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The role of lymphoscintigraphy and groin sentinel node biopsy in early stage vulvar cancer

Vloga limfoscintigrafije in biopsije varovalne bezgavke pri začetnem stadiju raka zunanjega spolovila

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Abstract

Vulvar cancer is a rare gynaecological malignancy which accounts to about 57 women in Slovenia every year. The most important prognostic factor is the presence of lymph node metastases in local or locally-advanced disease. Since only 20–30% of women with early- stage vulvar cancer have groin metastases, inguinofemoral lymphadenectomy is an over-treatment in 70–80% of these patients and is often associated with intra- and postoperative complications such as wound infection, wound dehiscence and lymphoedema of the lower extremities.

The sentinel node biopsy is a minimally invasive and safe procedure in women with early stage vulvar cancer (FIGO stage IB/II), where the tumour is unilateral, less than 4 cm in diameter, and without clinical/radiological evidence of lymph node metastases. This reduces the intra- and postoperative morbidity in patients with early stage vulvar cancer.

Izvleček

Rak zunanjega spolovila je redka maligna ginekološka bolezen, ki v Sloveniji prizadene približno 57 žensk na leto. Zasevki v ingvinalno-femoralnih bezgavkah so najpomembnejši napovedni dejavnik pri lokalizirni in pri lokalno napredovali bolezni. V začetnem stadiju bolezni so le-ti prisotni pri 20–30 % bolnic. To pomeni, da 70–80 % žensk po kirurškem zdravljenju nima koristi od ingvinalno-femoralne limfadenektomije, ki je povezana z visoko stopnjo obolevnosti med in po operaciji (okužba in dehiscenca rane, limfedem spodnjega uda).

Biopsija varovalne bezgavke pri raku zunanjega spolovila je minimalno invaziven in varen poseg, ki ga je smiselno opraviti pri začetnem stadiju bolezni (FIGO stadij IB in II), pri katerem gre za enožariščni tumor, ki v premeru meri manj kot 4 cm, ni pa kliničnih/radioloških znakov za razsoj bolezni v ingvinalne bezgavke. S tem se zmanjša obolevnost med operacijo in po njej pri ženskah z začetnim stadijem raka zunanjega spolovila.

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1 Introduction

Vulvar cancer is a rare disease with an incidence rate of 1.5–3 per 100,000 women in Europe (1). In 2016, 57 women were diagnosed with it in Slovenia (5.5/100,000 women) (2).

There are two pathways for the onset of the disease. In younger patients, the disease is more often associated with the human papillomavirus (HPV) infection, most commonly with strains 16 or 18. In older patients, however, onset of the disease does not depend on the HPV infection (3). Histologically, 90% of vulvar cancer is defined as squamous cell carcinoma (4). It most commonly spreads lymphogenically to the inguinofemoral lymph nodes. However, in the case of a tumour growth in the area of the clitoris or perineum, the literature also describes direct metastasis to the pelvic lymph nodes (5).

The most important prognostic factor in the non-metastatic form of vulvar cancer is inguinal lymph node involvement. In the case of unaffected inguinal lymph nodes, the 5-year survival rate is 95%, and in the case of lymph node metastases, the 5-year survival rate is reduced to 62% (6).

The standard surgical treatment of early stages of vulvar cancer (FIGO stage IB/II) without typically enlarged inguinal lymph nodes was a wide tumour excision with a safety margin, simple vulvectomy, and unilateral or bilateral inguinofemoral lymphadenectomy. Only 20–30% of women with early-stage vulvar cancer have metastases present in the inguinal lymph nodes, so inguinofemoral lymphadenectomy is not required in most of these patients. 70% or more of patients do not benefit from additional surgery, while there is a significant increase in morbidity and decrease in the quality of life due to postoperative complications such as cellulitis, lower extremity lymphoedema, and wound dehiscence (7). As a result, supplemental irradiation, if planned, may also have to be delayed.

Sentinel lymph node biopsy is a minimally invasive procedure used to determine the presence of metastases in the lymph nodes. This is explained by the fact that the sentinel lymph node is the first in the chain of lymph nodes where the primary tumour drains. Negative sentinel lymph node biopsy is associated with a low incidence of disease recurrence in the inguinofemoral region (8,9), with fewer complications during and after surgery (8,10), and with shorter duration of surgery and hospitalization (11). Today, sentinel lymph node biopsy is a safe replacement for inguinofemoral lymphadenectomy in selected women with early-stage vulvar cancer (12).

