# Use of the Sentinel Lymph Node Technique Compared to Complete Inguino-femoral Lymph Node Removal in Patients with Invasive Vulvar Cancer in Germany

## Verbreitung der Sentinellymphknotentechnik im Vergleich zur kompletten inguinofemoralen Lymphknotenentfernung beim invasiven Vulvakarzinom in Deutschland

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**Key words**
- Vulvar cancer
- sentinel lymph node dissection
- complete inguino-femoral lymphadenectomy

**Schlüsselwörter**
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- komplette inguinofemorale Lymphonodektomie

## Abstract

In the current S2 guidelines, the standard surgical therapy for patients with vulvar cancer also includes inguino-femoral lymphadenectomy. However, in view of the severe side-effects associated with this approach such as problems with wound healing, lymphoceles and lymphoedema, the search is on for alternative treatments that could decrease treatment-associated morbidity and improve patients' quality of life, particularly for node-negative patients. The sentinel lymph node technique is currently the gold standard in the treatment of unifocal breast cancer (clinically negative axilla), and studies on the use of this technique in the treatment of vulvar cancer are promising. To date, the diagnostic accuracy of this method in vulvar cancer has only been evaluated in a single, one-arm, non-randomised, multicentre study. In preparation for a multicentre study, in 2010 we surveyed 41 German hospitals to investigate how often they used the sentinel lymph node technique compared to inguino-femoral lymphadenectomy. The hospitals were grouped according to hospital size and number of patients treated for vulvar cancer. The decision criteria to determine the type of procedure performed were also investigated. Finally, the hospitals were asked whether they would be willing to participate in a prospective clinical study to evaluate the sentinel lymph node technique in patients with vulvar cancer. The majority of surgeons questioned (73%) already had some experience with this technique in patients with vulvar cancer. In our survey, 27% of hospitals carried out inguino-femoral lymphadenectomy, 10% used the sentinel lymph node technique, and 63% used both methods. In 24% of hospitals, the standard procedure consisted of the sentinel lymph node technique supplemented by inguino-femoral lymphadenectomy. Only 20% of the institutions surveyed in our study carried out

## Zusammenfassung

Die inguinofemorale Lymphonodektomie stellt nach aktuellen Leitlinien das Standardverfahren beim Vulvakarzinom dar. Aufgrund erhöhter Raten an Wundheilungsstörungen, Lymphozelen und Lymphödemen könnten alternative Behandlungsmethoden insbesondere für nodalnegative Patientinnen zu einer Senkung der krankheitsassoziierten Morbidität und zu einer Steigerung der Lebensqualität führen. Die Sentinellymphonodektomie stellt beim unifokalen Mammakarzinom (klinisch unauffällige Axilla) den Goldstandard dar, und Studien zum Einsatz beim Vulvakarzinom weisen vielversprechende Ergebnisse auf. Bisher wurde in lediglich einer einarmigen, nicht randomisierten Studie die Wertigkeit dieser Methode überprüft. In einer Umfrage unter 41 deutschsprachigen Kliniken wurde 2010 die Verbreitung der Sentinellymphknotentechnik im Vergleich zur inguinofemoralen Lymphonodektomie erfasst. Die Kliniken wurden nach Größe und nach Anzahl der Vulvakarzinom-Patientinnen unterteilt. Erfasst wurde, welche Art der Lymphonodektomie nach welchen Entscheidungskriterien angewandt wird. Abschließend wurde die Bereitschaft zur Teilnahme an einer klinisch-prospektiven Studie zur Evaluation der Sentinellymphonodektomie beim Vulvakarzinom ermittelt. Die Mehrheit der Befragten (73%) hatte Erfahrung mit dieser Technik beim Vulvakarzinom. In 27% der Kliniken wurde die inguinofemorale, in 10% die Sentinellymphonodektomie und in 63% wurden beide Methoden angewandt. Eine Komplettierung der Sentinellymphknotentechnik wurde in 24% der Kliniken grundsätzlich durchgeführt. Bei der Sentinellymphonodektomie gaben 20% der Befragten an, gemäß Kriterien zu verfahren, die in den Konsensusempfehlungen empfohlen wurden. Die Mehrheit der befragten Kliniken würde an einer randomisierten klinisch-prospektiven Studie zur Evaluation der

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sentinel lymph node biopsy alone in accordance with the criteria of the consensus recommendations. The majority of the investigated institutions were willing to participate in a randomised prospective clinical study to evaluate the effectiveness of sentinel lymph node sampling in patients with vulvar cancer.

