Treatment Outcome of Women with Vulvar Cancer Treated in Bangladesh

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Abstract: Vulvar cancer has not been well studied in Bangladesh. This retrospective review reports on the experience of ten women with vulvar cancer who were treated at the National Institute of Cancer Research Hospital and Delta Private Hospital from October 2010 through March 2011. Survival was analyzed by age, stage and grade of the cancers. The ages of ten women with vulvar cancer ranged from 45 years to 70 years with a median of 59 years. The majority of patients (nine) presented with stage III disease. One patient had a stage II cancer. Nine women had squamous cell cancers and one had an adenocarcinoma of the Bartholin's gland. All patients underwent surgery and nine underwent either preoperative or postoperative radiation therapy. At 24 months of follow-up, eight patients are currently alive and disease free.

Key words: Vulvar cancer, squamous cell cancer of the vulva, surgery and radiation for vulva cancer.

1. Introduction

Vulvar carcinoma is a rare malignancy worldwide. It accounts for only 3.5% of all gynecologic malignancies [1]. Vulvar cancer is reported to be a disease of older women with an average age at diagnosis of 67 years. Over the past decade there has been an increase in vulvar intraepithelial neoplasia (VIN) and VIN-related invasive vulvar cancer in women younger than age 50 years due to its association with Human Papillomavirus (HPV) infections worldwide [2]. In one study utilizing specimens from 39 countries, 2,296 cases of vulvar neoplasia were analyzed for HPV subtypes [3]. They found that 587 were VIN and 1,709 were invasive vulvar cancers (IVC). HPV-DNA was detected in 86.7% and 28.6% of the cases respectively. HPV-related IVC cases had the highest prevalence in younger women [3].

The incidence of vulvar cancer in Bangladesh is unknown. Women with vulvar cancer commonly come

to medical attention when their cancers are advanced. The cultural and social reasons are complex and include missed diagnoses, embarrassment and denial [2]. This report reviews the demographics, cancer variables, and treatment of women treated at the National Institute of Cancer Research and Hospital (NICRH) and Delta Private Hospital in Dhaka Bangladesh. The purpose of the study is to review the management options for women with vulvar cancer and to identify the unique challenges encountered in the management of their malignancies.

2. Materials and Methods

Ten women with vulvar cancer were cared for at either NICRH or at Delta Private Hospital between October 2010 and March 2011. Their records were reviewed and information about their age, stage of disease, histological type, grade of the cancer, type of surgical treatment and radiation therapy were recorded. The decision about the specific therapy for each patient was discussed at the respective NICRH and Delta Hospital tumor boards. The FIGO staging system was

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used for all patients [4]. Table 1 summarizes the 2009 modification of the FIGO staging system for vulvar cancer [5].

An algorithm for therapeutic intervention was developed and is shown in Table 2. Early stage disease is defined as stage I and II cancers. Advanced stage disease is defined as advanced stage disease.

Treatment included vulvar surgery, local and regional radiation, or radiation with chemo-sensitization. The goal of surgery was to accomplish the complete resection of the cancer with a 1 cm margin. The technique of radical resection included resection of the tumor and removal of the deep vulvar skin appendages down to the level of deep urogenital diaphragm.

External beam radiation was given either with a linear accelerator or with a cobalt machine. 180-200 cGy was used per fraction for 5 weeks in both groin and pelvis. The para-aortic region was not included. Cisplatin at a weekly dosing of 35 mg per metered squared was used as the radiation sensitizer.

After completion of therapy, patients were seen at an initial six week postoperative examination and then followed by examinations every three months.

3. Results

Ten patients were treated from October 2010 through March 2011. The age range of the ten patients

was 45 years to 70 years with a median of 59 years. One patient presented with stage II disease. Nine patients received a diagnosis of stage three vulvar cancers. Table 3 summarizes the stage, nodal status and histologic features of the ten women with vulvar cancer. The majority of patients had advanced stage disease in 90% of patients and 70% had more than one positive lymph node.

All patients underwent surgical excision of their cancers. Two patients underwent wide local excisions. Eight women were treated by modified radical vulvectomies.

Nine women received either preoperative or postoperative radiation therapy. Five patients received radiation with the cobalt machine and four in the linear accelerator. Seven of these nine patients had concurrent chemotherapy sensitization. Only one patient had surgery alone and no radiation treatment. Table 4 summarizes the experience with adjuvant radiation and chemo-radiation.

