review

Modern treatment of vulvar cancer

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Background. Vulvar cancer accounts for 3–5% of malignant diseases of the female genital tract. The Slovenian incidence rate is 5.5/100,000, which means 57 new cases per year. The most common histological type (90%) is squamous cell carcinoma. Based on etiology, it can be classified into the first type which correlates with human papillomavirus (HPV) infection and the second type which is not associated with HPV. The most common and long-lasting symptom of vulvar cancer is pruritus. The preferred diagnostic procedure to confirm the diagnosis is a punch or incision biopsy. Surgery in combination with radiotherapy is the standard treatment for vulvar cancer. Sentinel lymph node biopsy with lymphoscintigraphy is now a standard part of surgical treatment. Chemotherapy is a palliative treatment option.

Conclusions. Vulvar cancer is a rare disease. Because of the pathogenesis, surgery and radiotherapy are the main treatment modalities. The sentinel node biopsy (SNB) represents a contemporary approach to the vulvar cancer treatment and significantly reduces morbidity. Improvements in treatment of vulvar cancer contributed to the decrease of mortality among Slovenian women.

Key words: vulvar cancer; surgical treatment; sentinel lymph node biopsy; lymphoscintigraphy; radiotherapy

Introduction

Vulvar cancer is the fourth most common gynaecological malignancy.[1] The basic treatment for vulvar cancer is still surgery, but the radical nature of the procedure has changed or decreased over the last twenty years. Historically treatment included radical vulvectomy and a radical inguino-femoral lymphadenectomy. The procedure was associated with a high rate of postoperative complications. For this reason, a minimally invasive surgical technique was developed. This is the sentinel lymph node biopsy, which is now a standard procedure in the treatment of patients with early-stage vulvar cancer. This procedure significantly reduced morbidity and improved quality of life.[2]

Epidemiology

Vulvar cancer accounts for 3–5% of all gynaecological cancers in the world. This puts it in fourth place among gynaecological malignancies. The first three places are occupied by cancer of the uterus, ovaries and cervix. Every year 27,000 women worldwide are diagnosed with vulvar cancer. The highest incidence is in Europe, North and South America, Oceania, and the lowest in Asia.[1]

In 2016, 57 women were diagnosed with vulvar cancer in Slovenia with an incidence of 5.5 / 100,000. An analysis of the time trends over the last 15 years shows an increase in incidence since 2003, while mortality has remained constant. It should be noted that this coincides with the introduction of the national program for the early detection of precancerous changes in the cervix. This has led to an increased number of gynaecological examinations, including the older population. Vulvar cancer occurs most frequently in women over 80 years of age. In 2016 there were no cases of women under 30 years of age in Slovenia. According to the 2016 data, 59.6% of patients had a limited stage of the disease at diagnosis, 29.8% an advanced stage and 7% of patients had metastatic disease.[3]

The survival of patients with vulvar cancer improved slightly over time. According to the Slovenian Cancer Registry, the 5-year survival rate of patients with vulvar cancer was 43% between 2004 and 2009, while between 2010 and 2016 5-year survival rate was 48%. Patients diagnosed with localized disease have significantly longer overall survival than patients with locally advanced disease.[4,5]

The international EUROCARE-5 study showed a relative 5-year survival rate for different cancers. In this study patients with vulvar and vaginal cancer were pooled. The average European relative 5-year survival rate in this study was 56% for patients between 2000 and 2007.[6]

Etiopathogenesis

More than 90% of cases of vulvar cancer are defined as squamous cell carcinoma. It can develop in two different ways. In younger women (aged 35–65 years), HPV infection plays a key role in the development of squamous cell carcinoma, especially strains 16 and 18. Risk factors include a history of genital warts and other sexually transmitted diseases, low socioeconomic status, smoking and immunodeficiency. The second type of development is independent of HPV and occurs more frequently in older patients (aged 55–85 years). It is a gradual process of development of cellular atypia leading to vulvar intraepithelial neoplasia (VIN) and then squamous cell carcinoma. The risk factor is the *lichen sclerosus*. The crossing of the two pathogenetic pathways is also possible.[7-9]

Clinical manifestation and diagnostic procedures

The most common symptom of vulvar cancer is persistent itching. Less common symptoms are bleeding from the vulvar skin, bleeding or discharge from the vagina, dysuria and pain. In advanced cases, a tumour can be seen on the vulva. The tumour may be ulcerated, leukoplactic or warty.[1]

