Sentinel Lymph Node Biopsy in Vulvar Cancer: A Health Technology Assessment for the Canadian Health Care Context

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Abstract

Objectives: Inguinofemoral lymphadenectomy for vulvar cancer is associated with a high incidence of groin wound complications and lymphedema. Sentinel lymph node biopsy (SLNB) is a morbidity-reducing alternative to lymphadenectomy. The objective of this health technology assessment was to determine the clinical effectiveness, cost-effectiveness, and organizational feasibility of SLNB in the Canadian health care system.

Methods: A review of the English-language literature published from January 1992 to October 2011 was performed across five databases and six grey-literature sources. Predetermined eligibility criteria were used to select studies, and results in the clinical, economic, and organizational domains were summarized. Included studies were evaluated for methodologic quality using the Newcastle-Ottawa Scale.

Results: Of 825 reports identified, 88 observational studies met the eligibility criteria. Overall study quality was poor, with a median Newcastle-Ottawa Scale score of 2 out of 9 stars. Across all studies, the detection rate of the sentinel lymph node was 82.2% per groin and the false-negative rate was 6.3%. The groin recurrence rate after negative SLNB was 3.6% compared with 4.3% after negative lymphadenectomy, and complications were reduced after SLNB. No economic evaluations were identified comparing SLNB to lymphadenectomy. Safe implementation of SLNB requires appropriate patient selection, detection technique, and attention to the learning curve.

Conclusions: Although study quality is poor, the available data suggest implementation of SLNB may be safe and feasible in Canadian centres with adequate procedural volumes, assuming that implementation includes careful patient selection, careful technique, and ongoing quality assessment. Cost-effectiveness has yet to be determined.

Key Words: Sentinel lymph node biopsy, vulvar cancer, lymphadenectomy, lymphedema, health technology assessment

Competing Interests: None declared.

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Résumé

Objectifs : La lymphadénectomie inguino-fémorale visant le cancer de la vulve est associée à une forte incidence de complications de plaie inguinale et de lymphœdème. La biopsie du ganglion sentinelle (BGS) est une solution de rechange à la lymphadénectomie qui permet d'atténuer la morbidité. Cette évaluation de la technologie du domaine de la santé avait pour objectif de déterminer l'efficacité clinique, la rentabilité et la faisabilité organisationnelle de la BGS au sein du système de santé canadien.

Méthodes : Une analyse de la littérature publiée en anglais entre janvier 1992 et octobre 2011 a été menée dans cinq bases de données et au sein de six sources de « littérature grise ». Des critères d'admissibilité prédéterminés ont été utilisés pour sélectionner les études et les résultats relevant des domaines clinique, économique et organisationnel ont été résumés. Les études admises ont fait l'objet d'une évaluation visant la qualité méthodologique au moyen de l'échelle Newcastle-Ottawa.

Résultats : Parmi les 825 rapports identifiés, 88 études observationnelles ont répondu aux critères d'admissibilité. La qualité globale des études était faible, le score médian sur l'échelle Newcastle-Ottawa étant de deux étoiles sur neuf. Dans ces études, le taux de détection du ganglion sentinelle était de 82,2 % par aine et le taux de faux négatif était de 6,3 %. Le taux de récurrence inguinale à la suite d'une BGS négative était de 3,6 %, par comparaison avec 4,3 % à la suite d'une lymphadénectomie négative; de plus, les complications étaient atténuées à la suite de la BGS. Aucune évaluation économique comparant la BGS à la lymphadénectomie n'a été identifiée. La mise en œuvre en toute sûreté de la BGS nécessite qu'une attention particulière soit portée à la sélection des patientes, à la technique de détection et à la courbe d'apprentissage.

Conclusions : Bien que la qualité des études ait été faible, les données disponibles semblent indiquer que la mise en œuvre de la BGS peut s'effectuer en toute sûreté et s'avérer faisable au sein des centres canadiens qui comptent des volumes d'intervention adéquats; bien sûr, cela présume que cette mise en œuvre inclut une sélection soignée des patientes, une technique rigoureuse et un contrôle continu de la qualité. La rentabilité demeure à déterminer.

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INTRODUCTION

Vulvar cancer is a rare gynaecologic malignancy, with an annual incidence in Canada of 2.4 per 100 000 women.[1] The incidence of vulvar cancer has been increasing over the last decade, with most of the increase attributed to human papilloma virus infection.[2] The cases related to HPV are thought to occur more often in younger women.[3,4] As vulvar cancer increasingly affects younger women, and cure rates continue to improve,[3] issues of quality of life and survivorship gain prominence. The treatment of early stage disease involves removal of the primary tumour and evaluation of the regional lymph node basin in the inguinofemoral region of the groin.[4] If the tumour is in a lateral position on the vulva, only the ipsilateral groin lymph nodes are removed, and if the tumour is within 1 cm of the midline, lymph nodes are removed bilaterally. Approximately one third of patients with stage 1 or 2 disease will have positive lymph nodes, thus two thirds of patients undergo a surgical procedure of no benefit. Unfortunately, there is no accurate non-invasive method for determining the presence or absence of lymph node metastasis.[5] Inguinofemoral lymphadenectomy has a high rate of short- and long-term complications, such as wound breakdown (in 17% of patients), infection (in 39% of patients), lymphocysts (in 40% of patients), and chronic lymphedema (in 28% of patients).[6] In fact, lymphedema is the complication associated with the lowest levels of quality of life in survivors.[7] A procedure that lowers the rate of complications associated with lymph node assessment without compromising survival is highly desirable.

