BARTHOLIN'S GLAND CARCINOMA

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ABSTRACT

Accounting for less than 5% of all vulvar malignancies, primary carcinoma of the Bartholin gland is a rare pathology. Adenocarcinomas or squamous cell carcinomas are the most common histologic types. Diagnosis is made in many symptomatic cases after resection of what was thought to be a Bartholin's cyst or abcess. Surgical options, depending of the extension of the disease, include radical local excision, radical hemivulvectomy and radical vulvectomy with or without inguinofemoral and pelvic lymphodissection. Adjuvant radiotherapy, in selected cases, may decrease the rate of recurrence.

Keywords: Bartholin gland, vulvar cancer, adenoid cystic carcinoma, radical vulvectomy, recurrence

INTRODUCTION

Vulvar carcinoma is the fourth most frequently malignancy of the female reproductive tract. Among vulvar neoplasms, 0.1% to 5% are of Bartholin gland origin, less than 1% of the neoplasms of the female genital tract (1).

The Bartholin glands are paired glands, not palpable, situated in the labia minora in the 4 – and 8 – o'clock positions. Each gland secretes mucus into a duct that emerge onto the vestibule at either side of the vaginal oriffice. The gland is composed of columnar epithelium and the ducts are lined by stratified squamous epithelium, which become transitional cell epithelium toward their terminal parts (2). Histologic classification of the neoplasms of Bartholin gland includes: scuamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma, adenoid cystic carcinoma, transitional cell carcinoma, small cell carcinoma, sarcoma (3). The two major histological types, squamous cell carcinoma and adenocarcinoma, account for 80% to 90% of the cases. Squamous cell carcinoma usually arises from vestibular orifice or at transition zones; human papilloma virus infection, particularly with HPV type 16, has been identified as a contributing factor in its carcinogenesis (4). Adenocarcinoma usually arises at transition zone or from mucin producing acini (5). Adenoid cystic carcinoma exhibits the classic "cribriform" adenoid cystic pattern, characterized by anastomosing cords of cells, surrounding acellular spaces (6). Immunohistochemistry may be needed for a more precise diagnosis and the tumor cells stain positively for smooth muscle actin, S100, smooth muscle myosin, vimentin, CD 117 and MYB (7). Ever since the first documentation by Klob in 1864, only approximately 350 cases of adenoid cystic carcinoma have been reported (8). The infiltration of perineural spaces is another microscopic feature of this type of tumor and many patients experience itching and burning sensations before a mass becomes palpable at physical examination. This pattern may also favour recurrence (9).

DIAGNOSIS

The diagnostic criteria for Bartholin's gland tumors, first published in 1887 by Honan, were revised in 1972 by Chamlin and Taylor: the tumor involving the area of the Bartholin gland is histologically compatible with the origin from the Bartholin gland; areas of apparent transition from normal elements to neoplastic ones are found in histologic study; there is no evidence of primary tumor elsewhere (10).

Bartholin gland tumors are typically solid, well circumscribed, but not encapsulated, with a deeply

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infiltrative pattern of growth and situated in the area of the gland. The size of the primary lesions ranges from 0.5 to 4 cm. (9) The mean age of diagnosis is 49 years, ranging from 25 to 80 years. The most common presentation of a Bartholin gland carcinoma is a painless vulvar mass, but some patients may complain of pain, burning sensation, pruritus, skin decoloration, bleeding or dyspareunia. Symptomatic Bartholin gland masses are often misdiagnosed and mistreated as Bartholin gland cysts or abscesses (11). Bartholin gland enlargement in a postmenopausal woman should raise suspicions of malignancy and a biopsy should be performed since the high local recurrence rate and the tendency for distant hematogenous metastasis (6,11,12). The differential diagnosis for a Bartholin gland tumor most commonly includes cysts, abscesses, and other vulvovaginal disorders, such as vulvar carcinoma, acrochordons, hidradenomas, condyloma acuminata (12).

The rich vascular and lymphatic networks present in the area of Bartholin's gland, explain the common distal metastasis, with lung and bone being the most common sites. Liver, kidney and brain metastasis may also occur (13). Distant metastasis may occur over a long period of time. In the review by Bernstein et al (14), five of 20 patients died from lung metastasis 4-23 years after initial treatment.

TREATMENT

Due to the lack of prospective and randomized controlled trials, no consensus regarding the optimal treatment of Bartholin gland carcinoma has been established. With the aims of minimizing morbidity and maximizing survival and psychosexual well-being, the treatment is based on the treatment guideline for vulvar cancer (11).

The preferred initial treatment is the surgical one and, according to the extent of the lesion, varies from radical local excision to radical hemivulvectomy or radical total vulvectomy with or without inguinofemoral lymphadenectomy (9). For early stage tumors a more conservative surgical excision is indicated. Surgical removal should achive lateral margins of at least 1 cm, and the deep margin should be the inferior fascia of the urogenital diaphragm. If the lesion is close to the urethra, 1 cm of the distal urethra may be resected without jeopardizing urinary continence. For tumors extending to the lower vagina, urethra or anus, a modified radical vulvectomy should be performed. For locally advanced vulvar cancer that extends to the upper vagina or urethra, bladder or rectal mucosa, radical vulvectomy or pelvic exenteration may be considered (6,15). Extensive surgery may lead to considerable morbidity, such as wound infection or breakdown, introital stenosis, psychosexual complications, urinary or faecal incontinence, as well as inguinal lymphocyst and lymphoedema in association with inguinofemoral lymphadenectomy (16).