Treatment of a woman with suspected malignant disease of the vulva starts with a thorough medical history, followed by a clinical examination. It is important to accurately describe suspicious changes, their size, number, position, mobility, assessment of infiltration of deeper structures and safety margins in case of excision. A bimanual vaginal and rectal examination should always be performed to assess vaginal and rectal involvement. Since HPV occurs in 86% of precancerous changes in the vulva and in 28.6% of vulvar cancers, the examination should also include a colposcopic examination of the vagina and cervix. Assessment of the size, mobility and consistency of the inguinal lymph nodes is mandatory. The condition of the skin above the inguinal lymph nodes should also be noted. Palpation of the supraclavicular lymph nodes is important as well. If there is already a pathology of the vulva (atrophic *lichen sclerosus*, pathological cytological smear of the vulva), vulvoscopy is also advisable.[2]

A targeted biopsy with histological examination of the tissue taken is necessary to make a definitive diagnosis. It is important that the sample is taken at the site of the vital tissue, so it is advisable to take a tissue sample near the edge of the alteration. Necrosis, granulation tissue, fibrin or inflammation are often found in the middle of the changes in the form of ulcers, blisters, atrophy and scarring. Such a hysto-pathological pattern is neither appropriate nor representative. The size of the biopsy taken should be at least 4 mm^3.[2] The preferred method of sampling is the punch biopsy. Excisional biopsy is not recommended as it may prevent proper further treatment. In patients with multiple vulvar lesions, a separate biopsy of all lesions should be performed and the sampling site should be indicated.[2]

Treatment

The treatment of vulvar cancer often involves a combination of surgery and radiotherapy. Systemic treatment is rarely used. Treatment can be long lasting and have a major impact on quality of life.[2,9]

Surgical treatment

*Primary vulvar lesion.*The basic criterion for the treatment of a tumour lesion is the depth of the stromal invasion into the biopsy tissue taken. If an early stage disease is defined as T1a (≤ 1 mm of stromal invasion), a wide local excision is performed. If the disease is defined as T1b (> 1 mm stromal invasion) or T2 ≤ 4 cm and the lesion is 1 cm from the median line, wide local excision or a modified radical vulvectomy and ipsilateral sentinel node biopsy (SNB) is performed. However, in the case of a lesion in the median line, a wide local excision and a bilateral SNB is required.

If the disease is locally advanced (T2 > 4 cm and T3) and the lesion is ≥1 cm from the median line, a radical vulvectomy and ipsilateral dissection of

the inguino-femoral lymph nodes is performed. If the lesion is in the median line, a radical vulvectomy and bilateral dissection of the inguino-femoral lymph nodes are performed. If the lymph nodes are positive, we opt for external beam radiotherapy (EBRT) of the primary tumour, lymph nodes and pelvis. In case of negative lymph nodes, we choose EBRT of the primary tumour and/or selected inguino-femoral lymph nodes. In all cases, adjuvant treatment follows.

If the patient has metastatic disease outside the pelvis (any T, any N, M1 outside the pelvis), we do not opt for surgical treatment, but for palliative EBRT and/or symptomatic treatment.[2,9]

Lymph nodes. The most basic method for determining the status of inguino-femoral lymph nodes is palpation, but its accuracy is only 9% preoperatively and 55% intraoperatively. The status can also be determined by ultrasound examination of the inguinal regions. The sensitivity and specificity of lymph node ultrasound examination for vulvar cancer is 76.3% and 91.3%, with positive and negative predictive values of 82.9% and 87.5%, respectively. Fine needle biopsy and cytological verification follow if lymph node involvement is suspected.[10,11] Other imaging methods have proven to be less reliable compared to ultrasound.[12,13]

In the absence of a reliable method for detecting inguino-femoral lymph node involvement, inguino-femoral lymphadenectomy was part of the standard treatment of vulvar cancer.[1] Metastases in the inguino-femoral lymph nodes in early stages of the disease are found in only 20–30% of patients, which means that all other patients do not benefit from a complete lymphadenectomy. The possible postoperative complications following a complete lymphadenectomy are lymphedema of the lower extremity (14–49%), lymphocyst formation (11–40%) and wound infections with dehiscence.[14,15]

