Is Sentinel Node Biopsy in Patients with Vulvar Cancer State of the Art?

Purpose
We analysed the most recent data on the sentinel concept in vulvar cancer.

Results
The incidence of vulvar cancer is low and accounts for about 5% of gynecologic malignancies. The current standard therapy includes the radical local excision combined with an complete inguinal-femoral lymphadenectomy. We remark a high rate of post-operative morbidity such as wound healing complications, lymphocles, lymphedema of the legs. For this reason, the quality of life is significantly affected. We think that the use of the sentinel lymph node biopsy is of great interest. At this time the method is limited for stages 1 and 2 for up to 4 cm of tumor size. In vulvar cancer, there have only been few studies that have led to an advance in the sentinel technique. We see that there is a very high risk of overlooking the inguinal lymph node and possible metastasis in the area. If we compare vulvar cancer to breast cancer, the recurrence of lymph nodes in vulvar cancer has a much serious prognosis and is associated with a high mortality rate (75%).

Summary
We perform the sentinel lymph node (SNL) biopsy technique only under stringent quality requirements, as well as with an extensive explanation to the patient regarding the high recurrence rate and serious possible complications. Principally, this method is limited to patients with T1 and T2 vulvar cancers that have been determined by imaging (ultrasound, CT, MRI), without possible signs of an inguinal-femoral lymph node metastasis. The question of oncologic safety has not been definitively assessed. Further studies are necessary.

Keywords
Sentinel lymph node in Vulvar cancer, Lymphadenectomy

Introduction
Investigations showed that there was a doubling in the incidence of the rather rare vulvar cancer in the last three decades. There was a quadrupling of the risk in younger patients, especially in those with vulvar cancer.

Sentinel lymph node biopsy
The Sentinel lymph node (SnL) biopsy technique, first introduced in 1992, is a minimally invasive method for identifying the lymph node that is the first to receive lymphatic drainage of a tumor. In vulvar cancer, this technique has been shown to be effective in identifying metastases and guiding surgical planning. However, there are limitations to the use of sentinel lymph node biopsy in vulvar cancer, including a high rate of positive nodes in early stages and a higher rate of complications compared to other malignancies.

Conclusion
Sentinel lymph node biopsy is a valuable tool in the management of vulvar cancer, providing important information about the risk of metastasis and guiding treatment decisions. However, further research is needed to fully understand the role of sentinel lymph node biopsy in this disease.
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which is most likely attributed to HPV high risk infections (1). In the pathogenesis of vulvar cancers, particularly in young women, HPV infection plays a significant role. Non-HPV associated vulvar cancer in older patients seems to indicate a worse prognosis. The treatment of choice in the early treatment of vulvar cancer is local radical excision. In the case of more widespread disease, the vulva is partially or completely removed. The goal of the operation is a R0 resection with a 10 mm cancer free margin (2).

With a depth of invasiveness of 1 mm and less (pT1a-Carcinoma), the inguinal-femoral lymphadenectomy becomes obsolete. In histological entities such as basalioma or verrucous carcinoma, lymphadenectomy is rarely indicated. The depth of infiltration of squamous cell carcinomas shows a correlation with the probability of a diagnosis of inquino-femoral lymph node metastasis.

Carcinomas with an infiltration depth of more than 1 mm and lateral location require an ipsilateral inguinal-femoral lymphadenectomy. In the case of carcinomas near the midline with a distance of less than 1 cm, a bilateral inguinal lymphadenectomy is the current standard. The risk for inguinal lymph node metastasis is around 10% for patients with a tumor under 2 cm and about 25% for tumors that are 2 cm and larger (3, 4). With tumor-free ipsilateral lymph nodes, the probability of a contralateral lymph node metastasis is 0.4%.

The resection of inguinal lymph nodes is associated with a high morbidity. Wound healing complications occur in 15-45%, lymphoceles in 30%, and lymphedema in the legs requiring treatment in 20-69% of cases (5, 6).

For this reason, after the first publication of the sentinel lymph node biopsy technique (7), treatment options to reduce surgical invasiveness were reported (8).

Initially, only a superficial inguinal lymphadenectomy was proposed. However, this was reflected in the GOG Study 74 as insufficient and associated with a high rate of recurrence (9). In 15.6%, local recurrences were reported, half of which affected the vulva and the other half being inguinal recurrences.

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The first report regarding the sentinel lymph node biopsy technique in vulvar cancers was published in 1993 by Levenback et al. (10).

Following this, several predominately retrospective case reports were published regarding the sentinel technique and the inguinal-femoral lymphadenectomy.

All of these studies completed the sentinel lymphadenectomy through subsequent radical lymphadenectomy and indicated a high identification rate through the use of Technetium radiocolloid and blue dye (Fig. 1, Fig. 2).

The negative predictive value in case of a negative sentinel lymph node was almost 100%. Only a few studies have been published on solitary sentinel lymphadenectomy in patients with vulvar cancer.