The opponents of the radical procedure demonstrated that recurrence rates are similar in patients with positive and negative resection margins and adjuvant radiotherapy reduce the local recurrence in case of inadequate surgical margins (17). Rosenberg et al. (18) and Copeland et al. (6) have reported the benefits of postoperative radiation in patients with Bartholin gland adenoid cystic carcinoma and positive surgical margins in which no local recurrence occurred after the treatment. Along with inadequate surgical margins, another indication for adjuvant radiotherapy is groin node positivity.Radiation fields in most cases, include the inguinofemoral, external iliac, and internal iliac lymph nodes. The upper border may be extended if there is extensive inguinal involvement or suspicion of pelvic node metastasis (19,20).

As alternative to the primary surgical approach, some authors prefer primary or neoadjuvant chemoradiotherapy. The surgical pathologic staging is lost in favour of downstaging with better quality of life and less morbidity compared to radical surgery. In such cases, the imaging techniques have an important role in the evaluation of the disease, the radiation field and assessement of tumoral response. A study from Massachusetts General Hospital was conducted by Lopez-Varela et al (8) evaluating primary chemoradiotherapy in 10 patients with Bartholin gland carcinoma. The median follow-up period was 87.2 months (range 45-142 months). The survival rates were 71.5% and 66%, at 3 and 5 years, respectively comparable to the outcomes after surgery and adjuvant radiotherapy. Similar, Moore et al. (21) reported a study by the Gynecologic Oncology Group examining 73 patients with stage III/IV squamous cell vulvar carcinoma who were treated with chemoradiotherapy followed by surgical excision and bilateral inguinofemoral lymphadenectomy. 33 patients had no visible vulvar cancer after primary chemoradiotherapy and the authors concluded that neoadjuvant chemoradiotherapy in advanced carcinoma of the vulva is feasible and may decrease the need for more radical surgery. It should be taken into consideration that, surgery performed after radiotherapy can be more complicated with an increased morbidity. All management options with their benefits risks should be discussed with each patient.

Reconstructive surgical techniques, which usually involves a plastic surgeon, should be considered when a major resection is planned, leading to large postoperative defects. Care should be taken in patients with recurrent disease or previous radiotherapy since the local tissues are prone to poor wound healing. Vulval reconstruction presents a challenge for several reasons: the anatomic area of the vulva has a complex three-dimensional shape, difficult to recreate; the vulva is situated adjacent to the groin creases and is prone to constant movement when walking; the proximity of urine and faeces makes wound contamination inevitable; the vulva is an area prone to swelling and difficult to dress. Reconstructive surgical options include skin grafts and flaps. Skin grafts are not reliable in scared or iradiated tissues. Flaps provide healthy vascularised tissue and do not rely on perfusion from the wound bed, thus are useful in poorly vascularized areas. Distant flaps (gracilis or rectus abdominis) provide a larger reconstruction with a good blood supply, but in a more complex intervention than local flaps (22).

In vulvar cancer, recurrence in the groin carries a very high mortality, thus the appropiate groin treatment is very important in reducing mortality (23). The overall 5-year survival of women with carcinoma of Bartholin's gland decreases to 18% when two or more inguinal lymph nodes are involved (24). Some recommend that both inguinal and femoral nodes be removed, as inguinal node dissection alone is associated with higher incidence of groin recurrence (25). Metastases to the inguinal lymph nodes may occur in up to 50% of cases and 18% of these cases have metastases to the external and common iliac lymph nodes. Pelvic lymph nodes are rarely involved unless the ipsilateral inguinal nodes are involved (24, 26). Lesions within 1 cm of the midline can drain bilaterally because of the rich lymphatic network across the midline. If vulvar carcinoma invades the vagina, bladder or rectum above the dentate line, nodal metastasis to the obturator or internal iliac nodes are possible (27).

The management of inguinofemoral nodes can be divided as follows: no surgery or sentinel node biopsy in cases of stage IA FIGO tumors (smaller than 2 cm with a depth of invasion less than 1 mm); unilateral inguinofemoral lymphadenectomy in cases of stage IB FIGO tumors - the incidence of positive contralateral nodes in patients with small lesions and negative ipsilateral nodes is less than 1%, so unilateral groin dissection is appropiate for such lesions (23); bilateral inguinofemoral lymphadenectomy in cases of locally advanced disease or in cases of positive ipsilateral nodes discovered at sentinel node biopsy or unilateral lymphadenectomy. A triple incision approach has better healing results than enbloc resection (28).