Eight women are alive and well after their treatment. One patient developed a local recurrence within six months and is currently alive. One patient died from recurrent cancer within one year of her treatment.

4. Discussion

Due to the rarity of vulvar cancer, there are no large randomized controlled trials to guide the treatment of

Table 1 Carcinoma of the vulva figo staging.

Stage	Description
IA	Tumor confined to the vulva or perineum, ≤ 2 cm in size with stromal invasion ≤ 1 mm, negative nodes
IB	Tumor confined to the vulva or perineum, > 2 cm in size or with stromal invasion > 1 mm, negative nodes
II	Tumor of any size with adjacent spread (1/3 lower urethra, 1/3 lower vagina, anus), negative nodes
IIIA	Tumor of any size with positive inguino-femoral lymph nodes (1) 1 lymph node metastasis greater than or equal to 5 mm (2) 1-2 lymph node metastasis(es) of less than 5 mm
IIIB	(1) 2 or more lymph nodes metastases greater than or equal to 5 mm (2) 3 or more lymph nodes metastases less than 5 mm
IIIC	Positive node(s) with extracapsular spread
IVA	(1) Tumor invades other regional structures (2/3 upper urethra, 2/3 upper vagina), bladder mucosa, rectal mucosa, or fixed to pelvic bone (2) Fixed or ulcerated inguino-femoral lymph nodes
IVB	Any distant metastasis including pelvic lymph nodes

FIGO—federation international gynecology obstetrics.

(Ref.[5]).

Table 2 Treatment algorithm for vulvar cancer at nicrh and delta private hospital.

Disease stage	Treatment algorithm
Early stage disease (stage I and II)	(a) Wide local excision (b) Modified radical vulvectomy with bilateral pelvic lymphadenectomy
Advanced stage disease	(a) Modified radical vulvectomy with bilateral inguinal lymphadenectomy plus RT alone or RT with chemotherapy (b) Preoperative chemoradiation followed by surgery

NICRH—national institute of cancer research and hospital.

RT—radiation therapy.

Table 3 Stage, nodal status and histologic features of the ten patients with vulvar cancer.

Feature	Number of patients (percentage)
Stage	
II	1 (10%)
III	9 (90%)
Histology	
Squamous Cell	9 (90%)
Adenocarcinoma	1 (10%)
Lymph node status	
No nodes involved	1 (10%)
One positive node	2 (20%)
Greater than one positive node	7 (70%)

Table 4 Treatment status of ten women with vulvar cancer*.

Treatment status	Number of patients (percentage)
Preoperative chemoradiation	4 (40%)
Postoperative chemoradiation	3 (30%)
Postoperative radiation	2 (20%)
No adjuvant therapy	1 (10%)

*All patients underwent surgical excision of the cancers. Weekly cisplatin dose was 35 milligrams per square meter body surface area for 7 patients. External radiation using 180-200 cGy per fraction for 5 weeks in both groin and pelvis was given. Para aortic region was not included. The cobalt machine was used for five patients and four were treated in the linear accelerator.

advanced vulvar cancer [6]. Surgical excision of the primary vulvar tumor along with groins node dissection have remained the cornerstone of treatment in vulvar cancer. There has been a trend towards a less radical approach in the surgical management of early stage disease. Except for massively large tumors, complete vulvectomy has been replaced by radical local excision with occasional plastic reconstruction. While complete unilateral or bilateral groin dissection is the standard of care, sentinel node biopsies have been advocated to reduce morbidity in patients who are identified as node negative [6]. The use of sentinel node dissection is now established for melanoma and breast cancer. This technique which limits the number of lymph nodes that are removed reduces the risk of

postoperative lymphedema. Conversely, when metastatic cancer is identified by sentinel node biopsy, a full lymphadenectomy is necessary.

In patients with advanced primary disease, treatment decisions are still a challenge. Adjuvant radiotherapy with or without concurrent chemotherapy is commonly instituted for patients with nodal metastasis [7].

