoli and Rottoli in 1982.(12,13). The advantages of this combined therapeutic approach used in these studies over exenterative surgery included bladder and/or rectal preservation, lower perioperative mortality and morbidity and good local control, particularly in patients with lymph node metastases. Based on these promising results, it seemed desirable to further investigate preoperativee radiation therapy in patients with locally advanced vulvar cancer.

Thomas et al used this approach both in the primary therapy and adjuvant setting. Among 9 patients who received the combined treatment as primary therapy, a complete response was achieved in 6 (66.6%) (14). Berek et al obtained complete tumor response in 8 of 12 stage III-IV patients (67%) treated with concurrent cisplatin and 5-fluorouracil chemotherapy and radiation therapy(15).Another study by Russell et al included 25 patients with primary or recurrent squamous cell carcinoma of vulva.A complete clinical response was achieved in 20 of 25 patients (80%) but the drawback was that the design of the study did not include surgical intervention after the chemoradiotherapy.(16) Our study showed pathological complete response of 33.33% and this is in accordance with other studies of preoperative chemoradiation treatment by the Gynecological Oncology group (GOG-101) that demonstrated that preoperative 5-FU (1000 mg/m2 over 4 days) and bolus cisplatin (50 mg/m2) on the first day with twice daily radiation therapy to a dose of 47.6 Gy delivered in a split course fashion resulting in a pCR rate of 31% (7).

The results of this pilot study seem to confirm the feasibility and the tolerability of the combined chemoradiotherapeutic regimen adopted. In fact, all but 3 of the nonresponding patients completed the scheduled treatment with managable adverse effects .15 out of 16 patients developed acute reactions which were managed conservatively.2 patients developed myelotoxicity.In GOG 101, grade 3 cutaneous, intestinal, hematologic, and bladder side effects were seen in 53%, 5.4%, 4%, and 1.4%, respectively (7). Regarding the postoperative morbidity in our study, post-operative complications rate was 83.33% (10 out of 12 patients) and wound complication rate was 25% (3 of 12 patients).This was comparable to several primary surgical series reporting 20% to 47% risk of wound breakdown with radical and modified radical vulvectomy .Regarding to response rate, an objective response rate (complete and partial response >50%) of 81.25% (13 of 16 patients) and pathologic complete response rate of 33.33% (4 of 12 patients) were observed. The good response to combined treatment rendered radical surgery possible in 81.25 % of patients, avoiding exenterative procedures in all patients.Analysing the nodal disease, there was no sign of nodal involvement in the pathologic specimen of 5 out of 9 patients (55.55%) with inguinal lymph node metastases ascertained upon entry in the study by means of fine needle aspiration biopsy.The preliminary results of the GOG 205 trial show improved pCR rates to 45% when escalating the dose to 57Gy at 1.8 Gy per fraction. A future GOG study is looking at incorporating gemcitabine along with cisplatin with increased total dose to 64 Gy, with the goal of further improving pCR rates(17). Regarding survival and recurrence in our series, follow-up was inadequate for conclusive analysis.

Our data demonstrates a good sensitivity of squamous cell carcinoma of vulva to the chemoradiotherapeutic regimen although due to limited number of patients and reduced follow-up period, it is difficult to comment on the definitive value of the combined approach.However, these results can be confirmed in larger controlled series with an adequate follow-up time. Another upcoming approach in radiotherapy involves using highly conformal treatment like IMRT (Intensity-modulated radiation therapy) which helps in reducing dose to normal tissues such as the small bowel, bladder and rectum and eliminating dose modulation across the overlapping region. A Study dne by Beriwal et al(18,19) showed that pre-operative chemoradiotherapy by IMRT resulted in pCR rate of 48.5% and no patient had grade>3 chronic gastrointestinal or genitourinary toxicity. The dosimetric advantage of IMRT in reducing skin dose translates into lower risk of skin toxicities in groin region(18,19).

Conclusion

The incidence of vulvar carcinoma is low and it is difficult for any single institution to have sufficient number of patients to do a meaningful prospective trial. However, prospective and multicenter clinical trials with sufficient number of patients and follow-up are necessary to determine the appropriate regimen of neoadjuvant therapy to be given in locally advanced cases.Our pilot study is an effort in this direction and more studies with larger number of patients are required to ascertain the results.Pathologic complete response continues to predict for better outcome and newer strategies should focus on improving responses by dose escalation and newer systemic agents.

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