ABBREVIATIONS

FNR	false-negative rate
GROINSS-V	GROningen INternational Study on Sentinel nodes in Vulvar cancer
HTA	health technology assessment
IFLD	inguinofemoral lymphadenectomy
IHC	immunohistochemistry
SLN	sentinel lymph node
SLNB	sentinel lymph node biopsy
Tc99	technetium 99

The sentinel lymph node concept is based on the premise that there is a first lymph node in a chain (or basin) of lymph nodes draining a particular area of the body. If the SLN is negative for metastasis, the remainder of the lymph nodes in the basin would also be free of tumour cells.[8] The main goal of the SLN procedure, which involves removing only one or two lymph nodes rather than the entire basin, is to decrease complications without affecting oncologic outcomes. Additional hypothesized advantages include detection of lymph nodes in unusual anatomic locations and improved detection of micro-metastases. The theoretical disadvantage is the potential to miss metastatic spread to the lymph nodes, which in vulvar cancer results in death of the patient 90% of the time. The SLN procedure has been used successfully in patients with breast cancer for assessment of the axillary lymph nodes, with lower rates of subsequent lymphedema of the arms than with full lymphadenectomy.[9] This procedure was first attempted for vulvar cancer in 1992,[10] using a radioactive technetium colloid tracer to identify the SLN. Since that time, several studies have been performed to assess the safety and efficacy of this procedure.

Identification of the SLN is accomplished using technetium 99 radio-labelled nanocolloid (a suspension of sulphur or albumin labelled with radioactive Tc99), or various colorimetric agents, or both. Tc99 is injected into the dermis surrounding the tumour on the vulva either the day before surgery or two to three hours before surgery, depending on the type of molecule used. The Tc99 nanocolloid then travels along the natural lymphatic channels to the SLN, which is by definition the first lymph node in that basin. The SLN(s) can then be visualized with lymphoscintigraphy (a gamma camera is used to visualize the radiation emitted from the Tc99-labelled molecules). At the start of surgery, the skin surrounding the tumour can be injected with a blue dye (e.g., patent blue, methylene blue, lymphazurin, or isosulfan blue), allowing lymphatic channels and the SLN to be visualized. Alternatively, a fluorescent agent (indocyanin green) may be injected, and the channels and node visualized using a near-infrared fluorescence imaging system.[11,12] The surgeon then makes a small incision overlying the expected location of the SLN. The location is predicted from lymphoscintigraphic images, by visualization of lymphatic channels, or by the use of a hand-held gamma probe, which identifies radioactivity. The blue and/or radioactive node is removed, and the surrounding area is examined for more blue or radioactive nodes.[13] Generally, if there is still radioactivity in the groin at a level of more than five to 10 times the background rate, then further searching for additional SLNs is performed.[14] Some authors recommend checking

for radioactivity in the groin (and at the site of injection of Tc99) again following removal of the vulvar tumour once background levels of radioactivity have fallen.[11]

During final pathologic examination, the SLN is often evaluated using ultrastaging. This time-consuming process entails examining more sections than usual in addition to IHC staining. Ultrastaging is feasible in SLNB because fewer lymph nodes will be examined; it is advocated by some to reduce the possibility of false-negative SLN and to enable identification of micro-metastases (≤ 2 mm) that may not otherwise have been identified using regular pathologic techniques.[12] These micro-metastases do appear to worsen prognosis.[12] If an SLN contains metastatic tumour cells, a full bilateral IFLD is recommended to remove any other potentially positive lymph nodes. Intraoperative frozen section of the SLN is performed at some institutions, allowing for completion of bilateral IFLD during the initial operative procedure in the case of a positive SLN.

Early publications assessed the false-negative rate of sentinel lymph node biopsy by removing the SLN and then completing a complete inguinofemoral lymphadenectomy regardless of the results of the SLN.[14–18] More recently, series in which only the SLNB procedure has been done have been reported.[12,18–24] Several recent publications have predicted that the SLNB procedure will become the standard of care for vulvar cancer, even though no systematic review of the effectiveness of this procedure has been completed.[22,25,26] Currently, several Canadian centres are performing SLNB for patients with early stage vulvar cancer, but most centres still perform a complete IFLD.