Wertigkeit der Sentinellymphonodektomie beim Vulvakarzinom teilnehmen.

## Introduction

In Germany, approximately 1600 women develop vulvar cancer every year, and around 620 women die of it. The incidence of vulvar cancer is approx. 2.5/100 000 and the mortality is 1.3/100 000 (RKI, 2006), although recent calculations by the Association of Population-based Cancer Registries in Germany indicate that the number of new cases every year in Germany may range between 3400 and 4000. The most common entity is squamous cell carcinoma (80–90%) [1]. The data from the Cancer Registries shows enormous differences between federal states in Germany with regard to age-specific incidence of vulvar cancer, which ranges from 2.1 to 8.1 (http://www.krebsregister-sh.de/datenbank/Vulva2011.pdf). The incidence of higher-grade HPV-associated vulvar intraepithelial neoplasias (VIN 3) is increasing, particularly among younger women [2–4]. One of the most significant prognostic factors for vulvar cancer is the presence or absence of lymph node metastasis. Depending on tumour size and infiltration depth, the standard surgical therapy for vulvar cancer consists of radical local tumour excision or complete/partial vulvectomy with unilateral or bilateral inguino-femoral lymphadenectomy. Excision of the inguinal lymph nodes does not merely remove potential lymph node metastasis, it also facilitates the correct staging for subsequent therapies and provides important information for disease prognosis. The argument for aggressive surgery in vulvar cancer is the high risk of death from missed inguinal involvement with subsequent regional or systemic metastasis. The argument against radical surgery is that approx. 70% of patients treated by complete removal of the inguinal lymph nodes had no metastasis [5–8]. Moreover, the radical surgical approach has a high morbidity: two thirds of patients subsequently have problems with wound healing, or go on to develop infections, lymphoceles or lymphoedema of the legs after removal of the inguinal lymph nodes [8–11, 21, 22].

Use of the sentinel lymph node technique could potentially be a less radical alternative in patients with vulvar cancer.

Forty-one hospitals treating differing numbers of patients for vulvar cancer were investigated. The survey aimed to evaluate the use of the sentinel lymph node technique to treat patients with vulvar cancer in Germany and compare the use of this technique with complete inguino-femoral lymphadenectomy. The survey investigated the extent to which hospitals complied with consensus recommendations and the willingness of hospitals to participate in a prospective clinical multicentre study to evaluate the oncological effectiveness of the sentinel lymph node technique in patients with vulvar cancer under real conditions.

## Methods

In a survey of hospitals performed by the Study Group for Gynaecological Oncology (AGO) in 2010, 41 hospitals in Germany answered questions on their use of the sentinel lymph node technique compared with complete inguino-femoral lymphadenectomy in patients with invasive vulvar cancer. The hospitals were divided into 4 categories: university hospitals, hospitals offering maximum care, tertiary care facilities and general hospitals. The hospitals were also differentiated into 4 groups according to the numbers of patients with vulvar cancer operated on annually: > 10 patients/year, 7–10 patients/year, 4–6 patients/year and < 3 patients/year. The gynaecological surgeons were asked about their experience with the sentinel lymph node technique for the treatment of breast cancer, endometrial cancer, cervical and vulvar cancer and about the surgical procedures used for lymph node dissection in patients with invasive vulvar neoplasias (inguino-femoral lymphadenectomy alone, full removal of lymph nodes with extirpation of the sentinel lymph nodes, or the sentinel lymph node technique alone, where indicated). If sentinel lymph node dissection alone was done, the preoperative criteria used in the respective hospital were investigated together with the incidence of inguinal lymphadenectomies performed to complete the procedure. Hospitals were also asked whether they were prepared to participate in a prospective clinical multicentre study to evaluate the oncological effectiveness of the sentinel lymph node technique in patients with vulvar cancer. The results of the survey were analysed using descriptive statistics.

