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10. The role of cytoreductive surgery in vulvar cancer. Is there an indication for aggressive surgical approach in FIGO Stage III/IV disease?

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Abstract. Primary surgery remains the treatment of choice for patients presenting with early stage vulvar cancer. Radiation therapy for early stage disease is generally restricted to patients with close or involved margins or positive nodes.

In patients with locally advanced vulvar cancer, surgery may involve very radical procedures, possibly requiring the permanent diversion of the urinary and/or faecal stream to achieve adequate surgical margins. Where the extent of the primary tumour or groin node metastases, render the tumour inoperable, chemoradiation may be considered for primary treatment. In some circumstances surgery at a later date may be appropriate. This approach reduces the morbidity of surgery and avoids the physical and psychological morbidity of loss of bowel and/or bladder function.

However there is evidence that the complications of neoadjuvant therapy may outweigh those of exenterative surgery. There may be an argument for primary exenterative surgery in well selected patients with locally advanced disease. Management of these patients is difficult, and will need to be tailored according to their individual needs.

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Introduction

Although carcinoma of the vulva is uncommon, representing only 5% of gynaecological cancer (1) its location within close proximity of urethra and anus can result in very difficult therapeutic challenges when locally advanced disease occurs. Although vulvar cancers are “surface” cancers and therefore readily available for clinical examination, advanced disease (FIGO Stage III or IV) occurs in 30 to 40% of cases at diagnosis. From a surgical perspective, those cases in which a standard radical vulvectomy cannot remove the primary tumour with an adequate margin are considered to be locally advanced. These cases are not infrequently associated with extensive and unresectable groin and pelvic node metastases.

Assessment of patients with vulvar cancer must include careful evaluation of nodal areas, midline structures and whether there is any involvement of urethra, anal sphincter, vagina and pubic bone. Examination under anaesthesia should be performed to determine the feasibility of adequate resection, keeping in mind the need for an adequate margin, that is at least 1cm. It may be helpful to have the radiation oncologist and reconstructive surgeon attend the EUA. Preoperative imaging with CT or MRI, and PET/CT should be considered in order to exclude as far as possible distant spread of disease.

For patients with early stage vulvar cancer, surgical management has become less radical in an effort to reduce the treatment toxicity for these patients without detrimental effect on overall survival.

Stanley Way was the first to describe the radical en bloc vulvectomy with groin node dissection using the butterfly incision which has been modified since (2). Radical en bloc vulvectomy was the standard treatment for all patients with vulvar cancer before the introduction of the less radical local excision which conserves more vulvar skin and makes primary closure easier. The current trend is to perform a radical local excision of the primary tumour in combination with inguofemoral lymphadenectomy with separate incisions. Data from observational studies suggest that excision of early lesions with a good margin all around, including the deep margin, does not change the overall survival compared to more radical procedures but does reduce the incidence of post operative wound breakdown and infection(3). The modified radical vulvectomy that is performed currently for women with early vulvar cancer currently aims to ensure a good margin of 1cm all around(8mm for pathology specimen) with the depth of excision taken down all the way to the deep fascia, the inferior fascia of urogenital diaphragm and periosteum of pubic bone. If inguinal nodes are to be removed they are done with separate incisions. Whether ipsilateral or bilateral inguinal

lymphadenectomy is performed depends very much on the site and size of the primary vulvar tumour. Superficial and deep inguinal nodes should be removed, as one prospective trial showed an increased rate of groin recurrence in patients with only superficial node dissection performed (4). Alternative approaches such as sentinel node biopsies are under investigation to help reduce the morbidity of lymphoedema associated with a complete inguinal lymphadenectomy. It is not yet the accepted standard of treatment as the margin for error is narrow and groin recurrences are often fatal (5-8).

Pelvic lymphadenectomy is rarely performed these days unless there are large bulky nodes which will need to be removed. A GOG trial has confirmed that there is no survival advantage in patients having a pelvic lymphadenectomy compared to patients having the pelvic area irradiated(9). Based on the pathological findings and prognostic factors from the surgical specimen obtained, the patient may receive adjuvant radiotherapy either to the primary area from where the tumour was excised (if the excision margins are narrow), to the groins and pelvic area if more than 2 micro metastatic ($\leq 5\text{mm}$) deposits in the lymph nodes, one macroscopic involvement of a lymph node ($\geq 10\text{mm}$) or capsular involvement is found(10-12).