Since the indication for the adjuvant radiation therapy is determined by the diagnosis of the lymph node involvement, an exact diagnosis of the lymph node is critical. The indication for an adjunct intraglandular radiation therapy is based on the presence of 3 or more lymph nodes metastases, and an extra-capsular extension, or a lymph node metastasis over 10 mm.

An additional recommendation includes carrying out the radiation or the pelvic lymph drainage areas or to conduct a pelvic lymphadenectomy.

**Studies in Sentinel Lymph Nodes**

The detection rate in case of using a combination of markers like technetium radiocolloid and blue dye in the sentinel lymph nodes is between 95% and 98%. If only radiocolloid blue dye is used, the results of the rates of detection were clearly worse, at around 69%. The number of false-negative results of the sentinel lymph nodes was under 3%, demonstrating a high sensitivity and a high negative predictive value.

In the prospective study GROINSS-V, published in early 2008, 467 Patients were studied in 15 large gynecologic-oncologic centers (enrollment was between the years 2000 and 2006) (11).

High standards for quality assurance were set at these operating centers. 276 patients had a median time of clinical follow-up of 35 months, and 202 patients were followed for at least 24 months. The inguinal-femoral recurrence rate was at 2.9%. The median of the recurrence time was 12 months. Based on the total number of patients, the rate of}

من حيث توصيات إضافية تتضمن:
- تطبيق المعالجة الإشعاعية أو تغذير العقد الملفاوية الحوضية أو استئصال العقد الملفاوية الحوضية.
- الدراسات حول العقد الملفاوية في الفرج
- إن معدل الكشف في حال استعمال كل من الواسطات مثل التغذير بالجذري والصباغ الأزرق في العقد الملفاوية في الفرج يتجاوز ما بين 95 – 98% إذا استعمل الصباي الأزرق الغرافي الشعاعي لوجد فإن معدل الكشف عن الانتقالات البؤرية حوالي 26%.
- ونجد الحالات التي يكون الاختيار سليم كاذب فقط 3% وبالتالي نظهر حساسية ونوعية إشارات الإصابة الفردية إلى الكشف عن حالات العقد الملفاوية في الفرج.
- وكان معدل النحس في المنطقة الأربانية الفخذية 23.9%.
- وكان المرضي 75.6% نصفها قصيرة.

هذا يوضح أن تردد الكشف في حالة استخدام الصباي الأزرق الغرافي الشعاعي لوجد في الحالات التي يكون الاختيار سليم كاذب فقط 3% وبالتالي نظهر حساسية ونوعية إشارات الإصابة الفردية إلى الكشف عن حالات العقد الملفاوية في الفرج.

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recurrence after 2 years was 0.03 (95% CI: 0.01 – 0.06), and in cases of unifocal vulvar cancer the rate was 0.023 (95% CI: 0.01 – 0.05). Within the group of 8 patients with inguinal recurrence, 2 patients presented with multifocal metastases, another 2 patients presented with a micro-metastases in the sentinel lymph nodes, which were not discovered during the primary histological examination. For 2 other cases, only one sentinel lymph node biopsy was removed, even though the pre-operative lymphoscintigraphy showed 2 sentinel lymph nodes. Six of the patients with inguinal recurrence died, indicating that secondary therapeutic interventions in the case of inguinal recurrence are associated with a poor prognosis. As expected, the mortality in the group of patients who underwent a complete lymphadenectomy due to affected sentinel lymph nodes. While the GROINSS-V study only recruited patients with vulvar carcinomas less than 4 cm in diameter, an American multicenter study, GOG 173, had an upper limit of 6 cm. The results of this study were reported at the ASCO 2009 meeting in a presentation by Levenback. This study had an accrual goal of 120 nodal positive patients. While the GOG 173 study did not set high standards regarding the level of experience of these participating institutions (47 member institutions, median number of patients per institution 6, range of patients 1-77), the time allotted for recruiting patients encompassed 10 years. 129 node positive patients were evaluated in the study. A sensitivity of only 89.9% was reached. The false negative predictive value was 4.4%. Patients with tumors greater than 4 cm had a doubly high chance of having a negative diagnosis by sentinel node procedure compared to patients with smaller tumors. In patients with a tumor of less than 4 cm, the study showed a false negative predictive value of 2.5%. Levenback concluded that the sentinel lymph node biopsy should be a subject of further studies. Additionally, the application of the sentinel lymph node biopsy technique is limited to patients with a vulvar carcinoma less than or equal to 4 cm in size. The surgeons performing the procedure mentioned the importance of a high index of suspicion for metastatic disease, and the need for further studies to determine the optimal indications for sentinel lymph node biopsy in patients with vulvar cancer.

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cEDURE should have extensive experience with the sentinel lymph node biopsy technique and should use a combination of tissue markers.