## Results

Of the 41 German hospitals which participated in the survey, 44% (n = 18) were university hospitals, 19% (n = 8) were hospitals offering maximum care, 22% (n = 9) were tertiary care facilities, and 15% (n = 6) were general hospitals. As regards the number of patients with invasive vulvar cancer treated, 54% (n = 22) of the hospitals treated > 10 patients/year, 22% (n = 9) of hospitals treated between 7 and 10 patients/year, 19% (n = 8) treated 6–4 cases/year and 5% (n = 2) of hospitals treated < 4 patients/year (**Fig. 1**). Almost all of the hospitals had some experience of the

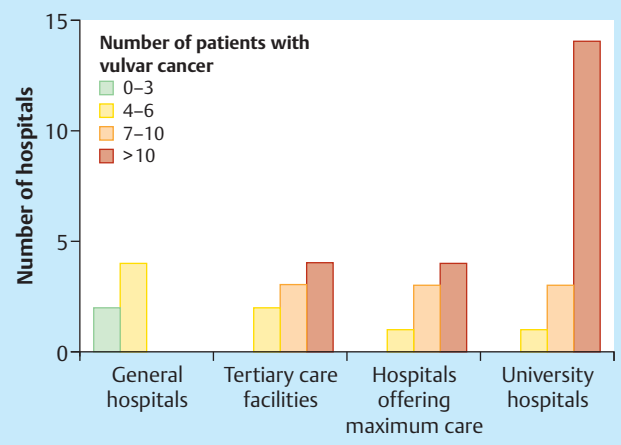


**Fig. 1** What is the average number of patients with vulvar cancer you have operated on in the past year?

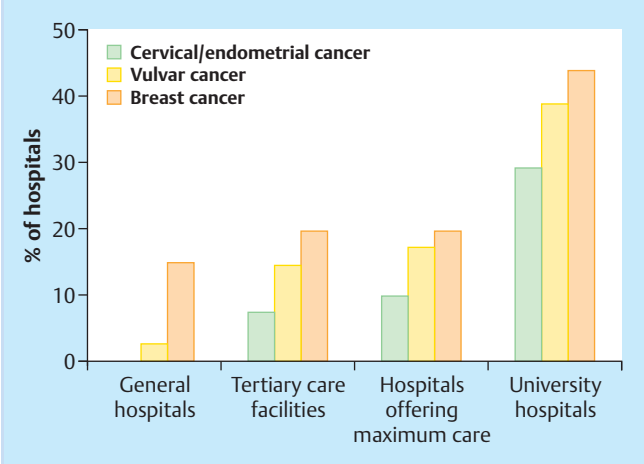


**Fig. 2** How experienced are you in sentinel lymph node dissection?

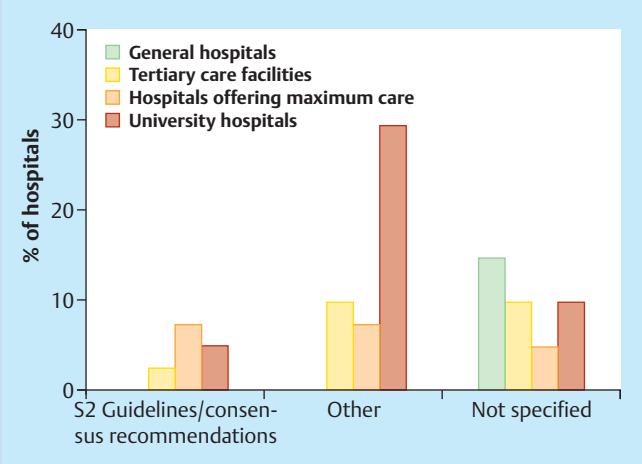


**Fig. 3** What is your technique for lymphadenectomy in patients with vulvar cancer?

sentinel lymph node technique, particularly in the treatment of breast cancer (97%; n = 40). In the survey, 73% (n = 30) of gynaecologists reported that they were experienced in treating patients with vulvar cancer, although the extent of experience depended on the hospital's status. In contrast, only 41% of gynaecologists (n = 17) were experienced in treating patients with cervical/endometrial cancer (**Fig. 2**). The surgical procedure used to treat patients with vulvar cancer was then differentiated further. In 2010, 27% of hospitals (n = 11) carried out only complete inguino-femoral lymphadenectomy while 10% of hospitals (n = 3) performed only sentinel lymph node extirpation, and 63% of hospitals (n = 26) routinely used both methods. 24% of hospitals (n = 11) carried out complete inguino-femoral lymphadenectomy after sentinel lymph node dissection in patients with advanced vulvar cancer. If sentinel lymph node biopsy alone was done, only 20% (n = 6) of surgeons complied fully with consensus recommendations (**Fig. 3**).