We wished to address this question: in patients with early stage vulvar cancer, is the sentinel lymph node procedure safe, clinically effective, cost-effective, and feasible in the Canadian health care system, compared with the current standard of complete inguinofemoral lymphadenectomy? The objectives of this assessment were to carry out a systematic literature review and to critically appraise and summarize the available information on the safety, clinical effectiveness, cost-effectiveness, and organizational implications of the SLN procedure for clinical stage 1–2 vulvar cancer.

The subject matter is relevant and timely, since many Canadian centres are in the process of switching their practice to include SLNB rather than IFLD, and only one previous health technology assessment has been completed for this intervention (available in Spanish only[23]). In addition, there are significant safety considerations for this intervention, as a false-negative evaluation of groin lymph nodes will generally lead to eventual death of the patient. The policy decision we wished to address was whether the SLN procedure should be adopted as the standard of care for treatment of Canadian patients with early stage vulvar cancer.

METHODS

This report follows the HTA reporting guidelines set out by the International Network of Agencies for Health Technology Assessment.[24]

A comprehensive literature search was designed with the aid of a library information specialist (online eAppendix 1). Both controlled vocabulary and free-text search terms were used to describe vulvar cancer, IFLD, and SLNB. The search was limited to studies published in 1992 or later, because both the concept of SNLB[27] and the first pilot study to evaluate lymphatic drainage in patients with vulvar cancer were published in 1992.[10] In addition, the search was limited to publications in English and those involving human subjects.

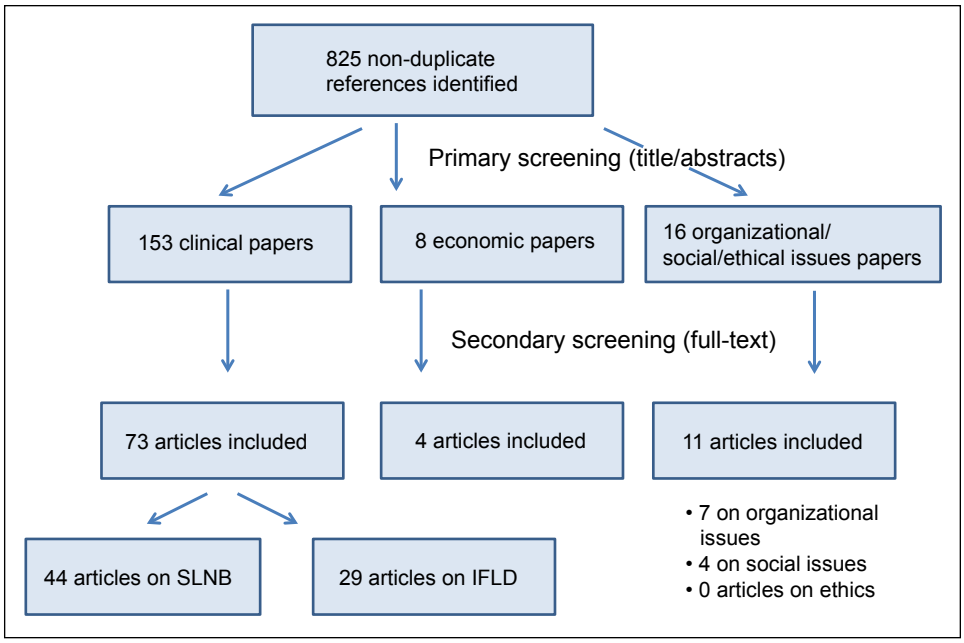
We searched the following databases using appropriate syntax and controlled vocabulary: HEED, OVID Medline (including in-Process and Other Non-Indexed Citations [PREM]), HealthStar, EMBASE, and the Cochrane library (including the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects, the Cochrane Central Register of Controlled Trials, the Health Technology Assessment database, and the Methods Studies, Economic Evaluations, and Cochrane groups). We also searched the following grey literature sources: ClinicalTrials.gov, CADTH, ICES, OHTAC, Institute of Health Economics, and the Centre for Reviews and Dissemination.

Primary screening was accomplished by reviewing titles and abstracts, and secondary screening was carried out using full-text articles. Screening criteria are provided in online eAppendix 2. Data were extracted from full-text articles that met the selection criteria (online eAppendix 3), and we applied a modified Newcastle-Ottawa Scale for observational studies to all articles on SLNB (online eAppendix 4).

RESULTS

The search results and the results of primary and secondary screening are shown in Figure 1. The reasons for study exclusion at full text screening are described in Figure 2. The search strategy identified 825 non-duplicate references, and 177 full-text articles were selected for

Figure 1. PRISMA flow diagram of article selection



secondary screening. Of these, 88 articles met the inclusion criteria and were included in this analysis.