Due to the lack of non-invasive techniques to determine the status of inguino-femoral lymph nodes, the absence of lymph node metastases in most patients with early stage disease and the frequent morbidity following inguino-femoral lymphadenectomy, the minimally invasive surgical technique, SNB biopsy was developed. SNB is now part of the standard treatment of early-stage vulvar cancer. Vulvar cancer has a predictable course of the lymphatic vessels and lymphatic drainage is predictable. Therefore, SNB of inguino-femoral lymph nodes is a safe replacement for inguino-femoral lymphadenectomy. The sentinel lymph node is defined as the first lymph node in the lymphatic basin into which the lymph of the primary tumour drains. Histological examination of the sentinel lymph node is representative for all other lymph nodes in the area, and histologically, a negative sentinel lymph node means the absence of metastases in subsequent lymph nodes.[16-19]

The sentinel lymph node is marked in two ways, with a nanocolloid bound to 99mTc (Technetium) and with a patent blue. This method is the most reliable, as the sentinel lymph node is found in 97.7% of cases. Only by injecting patent blue the sentinel lymph node is identified in 68.7%, and only by the nanocolloid bound to technetium in 94%.[20,21]

At the Institute of Oncology Ljubljana, the technique has changed over the years. It is crucial that patent blue is injected intradermally and not subcutaneously. The volume of the injected, undiluted dye is 2 ml. On the day of surgery, 0.5 ml of technetium-labeled nanocolloid is injected intradermally with a thin needle at four points near the outer edge of the tumour. Lymphoscintigraphy with a gamma camera follows. The first active accumulation point of the radiopharmaceutical is the sentinel lymph node, and its position is marked on the skin. Sometimes several points of high activity appear, in this case we mark them all. Immediately before the beginning of the surgical procedure, 2 ml of patent blue is injected intradermally in the same place as radiopharmaceutical. Then a 3 to 4 cm long skin incision is made at the marked site. The tissue is carefully dissected until a blue stained lymph node is found. Its activity is checked with a hand-held gamma detector and then removed.[2]

Women with histologically confirmed unifocal vulvar carcinoma, less than 4 cm in diameter, with an invasion depth of more than 1 mm, and in whom there are clinically no metastases in the inguino-femoral lymph nodes, are candidates for sentinel lymph node biopsy.[2,22]

A tumour located 1 cm or more from the midline of the vulva is usually drained into the unilateral lymphatic system, so a sentinel lymph node biopsy is performed on the same side. Bilateral drainage is present in tumours that are central or less than 1 cm from the median line. In this case a biopsy of the sentinel lymph node should be performed bilaterally. If the lymph node is detected in the lymphoscintigraphy on one side only, inguino-femoral lymphadenectomy on the opposite side is recommended to avoid a false negative result.[2,9,22]

Patients with a multifocal tumour are not suitable candidates for sentinel lymph node biopsy because they have a higher incidence of disease recurrence (10.5%) compared to patients with a unifocal tumour (2.3%).[23] Previous surgery and

excisions of the vulva that may interfere with lymphatic flow in the inguino-femoral region are relative contraindications for sentinel lymph node biopsy, but the decision in these cases is made on a patient-specific basis. Lymphadenectomy is recommended in patients with recurrent disease or in patients who have already had an inguino-femoral sentinel lymph node biopsy.[2,20]

Radiotherapy

The purpose of postoperative radiotherapy is to reduce the likelihood of local and/or regional recurrence, prolong disease-free survival and overall survival.[2] Due to the low incidence of vulvar cancer, the number of randomized clinical trials and evidence-based treatment outcomes is also low. As a result, there are no standard indications and recommendations for adjuvant treatment of vulvar cancer. The data collected suggest that adjuvant treatment is not necessary in patients with early-stage cancer, negative inguino-femoral lymph node status and a favourable prognosis.[24]