73% of hospitals surveyed in the study were willing to participate in a prospective clinical study to evaluate the effectiveness of the sentinel lymph node technique in patients with invasive vulvar cancer.

## Discussion

Use of the sentinel lymph node technique to treat patients with vulvar cancer (**Fig. 4**) could reduce surgery-associated morbidity. However, this approach should only be used after careful diagnosis and in strict accordance with oncological guidelines. The patient must be fully informed about the potentially lethal consequences of inguino-femoral recurrence.

Our results showed that use of the sentinel lymph node procedure alone in the treatment of vulvar cancer was still not very common at the time of our survey in 2010, although a prospective observational study showed a clear benefit of this method, provided the oncological guidelines were strictly complied with [12]. It should be noted, however, that use of the sentinel lymph node technique in vulvar cancer was only included in the S2 guidelines in 2009. The reported rates for sentinel lymph node detection are between 95 and 98% using combined labelling compared to the use of patent blue labelling alone (69%). Radionuclide labelling and intraoperative detection were reported to have a high sensitivity, a high negative predictive value and a low false-negative rate of less than 3% [13].

127 patients who underwent supplementary lymphadenectomy were included in the German multicentre sentinel lymph node study of the AGO Vulva. The sensitivity was 92.3% and the false-negative rate was 7.7% [14]. The results of the prospective observational GROINSS-V1 study for the period 2000 to 2006 were published in 2008. A total of 457 patients from 15 large gynaecological-oncological centres were included in this study. However, follow-up was short, with 276 patients followed up for 35 months and a total of 202 patients followed up for at least 24 months. The rate of inguino-femoral local recurrence was 2.9% and the median interval to recurrence was 12 months. However, the detection of metastasis in the sentinel lymph node was only possible using pathologic ultrastaging, (i.e. serial processing and immunohistochemical staining for cytokeratin [**Figs. 5** and **6**]), otherwise metastasis would have been missed in 42% of cases.

Six of the 8 patients with inguino-femoral recurrence died. Two of them had multifocal recurrence, two patients had micrometastasis of the sentinel lymph node not found at primary diagnosis,

**Fig. 4** Vulvar cancer extending from the left labium majus.

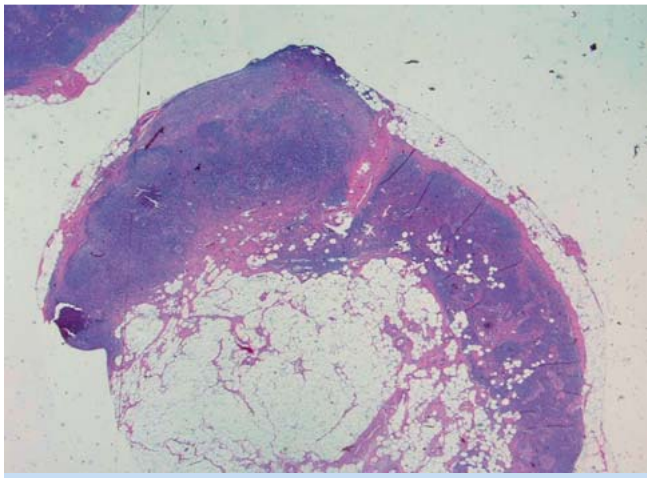

**Fig. 5** Conventional H & E staining shows no indication of sentinel lymph node metastasis.

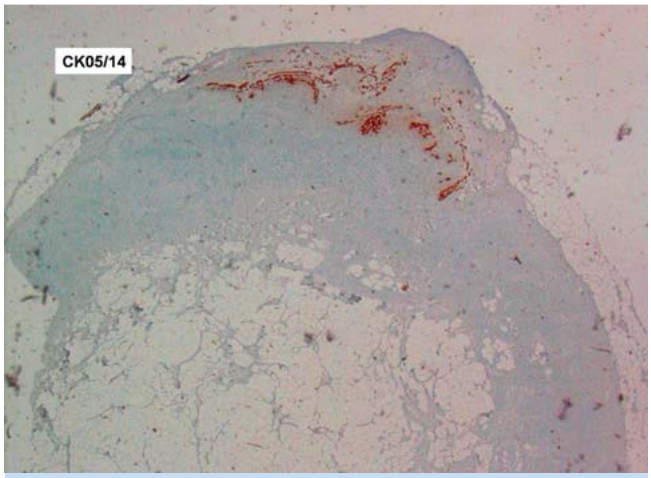


**Fig. 6** Ultrastaging of the same sentinel lymph node: serial processing and immunohistochemistry (cytokeratin CK 05/14) shows metastatic involvement.