One HTA was retrieved on the topic of SLNB in vulvar cancer.[23] This HTA, produced by the Galician Agency for Health Technology Assessment (Avalia-t) and published in Spanish, included literature published up to September 2009. The English abstract stated that the 19 studies included in the HTA demonstrated an overall detection rate of the SLN of 81% with blue dye and 98% with the combination of Tc99 and blue dye, an FNR of less than 2%, and a groin recurrence rate of 3%. No economic information was included in the abstract. The authors concluded that SLNB is a reasonable alternative to IFLD in selected patients with clinically early-stage vulvar cancer, provided the procedure is performed by an experienced multidisciplinary team. There is one ongoing HTA in the United Kingdom investigating the clinical- and cost-effectiveness of sentinel lymph node biopsy in patients with vulvar cancer, and this will provide a decision analytic model for economic evaluation of the procedure.[28]

We identified four randomized controlled trials that included patients having IFLD for vulvar cancer.[29–32] The IFLD arms of these trials were included in this HTA because they reported either complication rates or groin recurrence rates after a negative IFLD. No RCTs that included patients undergoing SLNB were identified.

All remaining reported studies (and all reported studies on SLNB) were observational in design. During primary screening, the articles were separated into the domains of clinical effectiveness, economic information, and organizational, social, and ethical issues. The results for each of these domains are discussed below. Where applicable, domains are divided into themes appearing in the literature.

Clinical Effectiveness

What are the detection and false-negative rates of SLNB?

Thirty-six studies performed SLNB followed by lymphadenectomy via separate groin incisions (the current standard approach to groin assessment) for each patient, allowing for calculation of the detection rate and the FNR of SLNB.[14–18,22,33–62] The following definitions are used for calculations of detection rate and FNR (since several authors did not use the correct definitions):

1. The detection rate is calculated as the number of groins in which an SLN is identified divided by the number of groins needing to be evaluated (bilateral groins must be evaluated for tumours within 1cm of the midline and only the unilateral groin for lateralized tumours);
2. The FNR is the number of false-negative SLNs (negative SLN but metastatic lymph nodes present in the same groin on IFLD) divided by the number of true positives plus false negatives (FN/TP+FN).

When no SLN is detected in a groin requiring evaluation, an IFLD should be performed. Therefore, finding positive lymph nodes in a groin in which no SLN is identified is not

Figure 2. Reasons for exclusion at full-text screening

Reasons for exclusion	Number of studies
Fewer than 5 patients treated	21
En-bloc lymphadenectomy only	8
Plastics procedures performed or foreign material used in wound closure	4
Includes only patients with stage 1A or advanced disease or with melanoma	18
Duplicate reporting (when overlapping series reported, only the most recent is included)	10
Not reporting complications of IFLD or SLNB, groin recurrence after negative IFLD or SLNB, or FNR of SNLB; not reporting outcomes separately for IFLD and SLNB patients; or not reporting outcomes separately for en-bloc lymphadenectomy and IFLD patients.	19
For economic or organizational/social/ethical papers: not reporting any issues relevant to vulvar cancer treatment or complications	9

considered a false-negative SLNB. Studies used a variety of methods to detect the SLN, including blue dye alone, Tc99 alone (with or without preoperative lymphoscintigraphy), or a combination of those methods.

The detection and false-negative rates for SLNB in patients who underwent SLNB followed by IFLD are shown in online eTable 1. The per-groin rate of detection is presented rather than the per-patient rate, since the decision to perform bilateral versus unilateral lymph node assessment is based on the location of the primary tumour. Three studies involving 111 patients assessed use of blue dye alone to detect the SLN.[17,18,33] The detection rate (per groin) for this group of studies was 63.5%, and the FNR was 8.7%. Seven studies involving 116 patients assessed use of only radiocolloid to detect the SLN.[34–40] The detection rate using this method was 82.6% (per groin) and the FNR was 8.8%. The combined techniques of blue dye plus radiocolloid were used in 1271 patients across 26 studies.[14–16,22,41–62] The detection rate was 86.3%, and the FNR was 5.8%. The 20 studies that assessed the combined technique and also the use of lymphoscintigraphy preoperatively[14,15,22,41–48,50,52–55,57–60] had a combined 1122 patients, a detection rate of 627/727 (86.2%), and an FNR of 16/244 (6.6%). The use of blue dye alone appears to lead to lower detection rates and higher false-positive rates. We recommend the use of either the combined technique or radiocolloid, with the addition of blue dye when an SLN cannot be identified.[63] The incremental benefit of lymphoscintigraphy is unclear from the published evidence, but may be helpful to determine the number and approximate location of SLNs.[63]

The quality of the studies included in online eTable 1 was generally poor. The Newcastle-Ottawa Scale score ranged from 1 to 4 out of a total of 9 stars, with a median score of 2 stars. No study was excluded because of low star rating because of the small numbers of patients in each study and the overall similarity in quality.

What is the recurrence rate after a negative SLNB?