The risk of lymph node metastases increases with age, greater tumor size, deeper invasion and higher tumor grade. One center evaluated 23 patients who developed disease recurrence (61% vulva, 35% groins, and 4% both) over a 36 month follow up period [8]. They identified a significant reduction in survival compared with node-negative patients and noted that disease-free patients after 2 years were as follows: 88%

in node-negative patients; 60%, 43% and 29% in patients with 1, 2 and >2 affected nodes, respectively ($P < 0.001$). They also reported that the effect of positive nodes differed significantly dependent on adjuvant treatment ($P = 0.001$). When patients did not receive adjuvant radiotherapy to the groins and pelvis, the number of metastatic nodes was highly relevant for prognosis. In contrast, for patients who were treated with adjuvant radiotherapy, this survival difference disappeared [8].

Vulvar cancers are commonly diagnosed when they are at an advanced stage because of misdiagnosis or because of cultural barriers. In the United States, the SEER (surveillance epidemiology and end results) database identified 7,973 women with vulvar cancer over a 35 year period [1]. Minority women, especially African American women, had a greater chance of having advanced disease. This may reflect disparities of care based on socioeconomic status and access to healthcare in the United States.

The Bangladesh experience shows that no woman was diagnosed with a stage I cancer and only one woman had negative lymph node metastases. This again may reflect the health care challenges in Bangladesh. In Bangladesh, the five most common cancers affecting women, in order of prevalence, are cervical, breast, ovarian, colo-rectal and stomach [9].

For women in Bangladesh, a predominantly Muslim society, there are issues of modesty and reluctance to be examined by male physicians. Poor women face the barriers to care that are common to other resource-poor areas but specific socio-cultural practices create unique difficulties as well. There is high illiteracy rate of 70% among poor women in Bangladesh. As husbands are the major decision makers and control the household finances, women frequently need their husbands' approval for most activities and to obtain healthcare. Women with cancer may be viewed as "bringing a curse to the family" and this can compound fears of disclosing a cancer diagnosis [10]. For instance, rural women with breast disease feared that their husbands

would abandon them if they found out that they had cancer [11].

There is sparse information on vulvar cancers in Bangladesh and there is limited information on vulvar cancer in south central Asia in general. There have been two retrospective case reviews from India and only one case report from Bangladesh. The first and only report on vulvar cancer from Bangladesh in 2009 described one 21 year old patient with a verrucous squamous cell carcinoma of the vulva [12].

Investigators from India reviewed their experience with vulvar cancer from 1998-2005 in a New Delhi Hospital [13]. Of the 60 women with vulvar cancer, the majority presented with advanced stage. The age ranged from 24 years to 92 years with a median 63 years. FIGO stage distribution was as follows: stage I: 2 patients; stage II: 17 patients; stage III: 31 patients; stage IV: 9 patients; and unknown stage: 1 patient. Thirty-three patients underwent surgery (wide local excision—3, radical vulvectomy—30). Eleven patients received postoperative radiation therapy, 12 received palliative radiation therapy (RT) and 15 underwent definitive RT (5 of them also received concurrent chemotherapy). The median follow-up period was 23 months (range 2-144 months). The 5-year overall survival for all stages was 41% [13].

Another retrospective review from Bangalore, India identified 37 cases of carcinoma of the vulva presenting between 1996 and 2000 [14]. Thirty-five percent of their patients also had advanced disease (Stage III, four patients; Stage IV, nine patients). The surgical treatment in 33 patients consisted of wide excision in one case, radical vulvectomy (RV) in six cases, radical vulvectomy and bilateral groin node dissection in 25 cases and radical vulvectomy and unilateral groin node dissection in one case. Nine of these 33 women with very large cancers also received adjuvant chemotherapy preoperatively to achieve better tumor-free surgical margins. Eight of the patients who received preoperative chemotherapy had a partial response and one case achieved complete response.

Histologically, the surgical margins were free in all these patients. One patient received neoadjuvant radiotherapy to the vulva and pelvis followed by radical vulvectomy and bilateral groin node dissection, which also revealed no residual tumor. Thirteen of the 26 patients (50%) who underwent groin dissection had inguinal node metastases. All the patients with negative nodes were free of disease while three of four patients with Stage III and two of nine patients with Stage IV with nodal metastases remained free of disease. The only patient with Stage III disease plus inguinal node metastases who recurred had multiple positive nodes with extracapsular spread [14].

In summary, the Bangladesh experience reported here mirrors the Indian experience with a younger cohort of women who predominantly are diagnosed at late stage. These women require both radical surgery and radiation with chemotherapy sensitization for the adequate treatment of their cancers.