Ultra radical surgery

While the treatment of patients with early vulvar cancer has been well defined, the treatment of patients with advanced vulvar cancers (stage III & IV) is not as straight clear. One of the therapeutic options for patients with locally advanced disease has been radical excision of the primary tumour and draining lymph nodes, with the excision extended to include involved adjacent organs such as the bladder or bowel, effectively converting the surgical procedure to some type of exenteration. Such radical procedures, when planned have to consider both the radical excision, which must clearly be feasible with a very high probability of ensuring adequate, indeed generous, margins, and the reconstruction required.

In patients with locally advanced disease, surgery may require not only an en-bloc radical vulvectomy and bilateral inguinofemoral lymphadenectomy, but also some kind of resection of urethra, vagina or anus, up to and including major exenterative surgery. In such circumstances the postoperative complications can be extremely severe and result in death or severe and permanent functional impairment. Furthermore, such ultraradical procedures may require extensive and complex reconstructive procedures, resulting in long hospital stay, multiple operations and significant disruptions to the patient's life, not to mention the high medical cost(13). Despite all the

problems associated with this procedure it still remains an important option for treatment for women with advanced stage vulvar cancer.

Combined therapy approaches

The difficulty of treating surgically patients with locally advanced vulvar cancer and the high morbidity and even mortality associated with exenterative surgery prompted efforts to limit the extent of the surgical procedures needed to control disease. (14,15). Boronow et al. in 1973 was the first to describe the use of a combined radiosurgical approach for patients with advanced vulvar cancer. He described the use of brachytherapy in the form of intracavitary radium alone or with the combination of teletherapy for internal genital disease and then surgery in the form of radical vulvectomy and bilateral inguinal lymphadenectomy (14). In 1984 Hacker et al described 8 patients treated with pre operative external radiation 44 to 54 Gy with one patient receiving brachytherapy in the dose of 24Gy. Satisfactory shrinkage of tumor occurred in seven of the eight patients (87.5%) thus allowing conservative surgical excision. In four of his patients (50%) there was no viable tumour left in the surgical specimen (16).

Another therapeutic option is combined chemoradiation pre operatively to shrink the tumour and then reassess operability. This approach is based on data obtained from studies of patients with anal and cervical cancers treated by this multimodality approach. A phase II GOG trial using preoperative radiation with concurrent cisplatin/5 fluorouracil concluded that the therapy is feasible and its use decreased the need for more radical surgery including primary pelvic exenteration(17). Although chemo radiation is increasingly becoming the preferred option of treatment for patients with advanced vulvar cancer, it is not without toxicity. A significant proportion of women who receive this treatment will suffer long term problems with perineal pain, radiation necrosis to the vulvar skin, lymphoedema, lymphorrhea and secondary radiation effects to bowel and bladder. A recent Cochrane meta analysis has cautioned that the use of combination chemoradiation in treating these patients results in significant toxicity which may be as disabling as that of primary radical surgery (18).

In our unit the patients presenting with advanced vulvar cancer undergo careful evaluation and treatment is individualized. The type of treatment recommended depends very much on the patient's age, co-morbidities, site, size and the extent of the primary tumour and the presence of demonstrable metastatic lesions. Surgery is the preferred treatment for patients presenting with primary tumors that can be excised with adequate margins. In patients where the recommended pathological margin of 8 mm cannot be achieved,

the primary tumor can still be surgically excised so long as the sphincter function can be preserved. Excision of these tumours may improve quality of life and will reduce the bleeding, discharge and foul odor transmitted from these tumors which can be very distressing for these patients. Where surgical margins are narrow, adjuvant radiation can be given to these areas. The inguinofemoral nodes should be assessed clinically and with imaging (CT abdomen and pelvis and preferably PET/CT) before surgery. If enlarged nodes are felt clinically or detected by imaging in the groin area, then excision of these large nodes and frozen section is undertaken without proceeding to a full lymphadenectomy if metastatic cancer is confirmed. This will help to reduce the morbidity of lymphoedema post radiotherapy.

Currently chemoradiation is the treatment of choice in patients presenting with primary tumors that cannot be excised without preserving sphincter function. This is also the case in patients presenting with ulcerated fixed nodes. After primary treatment with chemoradiation the primary tumour and the groin nodes are assessed for operability. Debulking of large pelvic nodes should be considered before performing radiotherapy in patients with stage IV disease. These patients usually have a poor prognosis and radiation alone to the pelvic nodes without debulking the large nodes may not change the final prognosis.

In conclusion, surgery remains a vital component in the treatment of vulvar cancer. Unfortunately the radicality of surgery for patients with stage III and IV is associated with significant complications. There is no difference in overall survival, progression free survival and recurrence rate in patients treated with primary surgery or primary chemoradiation(19). The trend of management currently has shifted towards less radical surgery and this has been made possible with the use of chemoradiation as the primary treatment for patients with advanced cancer.

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