Studies reporting on the recurrence rate after a negative SLNB included patients who had no further treatment after a negative SLNB. In general, patients who have a positive SLN go on to bilateral IFLD and are also treated with radiation therapy to the groins and pelvis if there is extracapsular spread or a metastasis 10 mm or larger in diameter, or if there are more than two micrometastases or bilateral micrometastases.[4]

A total of 11 studies including 591 patients evaluated the question of the groin recurrence rate after a negative SLNB (online eTable 2).[19–22,34,53,54,64–67] Over all the studies, the recurrence rate in the groin was 3.6% (range 0 to 22.2%). Follow-up in these studies was variable, but in most was at least two years, which is within the expected time-frame for groin recurrence. The quality of these studies was generally poor with a range of 0 to 5 stars and a median score of 3 stars.

What is the recurrence rate after a negative IFLD?

To determine whether a groin recurrence rate of 3.6% after negative SLNB is acceptable, it must be viewed in comparison with the groin recurrence rate after a negative

IFLD with separate groin incisions. We grouped studies examining recurrence rates after negative groin node dissection by the type of surgical procedure performed. If a study report simply stated that a "complete" or a "superficial" dissection was performed, these definitions were accepted. Otherwise, if the procedure was described, "complete dissection" was used to describe inguinal lymphadenectomy plus an attempt to remove the deep femoral lymph nodes, while "superficial dissection" was used to describe procedures in which no attempt was made to remove the deep femoral lymph nodes. Treatment of the saphenous vein or skeletonization of the femoral vessels did not affect the assignment of studies to the superficial or complete group.

Thirteen studies including 1077 patients reported the groin recurrence rate after a negative IFLD (online eTable 3).[68–80] The overall recurrence rate was 4.3%. In general, there was longer follow-up in these studies than in the studies of SLNB. Studies specifically reporting superficial lymphadenectomy had a recurrence rate of 5.7%, while studies reporting complete lymphadenectomy had a recurrence rate of only 1.3%. Patients having either superficial or complete lymphadenectomy had a recurrence rate of 9%, which was higher than expected, given the results of the other reported studies. Complete IFLD appears to lead to fewer groin recurrences than superficial inguinal lymphadenectomy, likely because of metastatic femoral nodes remaining in situ. Overall, these studies suggest the recurrence rate after lymphadenectomy is similar to that in patients undergoing SLNB.

What are the complication rates after SLNB?

The objective of the SLNB procedure is to reduce complications from groin lymph node assessment. Studies that reported complication rates after SLNB alone by necessity include only patients with negative groin lymph nodes, since those with positive lymph nodes then undergo bilateral IFLD with or without radiation therapy.

Six studies with a total of 532 patients evaluated complication rates after SLNB (online eTable 4).[19–21,54,55,67] Most studies reported complications per patient, but some reported complications per groin, making comparative analysis difficult. For the purposes of this review, we combined per patient and per groin complication rates, since excluding one or the other would further decrease the already small samples. Generally, study quality was poor with a median Newcastle-Ottawa Scale score of 3.5 stars.

Wound infection was reported in three studies including 316 patients, and the rate was 4.4% across all studies.[19–21] Wound breakdown was described in five studies with 378 patients and was found in 9.5% of patients.[19–21,55,67] Lymphocysts (fluid collections in the groin) were reported in three studies with a total of 80 patients and was present in 3.8%.[20,21,55] Finally, long-term lymphedema (> 6 months' duration) was reported in four studies that included 339 patients.[19,21,54,55] The overall rate of chronic lymphedema after SLNB was 1.5%.

What are the complication rates after IFLD?

To compare the complication rates after SLNB, studies that reported complication rates after IFLD are shown in online eTable 5. Some studies included patients undergoing SLNB followed by IFLD, and some included patients having IFLD alone. Studies were excluded if they used the "en-bloc" lymphadenectomy technique, as this procedure leads to very high rates of complications and is now not commonly performed.[6]

Studies were divided by the type of lymphadenectomy performed: superficial, complete, or mixed/undetermined. Overall, 27 studies including 2135 patients reported on complication rates after IFLD.[6,19,29–32,54,55,67–70,73,75,76,79,81–91] The rate of groin wound infection across all studies was 30.7%, groin wound breakdown occurred in 23.2%, and lymphocysts occurred in 15.5%. Chronic lymphedema occurred in 22.9% across all studies. Small differences were noted between surgical techniques, with the rates of lymphedema at 16.9%, 29.1%, and 22.8%, respectively, for the superficial, complete, and mixed groups.

Cost-Effectiveness

Four articles that included some information regarding the costs of treatment of vulvar cancer were identified.[92–95] Details of screening criteria and data extraction are provided in online eAppendix 3.

There were no published economic evaluations of SLNB for vulvar cancer or for the use of IFLD in vulvar cancer. Articles identified did provide information regarding the general cost of treatment of patients with vulvar cancer. These data are summarized in online eTable 6.