However, treatment of locally advanced disease sometimes requires adjuvant treatment following surgery. Lymph node metastases, large primary tumours, deep stromal invasion, lymphovascular invasion and close surgical margins are associated with a higher incidence of disease recurrence. The role of adjuvant therapy in these patients is still not fully understood. Radiation or radiation combined with lymph node dissection is very effective in preventing disease recurrence in the inguino-femoral lymph nodes in patients with squamous cell carcinoma of the vulva. According to the recommendations of the Gynecologic Oncology Group (GOG), adjuvant radiation is considered the standard treatment for squamous cell carcinoma of the vulva in patients with 2 or more positive lymph nodes with extracapsular spread or inguino-femoral dissection is not feasible. The benefit of adjuvant radiotherapy has been demonstrated in patients with two or more positive inguino-femoral lymph nodes, while the role of irradiation of patients with only one positive inguino-femoral lymph node remains undetermined.[2,24,25]

Systemic treatment

Data on the role of systemic therapy in the treatment of vulvar cancer are very sparse, as they are based on small, non-randomized phase II clinical trials involving fewer than 50 patients treated with various regimens of chemotherapy. Currently, chemotherapy is not recommended as a stand-alone preoperative (neoadjuvant) or postoperative (adjuvant) systemic treatment. Chemotherapy can only be considered as a palliative treatment for metastatic disease if other treatments are not feasible. Various cytostatic drugs (cisplatin, paclitaxel, bleomycin, navelbin, 5-fluorouracil) were used in the trials in combination or monotherapy. The response rate was 0–40%, progression-free survival 1–10 months and overall survival up to 19 months. Due to the toxicity of cisplatin, the less toxic carboplatin has been increasingly used in recent years to treat metastatic vulvar cancer. In analogy to metastatic cervical cancer, the combination of carboplatin and paclitaxel has been increasingly used in recent years for the treatment of metastatic vulvar cancer because the combination is similarly effective and less toxic than the combination of cisplatin and paclitaxel.[26]

Chemotherapy can be used in combination with concomitant radiation (chemoradiotherapy), either as a stand-alone treatment or as preoperative (neoadjuvant) treatment in patients with locally advanced disease. Various cytostatic drugs (cisplatin, 5-fluorouracil, mitomycin-C) are used in chemoradiotherapy to improve the local effect of radiation (chemosensitization). Since concomitant treatment with chemotherapy and radiation is associated with higher toxicity, lower doses of cytostatic drugs are used during radiation, so in this case it is actually a topical rather than a systemic treatment.[26,27]

The role of targeted therapeutics in the treatment of advanced vulvar cancer is still unknown. We have data from a small clinical trial with the targeted therapeutic erlotinib, an epidermal growth factor receptor (EGFR) inhibitor, which included 41 patients with advanced disease. Partial response was achieved in 27%, progression-free survival was short (median treatment time 3 months), and treatment was associated with many adverse events.[28,29]

Follow-up

There is currently insufficient evidence to support a uniform follow-up pattern after radical treatment of vulvar cancer. Experts and professional associations therefore disagree on follow up schedule. Local recurrence can occur at any time, so lifelong follow-up is recommended.

Depending on the type of treatment, the European Society of Gynaecological Oncology (ESGO) suggests the following follow-up scheme.

After primary surgical treatment, the first examination is performed 6–8 weeks after the surgical procedure, then clinical examinations of the vulva and groin region are performed every 3–4 months for a period of two years. In the following three years, follow-up examinations are scheduled twice a year. After this period, it is advisable to perform annual clinical examinations. This is particularly important for patients at increased risk, such as patients diagnosed with *lichen sclerosus* / *planus*.

10–12 weeks after chemotherapy or radiotherapy, a computed tomography or positron emission tomography-computed tomography (PET-CT) examination is recommended to confirm remission. Later, clinical examinations of the vulva and groin region are recommended every 3–4 months for the first two years, followed by examinations twice a year for 3 years and then annual examinations.

If a local recurrence is suspected, a biopsy should be performed, and if there is a suspicion of groin region relapse of the disease or extended disease, appropriate imaging diagnostics should follow. The early detection of malignant recurrences that can still be treated surgically can significantly improve quality of life, but there is currently no firm evidence of the effects on morbidity and mortality.[2,6,30]

Conclusions

Surgical treatment is still standard treatment of vulvar cancer. The greatest progress in this field in recent years has been the development of a minimally invasive surgical technique, sentinel lymph node biopsy, which is now standard treatment in selected cases. The replacement of inguino-femoral lymphadenectomy with this procedure significantly reduced morbidity and improved quality of life. Due to the rarity of vulvar cancer, patients should be treated in specialized centres where appropriate equipment, knowledge and experience are available.

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