5. Conclusions

This is the first case series of vulvar cancers reported from Bangladesh. Women in this cohort were younger and all had advanced disease. With an aggressive treatment program of radical surgery followed by radiation therapy plus chemotherapy, the survival rate has been high. The next important goal for cancer care for women in Bangladesh will be earlier detection of vulvar and anogenital cancers. Early stage vulvar cancer carries both a lower risk of nodal metastases and cancer-related death and a reduction in surgical disfigurement from large surgeries.

References

- [1] J.A. Rauh-Hain, J. Clemmer, R.M. Clark, L.S. Bradford, W.B. Growdon, A. Goodman, et al., Racial disparities and changes in clinical characteristics and survival for vulvar cancer over time, *American Journal of Obstetrics Gynecology* 209 (5) (2013) 468.e1-468.e10.
- [2] Z. Kutlubay, B. Engin, T. Zara, Y. Tüzün, Anogenital malignancies and premalignancies: Facts and controversies, *Clinics in Dermatology* 31(4) (2013) 362-373.
- [3] S. de Sanjosé, L. Alemany, J. Ordi, S. Tous, M. Alejo, S.M. Bigby, et al., Worldwide human papillomavirus genotype attribution in over 2,000 cases of intraepithelial and invasive lesions of the vulva, *European Journal of Cancer* 49 (16) (2013) 3450-3461.
- [4] S. van der Steen, H.P. de Nieuwenhof, L. Massuger, J. Bulten, J.A. de Hullu, New FIGO staging system of vulvar cancer indeed provides a better reflection of prognosis, *Gynecologic Oncology* 119 (3) (2010) 520-525.
- [5] D.G. Mutch, The new FIGO staging system for cancers of the vulva, cervix, endometrium, and sarcomas, *Gynecologic Oncology* 115 (2) (2009) 325-328.
- [6] L. Woelber, L. Kock, F. Giesecking, C. Petersen, F. Trillsch, M. Choschick, et al., Clinical management of primary vulvar cancer, *European Journal of Cancer* 47 (15) (2011) 2315-2321.
- [7] S. Mahner, F. Trillsch, L. Kock, D. Rohsbach, C. Petersen, A. Kruell, et al., Adjuvant therapy in node-positive vulvar cancer, *Expert Reviews of Anticancer Therapy* 13 (7) (2013) 839-844.
- [8] L. Woelber, C. Eulenburg, M. Choschick, A. Kruell, C. Petersen, F. Giesecking, et al., Prognostic role of lymph node metastases in vulvar cancer and implications for adjuvant treatment, *International Journal of Gynecologic Cancer* 22 (3) (2012) 503-508.
- [9] S.I. Talukdar, M.A. Haque, M.O. Alam, M.H. Huq, M.S. Ali, C.R. Debnath, et al., Histopathology based cancer pattern in Mymensingh region of Bangladesh, *Mymensingh Medical Journal* 16 (2) (2007) 165-169.
- [10] S. Dein, Attitudes towards cancer among elderly Bangladeshis in London: A qualitative study, *European Journal Cancer Care* 14 (2) (2005) 149-150.
- [11] H.L. Story, R.R. Love, R. Salim, A.J. Roberto, J.L. Krieger, O.M. Ginsburg, Improving outcomes from breast cancer in a low-income country: Lessons from Bangladesh, *International Journal of Breast Cancer* 2012 (1) (2012) 1-9.
- [12] N. Kabir, I. Ara, A. Ahmed, A.U. Muhsin, Verrucous carcinoma of vulva, *Mymensingh Medical Journal* 16 (2) (2007) S53-S56.
- [13] D.N. Sharma, G.K. Rath, S. Kumar, N. Bhatla, P.K. Julka, P. Sahai, Treatment outcome of patients with carcinoma of vulva: Experience from a tertiary cancer center of India, *Journal of Cancer Research and Therapeutics* 6 (4) (2010) 503-507.
- [14] U.D. Bafna, U.M. Devi, K.A. Naik, S. Hazra, N. Sushma, N. Babu, Carcinoma of the vulva: A retrospective review of 37 cases at a regional cancer centre in South India, *J. Obstet Gynaecol.* 24 (4) (2004) 403-407.