SLNB is likely to be more costly to perform than IFLD because of the involvement of nuclear medicine staff (although surgeons inject radiocolloid in the operating room in some settings), the need for isotopes, lymphoscintigraphy (not absolutely required) and gamma-probe equipment, and ultrastaging of sentinel nodes (requiring more time involving pathology personnel and costly IHC stains). Management of a positive SLNB may also incur increased costs if intraoperative frozen section diagnosis is not employed and a second operation is recommended for IFLD. There would, however, likely

be some cost savings from shorter operating times and hospital stays, fewer outpatient visits to manage drain care, wound complications, and lymphedema, and fewer costs for the patient related to managing long-term complications together with an earlier return to work. Unfortunately, no published economic evaluations were identified for this intervention.

Organizational Issues

The SLN procedure requires a multidisciplinary team, which may include nuclear medicine experts or gynaecologic oncologists (to inject the technetium colloid and perform a preoperative lymphoscintigram), gynaecologic oncologists (to accurately identify and remove the SLN using a hand-held gamma-probe, with or without visualization of blue-stained lymphatic channels), and pathologists (to perform ultrastaging[96] with or without frozen section).[63] Each of these participants must have training and experience in performing these duties. Currently, this multidisciplinary approach is used in some cancer centres for patients with breast cancer and cutaneous melanoma. Therefore, in some centres the only member of the team who may not be familiar with the procedure is the surgeon. Implementation of this procedure can be a complex undertaking, especially in centres in which SLNB is not currently performed for other forms of cancer. The five major issues raised by the articles identified were patient selection,[97] learning curve,[98] method of identification of the SLN,[99] frozen section,[100] and ultrastaging.[23,101,102] These are discussed below.

Patient selection

Most recent articles suggest patients should be well-selected before surgeons perform SLNB alone.[63,97] Patients with less than 1 mm invasion have a low likelihood of lymph node metastasis, and therefore do not require any groin lymph node assessment. SLNB should be restricted to those patients with tumours less than 4 cm in diameter, because data on the safety of SLNB in the setting of larger tumours is lacking.[97] There should be no obvious metastatic spread to the groin lymph nodes on clinical examination or imaging.[63] In fact, when a lymph node is completely replaced by tumour cells, the lymph flow does not seem to occur in the usual fashion, and a metastatic lymph node can be missed by the SLNB procedure.[98] Whether performing routine preoperative imaging studies on the groins prior to SLNB reduces the FNR is unknown, but such imaging is recommended by some authors to avoid missing an enlarged metastatic node replaced by tumour.[63,98] Finally, the GROINSS-V study found an increased rate of groin recurrence after negative SLNB in patients with multifocal disease, and the investigators amended their study protocol to exclude such patients.[19] The authors of this study reported groin recurrence in two of 17 patients (11.8%) with negative SLNB and multifocal disease, compared with six of 259 patients (2.3%) with negative SLNB and a unifocal vulvar lesion. Careful selection of patients with unifocal vulvar tumours 4 cm or less and clinically negative groins, with or without preoperative imaging, is recommended to improve the safety of SLNB.

Learning curve

During the learning curve for SLNB, metastatic lymph nodes can be missed when performing the SLNB procedure. Several authors have suggested surgeons should perform at least 10 successful SLNB procedures followed by complete IFLD without any false-negative results prior to performing SLNB alone.[63,98] In addition, five to 10 SLNB procedures should be performed annually to maintain this complex skill set and the organizational infrastructure.[19] The only study to compare results in the learning curve period with those in a later timeframe is that of Levenback et al. in 2001.[17] These authors reported a failure to detect the SLN in 36% of groin dissections in the first two years of performing this procedure, and a subsequent rate of non-detection of only 15% thereafter. Since vulvar cancer is rare, acquisition and maintenance of the skills necessary for performing SLNB poses a challenge for its implementation in Canada.

Method of identification of SLN

Most authors recommend that the combined technique of radiocolloid and blue dye should be used to identify the SLN.[63] Alternatively, radiocolloid could be used initially, with blue dye used intraoperatively if the SLN cannot be detected using radiocolloid.[63,98] This would prevent the rare side effect of allergic reaction to blue dye.[99] Regardless of the method of detection, the lymph nodes must be assessed unilaterally for lateral lesions, and bilaterally for lesions within 1 cm of the midline. If an SLN is not detected, an IFLD should be performed to assess the lymph nodes.