and in 2 only one sentinel lymph node was dissected instead of the two detected at preoperative lymph scintigraphy. Thus, inguino-femoral recurrence was associated with a fatal outcome in most patients with vulvar cancer even after secondary surgery or radiotherapy. Surprisingly, the EORTC observational study did not find a strong difference in quality of life between patients treated with sentinel lymph node dissection and patients treated by complete lymphadenectomy [12, 15].

The GROINSS-V2 study was initiated in January 2006, based on results of the GROINSS-V1 study which had demonstrated the importance of adjuvant therapy in patients with positive sentinel lymph node involvement. One of the conclusions of the GROINSS-V1 study was that additional therapy was indicated if metastasis of any size was detected during sentinel lymphadenectomy. Although elective radiotherapy is already being used successfully in the therapy of squamous cell carcinoma of other origin, the data on the safety of this method for the treatment of patients with primary vulvar cancer and sentinel lymph node metastasis is controversial. In a case-control study by Manavi et al., 65 patients with T1 vulvar cancer and clinically unsuspicious inguino-femoral lymph nodes underwent inguino-femoral radiotherapy. The local rate of recurrence was 4.6% [16]. The study by Perez et al. [17] reported a recurrence rate of 10.5%, but tumour sizes in their study were larger (T1/T2) than in the study by Manavi et al. In a randomised control study, Stehmann et al. compared the outcomes after primary surgery for T1, T2 and T3 vulvar tumours with those after inguino-femoral radiotherapy of clinically unsuspicious lymph nodes. There was no recurrence after surgery (0/25), while 5/27 patients had recurrence after primary radiotherapy (rate of recurrence: 18.5%) [18]. The criticism that could be levelled at all of these studies is that deep lymph nodes were probably not adequately irradiated. In a retrospective analysis of 227 patients with vulvar cancer, the rates of local recurrence were similar for patients treated with inguino-femoral lymphadenectomy alone, with radiotherapy alone and with a combination of both methods. The authors' conclusion was that elective inguino-femoral radiotherapy in patients with vulvar cancer and minimal or microscopic tumours could help prevent most cases of local recurrence [19]. Based on the results of all studies to date, irradiation therapy could be used to prevent local recurrence in patients with vulvar cancer and minimal/microscopic inguino-femoral tumours, provided the dosage is adequate, the target volume is correct and the penetration depth is sufficient.

The rationale behind the GROINSS-V2 follow-up study on sentinel lymph node metastasis was to evaluate the safety of combined sentinel lymph node dissection and radiation compared with the standard procedure of additional inguino-femoral lymphadenectomy. According to the study protocol of the GROINSS-V2 study, adjuvant radiotherapy with 50 Gy was indicated in cases with sentinel lymph node involvement. Inclusion criteria for the study were squamous tumours with diameters of < 4 cm, an infiltration depth > 1 mm and no clinical indications of tumours in the inguino-femoral region. Criteria for terminating the study were defined prior to the start of the study; the criterion was a rate of recurrence of between 4 and a maximum of 6% for a collective of 135 recruited patients with vulvar cancer. In June 2010, no further patients were enrolled in the study as the upper limit for the rate of recurrence of 6% had been exceeded. At that point a total of 82 patients had been enrolled in the study, and 10 of these had recurrence in the inguinal region. An analysis of the cases in accordance with the study protocol showed that the number of inguinal recurrences was significantly higher in patients with sentinel lymph node metastases > 2 mm (9/45 vs. 1/46, $p = 0.008$). In addition, extracapsular extension of a lymph node metastasis was also associated with a higher risk of inguinal recurrence (4/15 vs. 5/74, $p = 0.04$).