Sentinel node mapping and biopsy, initially used in the treatment of breast cancer and cutaneous melanoma, are being used in some centers as a part of surgical management of inguinofemoral nodes in vulvar cancer. It can be an alternative to inguinofemoral lymphadenectomy in all cases that require lymphadenectomy without clear evidence of nodal metastasis at imaging or clinical examination. This practice can reduce unnecessary lymphadenectomy and morbidity (29).

Preoperative information about regional nodal metastasis and depth of tumor invasion is essential in tailoring the treatment. Imagistic evaluation with ultrasound, CT, MRI and PET/CT, and sentinel node mapping and biopsy have advantages over clinical examination in guiding the appropriate treatment. Combined ultrasound imaging and ultrasound-guided fine-needle aspiration biopsy has very high specificity (82–100%) and sensitivity (80–93%). Sampling is minimally invasive but operator-limited and with sampling error in cases of micrometastasis in groin nodes. The sensitivity of MRI in detecting nodal metastasis varies among studies (50–89%), but the specificity is high (89–100%) (30,31).

A randomized trial conducted by Stehman et al.(25) showed superior results in groin dissection with postoperative radiation for patients with positive groin nodes compared to groin irradiation. They demonstrated superior results for pelvic and inguinal radiation compared with pelvic node dissection for patients who had an inguinal lymph node dissection with findings of grossly positive or more than one positive node. A recent retrospective, multicenter German study also reported the benefice of adjuvant radiotherapy directed at the groins for patients with positive groin nodes (20). Several studies have emphasized the prognostic significance of the morphology of positive groin nodes, particularly the size of the metastasis and the presence or absence of extracapsular spread. Patients with one small lymph node metastasis do not appear to benefit from adjuvant radiation therapy; several series suggest that their prognosis is good after inguinofemoral lymphadenectomy alone (32,33). In a multicenter Dutch study of 75 patients with vulvar cancer and one positive lymph node of all sizes, Fons et al reported that adjuvant radiation was only beneficial if extracapsular spread was

present (34). The benefits of perfoming either unilateral or bilateral inguinofemoral lymphadenectomy remain controversial in the treatment of Bartholin gland carcinoma; however, the main determinant of survival is the status of the lymph nodes (35). Leuchter et al have reported a 5-year survival of 52%, 36% and 18 % with zero, one or multiple positive nodes, respectively (36).

Few trials have evaluated the benefice of chemotherapy in this type of cancer and a consensus is to reserve chemotherapy for palliation of patients with symptomatic metastases or rapidly progressing disease who are not candidates for other treatment modalities (37,38).

RECURRENCE AND FOLLOW-UP

Local recurrence rates are 10-15% among surgically treated patients. The predominant site of recurrence is the perineum (43-54%), even when radical operations are performed (39). Other sites of recurrence include groin, pelvis and distal sites. It is a common belief that the most important aspect of treatment in order to prevent recurrence is to obtain tumor-free surgical margins. In a review of the literature, Yang et al (17) suggested that there is a higher recurence rate in patients undergoing simple exision compared with radical vulvectomy. They found 68.9% rate of recurrence in patients with simple excision compared with 42.9% in patients with radical vulvectomy. The positivity of resection margin was 48% in the simple excision group and 30% in the radical vulvectomy group. Even if radical vulvectomy can reduce local recurrence, it has no impact on distant metastasis (9). Postoperative adjuvant radiotherapy has been shown to be effective in controlling the disease in patients with positive margins and local recurrence (40). Distant metastasis generally occurs after a long time since the initial diagnosis (41).

Management of recurrent disease is determined by previous treatments, age and performance status of the patient. In the postoperative follow-up, recognition of recurrence as early as possible is very important in order to improve survival. The Society of Gynecologic Oncologists recommends that patients with low-risk disease, early stage, undergo follow-up with review of symptoms and physical examination every 6 months for the first 2 years and then annually (42). For patients with high-risk disease, advanced stage, it is recommended the surveillance every 3 months for the first 2 years, every 6 months for years 3 through 5, and then annually. Since late recurrence is sometimes encountered, the follow-up is required for many years. CT and PET/CT are useful for evaluation of groin and distant recurrences (30).

The survival rates for 5 and 10 years range from 71% to 100% and 59% to 100%, respectively. (43). According to Copeland et al, the 5-year progression-free interval is 47% and the 5-year survival rate is 71%. The progression-free intervals and survival rates are 38% and 50% at 10 years, and 13% and 51% at 15 years, respectively (6). The presence of pathologic high-risk factors including the involvement of surgical resection margin, inguinal lymph node metastasis, lymphovascular and/or perineural invasion indicate aggressive oncogenic behaviour (11). Survival is better with adenoid cystic carcinoma than with other forms of carcinoma of the Bartholin's gland (6).

CONCLUSIONS

Bartholin gland carcinoma are rare, slow growing tumors, but locally highly aggressive with remarkable capacity for recurrence. Despite its rarity, the examiner must recognize the increased possibility of this diagnosis in any woman older than 40 years presenting with a Bartholin gland mass. Appropriate biopsies and histological evaluation should be undertaken. Radical surgical excision should be performed in order to obtain adequate negative margins. In the presence of high risk factors, adjuvant radiotherapy decreases the recurrence rate.

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