2 Epidemiology

Vulvar cancer accounts for 3–5% of all gynaecological cancer cases in the world and is the fourth most common gynaecological malignancy. It is estimated that about 27,000 women fall ill each year. The highest incidences are recorded in Europe, South America and North America. The occurrence of this type of cancer in Asia and Africa, however, is rare (13,14).

In Slovenia, vulvar cancer accounts for 4% of all cases of gynaecological cancer and is one of the rare types of cancer, which include all types of cancer with an incidence < 6 per 100,000 population. In 2016, 57 women (5.5/100,000 women) fell ill in Slovenia. In the time-trend analysis of the last 15 years, a significant increase in incidence since 2003 is observed, while mortality is constant during the entire observation period. This increase in incidence coincides with the introduction of ZORA, the National Screening Programme for the Early Detection of Precancerous Changes of the Cervix (2). We can conclude that this is related to the ageing population and more frequent visits to primary gynaecologists in the elderly population as well.

Vulvar cancer affects older women, most often women over the age of 80. A smaller peak in incidence is also recorded in women around 55 years of age. According to data from 2016, 59.6% of patients were diagnosed with a limited stage of the disease, 29.8% with an advanced stage of the disease, and 7% with metastasis. In the remaining 3.5%, the stage of the cancer was unknown (2).

The survival of patients with vulvar cancer is slightly improving over time. The observed 5-year survival rate of patients between 2004 and 2009 was 43%, while the group of those diagnosed with vulvar cancer in the period 2010–2016 had a 5-year survival rate of 48% (15). Patients in whom a localized form of the disease has been detected have a significantly longer overall survival rate than those who already have a locally advanced cancer at the time of diagnosis. For patients between 2010 and 2016, the 5-year survival rate was observed: for the localized form of the disease it was 64%, and for the locally advanced form, 35%. None of the 8 patients from this period who had a systemically advanced disease at the

time of diagnosis or whose stage was not determined survived 5 years after diagnosis (15).

The international EUROCARE-5 study shows the relative 5-year survival rate for a group of patients with vulvar and vaginal cancer. The average European relative 5-year survival rate in this survey for patients who fell ill between 2000 and 2007 was 56%, in Slovenia 60%. The best survival rate was in the Netherlands, 65% (16).

3 Aetiopathogenesis

Infection with oncogenic human papillomavirus, most commonly strains 16 and 18, plays a key role in the development of vulvar squamous cell carcinomas. Women with a larger number of sexual partners and those who have started having sex early have a higher risk of cancer. Similar to cervical cancer, smokers and immunocompromised patients are more at risk. Women who have already had one of the anogenital cancers and women with vulvar cancer *in situ* are also at higher risk (17,18).

There are three pathways of the spread of vulvar squamous cell carcinoma. The lymph cancer most commonly metastasizes to the inguinofemoral lymph nodes. Haematogenous spread as well as direct proliferation are rare (5).

4 Assessment of inguinofemoral lymph nodes before surgery

There is no reliable diagnostic method for determining the status of inguinofemoral lymph nodes before surgery. As with breast cancer, palpation is the most basic method for determining the condition of the inguinofemoral lymph nodes due to the superficial position of the lymph nodes, but the accuracy is only 9% before surgery and 55% during surgery (19).

Assessment of lymph node involvement can be performed by ultrasound examination (US) of the inguinal fossae. According to some data, the sensitivity and specificity of ultrasound of the lymph nodes in vulvar cancer are 76.3% and 91.3%, with positive and negative prognostic values of 82.9% and 87.5%. If lymph node involvement is suspected after imaging, a biopsy can be performed using the fine- or thick-needle method. Ultrasound-guided fine-needle biopsy allows cytological examination of the lymph nodes and has an estimated sensitivity of 80%, specificity of 100%, and negative and positive predictive value of 93% and 100% (19-22). Pathological lymph nodes have an altered ratio between the length and width of the lymph node, are round and have an unevenly thickened or no longer visible cortex. The most reliable signs of malignant infiltration are peripheral lymph node blood flow and central necrosis.

Other imaging methods have proven to be less appropriate compared to ultrasound. The sensitivity of computed tomography (CT) and its positive predictive value are 58% and 58%, while in magnetic resonance imaging (MRI) they are only 52% and 46%. The data indicate that both MRI and CT are unsuitable tests for determining metastases in the inguinofemoral lymph nodes (23-27).