The current S2 guidelines specifically emphasise the importance of careful examination and dissection prior to and during sentinel lymph nodectomy in patients with vulvar cancer. Prior to surgery the patient must be fully informed about the potentially higher rate of recurrence and the associated poorer prognosis. Patients must be followed up closely after surgery. According to the S2 guidelines, this method should only be used in patients with a tumour size ≤ 4 cm (FIGO I) and no clinical or sonographic evidence of lymph node metastasis. Surgeons must be experienced in the use of technique, with at least 10 previous sentinel lymph node dissections performed in patients with vulvar cancer. Biopsied tissue should be fully embedded and serial sections cut at intervals of 200 µm for immunohistochemical ultrastaging

(anti-cytokeratin pan antibodies) to detect micrometastasis. If histology is negative for metastasis, immunohistochemistry can be used for the detection of epithelial markers [20]. The patient should additionally be informed about the necessity for secondary inguino-femoral lymphadenectomy in the event of micrometastasis. A review of all currently available study results shows that the use of sentinel lymph node dissection alone is acceptable provided that all of the above criteria as described in the S2 guidelines are met.

The 6th Biennial International Sentinel Node Society Meeting 2008 held in Sydney, Australia formulated similar consensus recommendations on the use of sentinel lymph node dissection to treat patients with unifocal vulvar cancer. They found that the experience of the surgical team played an important role, with better results reported for surgeons who operated greater numbers of patients per year, generally more than 5–10 cases annually. The criteria for performing the procedure in patients with unifocal squamous cell carcinoma of the vulva were a maximum tumour diameter of ≤ 4 cm, preoperative lymph scintigraphy with identification and extirpation of all sentinel lymph nodes and the identification of the sentinel lymph nodes on both sides in cases with midline tumours. However, they recommended performing complete lymphadenectomy when inconsistencies or suspicious lymph nodes were present. The recommended postoperative follow-up of patients was at 3-month intervals.

In our survey of the criteria for sentinel lymph node dissection in patients with vulvar cancer, only 20 % of the surveyed institutions stated that they carried out sentinel lymph node extirpation in accordance with the above-listed criteria (**Fig. 3**). This could indicate these recommendations have not been sufficiently disseminated and therefore that the preconditions for performing sentinel lymphadenectomy alone in patients with vulvar cancer are insufficiently known. However, our survey found that experience of the sentinel lymph node technique was increasing, although experience largely depended on hospital size (**Fig. 2**). 73 % of surveyed hospitals were prepared to participate in further evaluations of this technique offering the possibility of further prospective clinical multicentre studies. Finally, it is important to qualify the results of our study by noting that only a limited number of the questionnaires distributed using the email list of the AGO were returned, and that this evaluation therefore does not reflect the real situation in German hospitals.

The modified GROINSS-V2 study could provide new information. It aims to evaluate the efficacy of adjuvant radiotherapy compared to supplementary inguino-femoral lymph node dissection in patients with unifocal vulvar cancer and sentinel lymph node metastasis of < 2 mm. AGO Vulva has planned a clinical observational study with strict inclusion criteria to evaluate the oncological safety of sentinel lymph node dissection alone in patients with vulvar cancer. In view of the rarity of this tumour entity, it is almost impossible to carry out a prospective randomised study, which would otherwise be preferable.

## Conclusion

The sentinel lymph node technique is increasingly being used in Germany to treat patients with invasive vulvar cancer. The current criteria for the comprehensive implementation of the sentinel lymph node technique to treat patients with vulvar cancer are based on the study of van der Zee et al. [12, 15]. Using the limited data available, our 2010 study showed that only a few hospitals used the sentinel lymph node technique in accordance with the guidelines on vulvar cancer or the strict conditions prescribed by international consensus recommendations. The majority of patients who had sentinel lymph node extirpation additionally underwent radical resection of the inguino-femoral lymph nodes, a procedure which is associated with increased morbidity. Only a few of the surveyed hospitals stated that they complied strictly with the criteria of the S2 guidelines published in 2008 and with the international consensus recommendations published in 2009. More information and a better dissemination of information are necessary. AGO Vulva has planned a clinical observational study to evaluate the oncological safety of the sentinel lymph node technique in patients with vulvar cancer. More than 73 % of hospitals that took part in our survey were prepared to participate in a prospective clinical observational study. However, given that the incidence of invasive vulvar cancer is 2.5/100 000 per year, it will be difficult to recruit sufficient numbers of patients to obtain statistically valid data.

## Conflict of Interest

The authors declare that they have no financial ties to any company mentioned in this article.

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