Frozen section

Frozen section allows histological evaluation of the SLN intraoperatively, prior to formalin fixation. The advantage of frozen section is that the surgeon is told intraoperatively whether the SLN is involved with tumour, allowing performance of IFLD at the initial operation. The sensitivity of frozen section is reported to be approximately 80% (frozen section will identify a metastasis that is present 80% of the time).[98] However, in the large multicentre GROINSS-V observational study, the sensitivity of frozen section was only 48%, with specificity of 100%, negative predictive value of 78%, and positive predictive value of 100%.[12] The disadvantages of this

technique include the time and cost required to perform it; in addition, the process (bisecting fresh lymph nodes and freezing one segment) can cause some tissue destruction, leading to the possibility of missing micrometastases.[103] Consensus has not yet been reached about whether frozen section should be performed on the SLN.[63] It was used in six of the 41 reported studies included in this HTA (15%).[15,16,42,52,55,56]

Ultrastaging

Ultrastaging includes finely sectioning the SLN at very small intervals and staining with H&E, followed by immunohistochemistry stains if no metastasis is identified with H&E. Ultrastaging is too time-consuming to be performed on all lymph nodes removed at IFLD, but since there are generally only one or two SLNs, ultrastaging is feasible in this setting. Ultrastaging was performed in 27 of the 41 studies included in this HTA (66%).[14–16,18–22,37,38,40,41,43–45,47,48,50,52–55,57,59,60,65,67] In general, most authors recommend ultrastaging, as it has improved the sensitivity of the diagnosis of lymph node metastasis.[98,104] For example, in the GROINSS-V study SLN metastases were found by routine H&E in 80/135 patients (59%), by ultrastaging with H&E in 55/135 (41%), and by ultrastaging with IHC in 36/304 patients (12%).[14] In this study, all three steps contributed to improved diagnosis. However, some authors have recommended ultrastaging with H&E, but omitting IHC, since that component of ultrastaging did not add any sensitivity to the technique in other studies.[101]

Social and Ethical Issues

The treatment of vulvar cancer can lead to long-term complications that impact the quality of life of survivors.[105] However, assessment of the lymph nodes is important to guide further treatment (usually radiation therapy), to determine prognosis, and also to improve survival by preventing groin recurrence. The SLNB procedure seems to reduce the rate of complications while maintaining the groin recurrence rate at a level similar to that of IFLD; however, this observation is based on poor-quality data. Communicating the SLN concept, the relatively small amount of data supporting the safety of the procedure, and the possible effect on quality of life after curative surgery can be time-consuming, but is important for true informed consent. Patients must have enough information to allow them to make treatment decisions consistent with their values. The literature discussing social and ethical issues related to SLNB in vulvar cancer is shown in online eTable 7.[105–108]

In general, patients who underwent SLNB alone had higher rates of satisfaction with their treatment than patients who underwent IFLD because of a positive SLN.[106] The SLNB group was more likely to recommend this procedure to a friend, regardless of the FNRs. They had fewer symptoms from complications, but this did not affect overall quality of life in the small study sample.[106] Patients who had undergone IFLD, either prior to the development of SLNB or because of a metastatic lymph node first identified by SLNB, were concerned about the possibility of false negatives with the SLNB procedure. These patients were more concerned about the risk of false negatives than were physicians who treat vulvar cancer.[107] In two studies assessing patient acceptance of various FNRs, 34% of patients preferred SLNB over IFLD if the FNR was 5%,[107] and only 48% of patients would recommend SLNB to a friend if the FNR was 10%.[106] Although the results of these studies are potentially biased by the treatment outcomes experienced by the participating patients, they point to the need for further qualitative research to fully understand the patient perspective. Clearly, the treatment of vulvar cancer has a significant impact on a person's social roles and self-image, and these issues should be discussed with patients preoperatively.[108]

DISCUSSION

The SLNB procedure for early stage vulvar cancer has been reported in 45 studies since 1992,[14,15–21,34,33–62,64–67,106,109] and is currently performed routinely in some centres. Across all published reports, the detection rate of SLN procedure is 82.2% and the FNR is 6.3%. For those patients undergoing SLNB alone, the groin recurrence rate after a negative SLNB is 3.6%, compared with a groin recurrence rate of 4.3% after IFLD through separate incisions. These results must be viewed with caution because they are based on observational studies, which were generally of poor quality. The Newcastle-Ottawa Scale was used to assess the methodological strength of each of the SLNB studies, and the median score was 2 out of 9 stars. Ideally, an RCT should be performed comparing a program of SLNB with FLD in the treatment of early stage vulvar cancer. Although this would provide necessary high-quality efficacy evidence to confirm the results of the observational studies, it is unlikely an RCT will be performed, because the incidence of vulvar cancer is very low.[19]

The importance of minimizing the FNR in vulvar SLNB cannot be overstated, since patients with vulvar cancer and negative groin lymph nodes do not receive any adjuvant treatment. Leaving behind a metastatic lymph node likely leads to a high incidence of recurrence in the groin, which is often fatal.[12] This situation is in contrast to SLNB in breast cancer, where FNRs are higher (ranging from 0 to 29%, with an average FNR of 7.3%),[110] but axillary recurrence rates remain low since most patients receive adjuvant treatment.[19]

Complications appear to be fewer after groin SLNB alone than after IFLD. Rates of wound infection are 4.6% after SLNB and 30.7% after IFLD; wound breakdown occurred in 9.5% versus 23.2% of patients, and lymphocysts occurred in 4.5% versus 15.5% of patients. Most importantly, chronic lymphedema occurred in 1.5% of patients after SLNB alone and 22.9% of patients after IFLD. Complications from evaluation of the groin lymph nodes negatively affect patients' social roles and self-image, and reduction of these complications is therefore an important goal in the management of vulvar cancer.