5 Why sentinel lymph node biopsy is the standard in treating early-stage vulvar cancer today

Surgery is still the basic treatment for the early-stage vulvar cancer, but the radicality of the procedure has diminished in the last twenty years. Treatment used to include vulvectomy and inguinofemoral lymphadenectomy. Lymphadenectomy is associated with a high rate of postoperative complications: surgical wound dehiscence (20–40%), lymphocysts, and lower extremity lymphoedema (30–70%) (7,28).

In the early stages of the disease, metastases are found in the inguinofemoral lymph nodes in only 20 to 30% of patients. The rest of the patients (70% or more) do not benefit from the procedure, and there is a significant increase in morbidity and decrease in the quality of life.

The most effective way to reduce morbidity in patients undergoing surgical treatment for vulvar cancer is to remove fewer lymph nodes, thereby minimizing lymph duct damage and disruption in lymphatic drainage. We should not, however, run the risk of obtaining false-negative histological results due to a smaller number of lymph nodes removed. Mortality from recurrence of vulvar cancer is as high as 75% (10).

Vulvar cancer has a predictable course of lymph ducts and lymphatic drainage. Therefore, and due to the previously described facts, the less invasive technique of sentinel lymph node biopsy has been extensively and thoroughly investigated. Research has shown that sentinel lymph node biopsy in selected women with early-stage vulvar cancer is a safe substitute for inguinofemoral lymphadenectomy, making it the standard investigation (29-32).

Vulvar cancer is a rare disease and treatment depends largely on the result of the sentinel lymph node biopsy. It is therefore important that operations are carried out centrally in all qualified centres (32,33).

At the Institute of Oncology Ljubljana, the first sentinel lymph node biopsies were performed in carefully

selected vulvar cancer patients in 2003. In the learning process, between the 2003–2006, the procedure was performed in 35 patients. In 10 (28.6%) patients the sentinel lymph node was positive, which is in line with publications in the literature. The 5-year survival rate in patients with a negative sentinel lymph node biopsy was 88%. In patients with a positive sentinel lymph node biopsy and subsequent inguinofemoral lymphadenectomy, the 5-year survival rate was lower, namely 40%. The data are comparable to studies describing the 5-year survival rate in the early-stage vulvar cancer, 70–93% in the negative sentinel lymph node and 25–41% in the positive sentinel lymph node (6,34,35). From 2007 to 2019, a biopsy of the sentinel lymph nodes was performed in another 181 patients with the early-stage vulvar cancer at the Institute of Oncology Ljubljana. In 48 patients (26.5%) the sentinel lymph node was positive and in 133 (73.5%) negative. No patient experienced inguinal wound complications after surgery (lymphocysts, lower extremity lymphoedema, or wound dehiscence).

6 Indications and contraindications for sentinel lymph node biopsy

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. A histologically negative sentinel lymph node means the absence of metastases in subsequent lymph nodes.

Based on the results of the GROINSS-V and GOG-173 studies, sentinel lymph node biopsy has become the standard diagnostic method in the treatment of women with early-stage vulvar cancer (9,34).

Suitable for sentinel lymph node biopsy are women with histologically confirmed monofocal vulvar cancer of less than 4 cm in diameter, with a depth of invasion of more than 1 mm, and where clinically there are no metastases present in the inguinofemoral lymph nodes. It must also be technically feasible to inject the necessary substances into the tumour area (33).

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 required for 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, inguinofemoral lymphadenectomy on the opposite side is recommended to avoid a false negative result (12,33).

Patients with a multifocal tumour are not suitable candidates for sentinel lymph node biopsy because they have a higher incidence of recurrence (10.5%) compared to patients with a unifocal tumour (2.3%) (10). Previous surgery and excisions of the vulva that could interfere with the lymphatic flow in the inguinofemoral region are relative contraindications for sentinel lymph node biopsy. The decision on the procedure in these cases is made for each patient separately (3,35,36). Lymphadenectomy is recommended as standard treatment in patients with recurrent disease or in patients who have already had an inguinofemoral sentinel lymph node biopsy (33,37).

7 The role of lymphoscintigraphy before sentinel lymph node biopsy

As a rule, the sentinel lymph node is marked in two ways, with a nanocolloid bound to ^{99m}Tc (Technetium) and with Patent Blue. This method is the most reliable, as the sentinel lymph node is found in 97.7% of cases. By only injecting Patent Blue, the sentinel lymph node is identified in 68.7%, and in 94% only by a nanocolloid bound to technetium (39-41).

A colloid bound to technetium (^{99m}Tc) is a lymphatic radiotracer most commonly used in sentinel lymph node biopsy. Technetium is a radionuclide that emits gamma rays, has a short half-life and represents a low radiation burden for both the patient and the medical staff. The most commonly used colloid in Europe is the nanocolloid albumin (40,41).