Data from the German multicenter study AGO Vulva regarding the sentinel lymph node technique showed, in a study of 127 patients who had undergone complete lymphadenectomy, a sensitivity of 92.3% (36/39 positive lymph nodes) and a false negative rate of 7.7% of cases (3/39). In all three cases the diameter of the tumor was located in the midline and was 1cm, 4cm, and 5.6 cm in size. In an additional case, the sentinel lymph node in the right groin tested positive, but there was a false negative on the left side (12).

Histological Workup of Sentinel Lymph Nodes
The results of the GROINSS-V Study indicate the vital necessity of a histopathological workup of sentinel lymph nodes. By first the pathologic ultra-staging with the preparation of a series of histological samples and then the implementation of immunohistochemistry by experienced pathologists, over 40% of the metastases in the sentinel lymph nodes could be discovered. Further studies have also supported the importance of using ultra-staging of the excised vulvar sentinel lymph node, since otherwise micrometastases can be overlooked in 20-30% of cases using conventional histology (13) (Fig. 3, Fig. 4).

The quintessence of all currently published studies regarding the sentinel lymph node technique in patients with vulvar cancer, specifically the results of the multicenter GROINSS-V Study and the GOG 173, set high requirements for performing a solitary sentinel lymphadenectomy. This came under consensus at the conference of the 6th Biannual International Sentinel Node Society Meeting 2008 in Sidney, Australia, and these requirements were again strictly formulated (14). Essential requirements should include the comprehensive qualifications and expertise of the whole team performing the procedure, in particular on the part of the surgeon.

As a minimal requirement, it was suggested that initially at least 10 sentinel lymphadenectomy

Fig. 4: The ultra-staging of the same vulvar sentinel lymph node with serial histological sections and immunochemistry (Cytoke...
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mies (with subsequent completion lymphadenectomy) had to be performed to gain sufficient experience in patients with vulvar cancer. Only clinical centers that deal with a relatively high number of patients with vulvar cancer and a yearly experience of more than 5-10 patients per surgeon are thus the conditions that must be met.

Further requirements include the monofocal squamous cell carcinoma of the vulva with a diameter under 4 cm as well as a pre-operative lymphoscintigraphy with surgical excision of all positively diagnosed sentinel lymph nodes. In the case of a midline tumor, the sentinel lymph nodes must be identifiable on both sides, and in the case of ambiguity, a complete lymphadenectomy should be performed. In patients with clinically positive or imaging suspicious lymph nodes, the sentinel lymph node biopsy technique should not be used. The use of ultra-staging for all sentinel lymph nodes (by immunohistochemistry, serial histological cuts) is essential, since in over 40% of cases only by ultra-staging the metastasis in sentinel lymph nodes

العقد اللمفاوية الفرجية والتي تم إدراجها في مركز هذه الدراسة، فإنها فقط المراكز التي تعامل مع عدد كبير نسبياً من المريضات اللواتي لدين سرطان المهبل سنوياً 5-10 مريضات لكل جراح، والشروط الأخرى تتضمن وجود سرطان شامل الخلايا وحيد البؤرة في المهبل وبقل الأقل من 4 سم، بالإضافة إلى إجراء تصوير اللمفاوي سكتنغرافي مع استئصال جراحي للعقد اللمفاوية الفرجية الإيجابية، في حال وجود الورم على الخط المتوسط فإنه يمكن التحري عن العقد اللمفاوية على الجانبين. وحتمي يتم إدراج المركز في هذه الدراسة، فإنها فقط المراكز التي تعامل مع عدد كبير نسبياً من المريضات اللواتي لدين سرطان المهبل سنوياً 5-10 مريضات لكل جراح، والشروط الأخرى تتضمن وجود سرطان شامل الخلايا وحيد البؤرة في المهبل وبقل الأقل من 4 سم، بالإضافة إلى إجراء تصوير اللمفاوي سكتنغرافي مع استئصال جراحي للعقد اللمفاوية الفرجية الإيجابية، في حال وجود الورم على الخط المتوسط فإنه يمكن التحري عن العقد اللمفاوية على الجانبين.

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can be diagnosed. Furthermore, clinical care and follow-up at three month intervals for two years should be ensured. Due to a very poor prognosis of inguinal recurrence, the patient must be educated in detail regarding the entire treatment plan.

Today the sentinel lymph node biopsy technique is not state of the art in vulvar cancer patients.

Since the abovementioned conditions indicate that a large-scale application of the sentinel lymph node biopsy technique at the current time is not possible, more multicenter studies must be carried out in order to determine what the true role of the sentinel lymph node biopsy technique is in vulvar cancer. The acceptable clinical conditions and safety standards must also be further investigated.

Literature


We found that the sentinel lymph node biopsy technique is a safe and effective method for identifying metastatic disease in patients with vulvar cancer. Further research is needed to determine the long-term outcomes of this technique. Additionally, education of healthcare providers is essential to ensure proper implementation of this method in clinical practice.