Some authors have suggested that in addition to reducing morbidity from complications, SLNB may actually improve overall detection rates of metastatic lymph nodes. In studies reported by de Hullu et al.,[14] Hauspy et al.,[16] and Van der Zee et al.,[19] rates of lymph node metastasis were higher than expected (34%, 39%, and 31.5% respectively) given the early stage of the selected patients, leading to the possibility that more metastases can be identified with SLNB. Detection of SLNs using lymphatic mapping allows nodes in unusual anatomic locations to be identified.[111] SLNs have been reported in a very medial location near the pubis,[41] and these nodes may not be removed with standard IFLD. Therefore, both macro- and micrometastases may be missed if they are present in a lymph node that would not be removed by IFLD, but may be identified by SLNB. Micrometastases that are too small to be detected on routine pathologic examination may also be detected more frequently by ultrastaging the SLNs.[16] Ultrastaging would be too labour-intensive to perform on all nodes removed by IFLD, and so can be used routinely only during SLNB. These micrometastases do appear to have prognostic significance, since there does not appear to be a size cut-off below which there is no risk of additional groin metastases.[12]

Research is being conducted to determine the best treatment for patients with a metastatic SLN. At this time, patients generally undergo bilateral IFLD, followed by groin and pelvic radiation if more than one lymph node is involved.[4] This combination of lymphadenectomy and radiation leads to a high incidence of morbidity. GROINSS-V-II is a multicentre observational study investigating the treatment of SLN-positive patients with radiation only instead of combined IFLD plus radiation.[12] This study is ongoing, and is expected to accrue patients for another three years.

There have been no economic evaluations of the treatment of vulvar cancer. Only simple cost data for some aspects of treatment were identified in our review. Although SLNB is expected to be more costly to perform than IFLD, there would likely be significant improvements in patient quality of life and savings related to fewer short- and long-term complications. Regardless of the expenditures or savings related to SLNB, the overall budget impact for the Canadian health care system is expected to be small, given that only 400 women are found to have vulvar cancer each year.[1] The lack of any economic evaluations for treatment modalities for vulvar cancer is a significant gap in our knowledge. Future trials of SLNB in vulvar cancer could consider collecting economic data to facilitate economic evaluation.

Significant organizational issues arise with the implementation of SLNB. The most important issues in the Canadian context are addressing the learning curve and maintaining surgeon competence when only 400 cases of vulvar cancer are diagnosed annually across the country and only a proportion of women with the disease would be appropriate candidates for SLNB. It is generally recommended that surgeons perform at least 10 successful SLNB procedures followed by IFLD prior to performing SLNB alone, and that five to 10 cases per year are needed to maintain competence.[63,98] Centres across Canada should examine the annual number of patients treated for early stage vulvar cancer to determine whether SLNB is feasible in their region. Although the treatment of vulvar cancer is already centralized in regional cancer centres, it is likely that one or two gynaecologic oncologists per centre would have to be designated to perform all procedures to maintain adequate volumes for competence.

Attention to the learning curve extends to all members of the multidisciplinary team. Centres considering implementation of SLNB for vulvar cancer must ensure all health care professionals involved obtain the skills necessary for their role in the SLNB procedure. In centres where nuclear medicine physicians perform the radiocolloid injections, training is needed to gain competence in this skill. The availability of specialist gynaecologic pathologists is preferable for interpretation of surgical specimens, but these individuals may benefit from additional experience with ultrastaging. Oncology nurses may require education on the potential risks and benefits of SLNB, as these nurses often participate in preoperative patient counselling. In addition, centres performing SLNB should adopt strict guidelines for patient selection and technique, and perform ongoing quality assurance measures to ensure groin recurrence rates are not higher than expected.

There are social and ethical issues inherent in treatment decision making in vulvar cancer, and these issues have received relatively little attention. Further qualitative research could enrich our understanding of the patient perspective and could guide future innovations in the treatment of this disease.

CONCLUSIONS

The evidence supporting the use of SLNB in vulvar cancer is of low quality. However, the available evidence suggests that SLNB has clinical effectiveness similar to IFLD with lower complication rates. This has led to the adoption of SLNB as standard management for early vulvar cancer in several Canadian centres. We must ensure that the clinical results reported in the literature are achieved in Canadian centres performing SLNB. Currently, implementation of the SLNB procedure appears to be safe and feasible in cancer centres with adequate patient volumes, assuming careful patient selection, meticulous technique by all members of the multidisciplinary team, and ongoing quality assurance programs. Quality assurance can be carried out in the context of clinical trials, or using patient registry databases that are periodically evaluated for groin recurrence and survival rates. Future studies should include outcomes important to patients and economic information to allow the performance of economic evaluations.

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