The most modern tracers today are hybrids, indocaine (ICG-) and a nanocolloid bound to ^{99m}Tc, which allow the simultaneous application of both radiopharmaceutical and fluorescent dye. This makes preoperative lymphoscintigraphy and interoperative visualization of the sentinel lymph node possible (39).

At the Institute of Oncology Ljubljana, the technique has changed and improved over the years. Optimal results are achieved if the Patent Blue is injected intradermally in a volume of 2 ml. In the morning of the day of surgery, 0.5 mL 30–100 MBq of technetium-labelled nanocolloid is injected with a thin needle into the skin at four points near the outer edge of the tumour. This is followed by lymphoscintigraphy with a gamma camera. The first active accumulation point of radiopharmaceuticals is the sentinel lymph node, so its position is marked on the skin. Sometimes, several points of high activity appear. In this case, we mark all the points. Immediately before the beginning of the surgical procedure, 2 ml of Patent Blue is injected into the skin in the same place where the

radiopharmaceutical was injected. Then a 3 to 4 cm long skin incision is made at the marked site, carefully dissecting the tissue until a blue-stained lymph node is found. Its activity is checked with a hand-held gamma detector. If the next blue-stained lymph node with lower activity is found, it is removed as well. This is followed by removal of the tumour on the vulva with a wide safety margin.

8 *Ultrastaging* of the sentinel lymph node

Careful examination of the sentinel lymph nodes in vulvar cancer is crucial because further treatment depends on it. A false-negative histopathological result of a sentinel lymph node biopsy leads to the omission of further surgery – lymphadenectomy, which triggers the rapid growth of metastases present in the lymph nodes (44).

Ultrastaging is a procedure used by pathologists to carefully examine a small number of lymph nodes. In classic inguinofemoral lymphadenectomy, an average of 9–10 lymph nodes are removed, so *ultrastaging* is impractical and rarely performed. In a sentinel lymph node biopsy, however, 1 or 2 lymph nodes are removed and *ultrastaging* is the standard procedure. Paraffin blocks with a thickness of 400–500 microM (2–3 mm at a classical examination) are stained with haematoxylin and eosin and immunohistochemically with cytokeratin, which allows the identification of micrometastasis.

In the lymph nodes, which are negative at a routine histopathological examination, *ultrastaging* shows micrometastasis in 12–42% of cases (43,44).

Examination of the lymph node by the frozen section method is not appropriate because it destroys the lymph node and prevents its further examination (e.g. *ultrastaging*).

9 Recurrence of the disease inguinally after the biopsy of the sentinel lymph nodes

In complete inguinofemoral lymphadenectomy, which involves dissection of large vessels and, if necessary, transposition of the sartorius muscle, the disease recurs in the inguinal fossa in 1% or less. The number of complications after this type of surgery is acceptable, and they occur mainly in the form of postoperative wound dehiscence and lower extremity lymphoedema (47). In superficial inguinofemoral lymphadenectomy, the disease recurs in 5–7%, which is historically unacceptably high compared to complete lymphadenectomy (48). After the removal of the sentinel inguinal lymph node, there is a recurrence of the disease inguinally in less than 3%, which is an acceptable risk given the low incidence rate compared to the morbidity after complete inguinofemoral lymphadenectomy (32).

10 Follow-up of patients with vulvar cancer after sentinel lymph node biopsy

There is currently not enough reliable evidence to support a uniform follow-up scheme for patients after early-stage vulvar cancer treatment. Local relapses can occur at any time, so close tracking, which is generally recommended for life, is crucial. After the primary surgical treatment, the first examination is performed after 2–8 weeks, followed by clinical examinations of the vulva and groin every 3–4 months for a period of two years. In the next three years examinations take place twice a year. At the end of this period, it makes sense to continue with annual clinical examinations (8,47).

11 Conclusion

With the development of a minimally invasive surgical technique for sentinel lymph node biopsy and the introduction of this method into the standard treatment of vulvar cancer, a major step has been taken to reduce morbidity and increase the quality of life of vulvar cancer patients. The proportion of patients in whom inguinofemoral dissection was performed unnecessarily decreased significantly. Finally, it should be emphasized again that vulvar cancer is a rare type of cancer. Therefore, it is sensible and necessary to treat patients in centres with a larger number of such cases and where the necessary logistics and knowledge are provided.

Conflict of interest

None declared.

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