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Evidence-Based Series 4-17 Version 2

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Sentinel Lymph Node Biopsy in Vulvar Cancer

Members of the Expert Panel on Sentinel Lymph Node Biopsy in Vulvar Cancer

Report Date: January 26, 2018

An assessment conducted in November 2023 deferred the review of Evidence-Based Series (EBS) 4-17 Version 2. This means that the document remains current until it is assessed again next year. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

EBS 4-17 is comprised of four sections. You can access the summary and full report here: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/496

Section 1:	**Guideline Recommendations (ENDORSED)**
Section 2:	**Evidentiary Base**
Section 3:	**Development Methods, Recommendations Development, and External Review Process**
Section 4:	**Document Assessment and Review**

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Evidence-Based Series 4-17 Version 2

Guideline Report History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES and KEY CHANGES
	Search Dates	Data		
Original version 2014	October 2011 to March 2013	Full Report	Web publication	NA
Current Version 2 January 2018	2013 to August 2017	New data found in Section 4: Document Assessment and Review	Updated web publication	2014 recommendations are **ENDORSED**

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Evidence-Based Series #4-17: Section 1

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Sentinel Lymph Node Biopsy in Vulvar Cancer: Guideline Recommendations

A Covens, C Reade, EB Kennedy, E Vella, W Jimenez, T Le, and the Gynecologic Cancer Disease Site Group

Report Date: July 17, 2014

These guideline recommendations have been ENDORSED, which means that the recommendations are still current and relevant for decision making. Please see Section 4: Document Assessment and Review for a summary of updated evidence published between 2013 and 2017, and for details on how this Clinical Practice Guideline was ENDORSED.

GUIDELINE OBJECTIVES

1. To determine whether sentinel lymph node biopsy (SLNB) can safely and effectively identify women with node-negative, early-stage vulvar cancer and can be used as an alternative to inguinofemoral lymph node dissection (IFLD).
2. To provide guidance with respect to the appropriate techniques and procedures in SLNB for women with early-stage vulvar cancer. These include:

- Selecting appropriate patients
- Determining the appropriate technique
    - learning curve and maintenance
    - which tracer to inject
    - whether lymphoscintigraphy should be used
    - where and when to inject
    - role of intraoperative frozen-section analysis
    - role of ultrastaging and the use of immunohistochemistry
- Management of patients with positive sentinel lymph nodes

TARGET POPULATION

Women in Ontario with early-stage (T1 or T2, <4 cm) squamous cell cancer of the vulva are the target population.

INTENDED USERS

This guideline is intended for use by gynecologic oncologists and other clinicians involved in the surgical management of early-stage vulvar cancer.

NOTE:

The use of SLNB in the case of previous excision of the primary tumour, or in recurrent disease was not covered in this guideline. The Working Group feels there is currently insufficient high quality evidence to warrant a review of this literature at this time. ***(added January 2018)***

RECOMMENDATIONS, KEY EVIDENCE, AND JUSTIFICATION

RECOMMENDATIONS FOR PATIENT SELECTION

- SLNB is recommended for women with unifocal tumours <4 cm in size and clinically nonsuspicious nodes in the groin.
- There is insufficient evidence to make a recommendation for or against SLNB for women with tumours ≥4 cm or women with multifocal disease.
- SLNB is not recommended when there are clinically suspicious groin nodes.

Summary of Key Evidence for Recommendations for Patient Selection

The studies in the literature were judged to be of lower quality because of the observational and mainly noncomparative study designs used and an absence of randomized controlled trials. There were similar detection rates for the combined technique of blue dye and radiocolloid (87%, 95% CI 81%-92%) and the radiocolloid alone group (84%, 95% CI 74%-93%). The pooled detection rate per groin was higher with the combination of blue dye and radiocolloid (87%, 95% CI 81%-92%) or radiocolloid (technetium-99 [Tc99]) alone (84%, 95% CI 74%-93%) compared to blue dye alone (63%, 95% CI 49%-77%). The false-negative rates were similar for the three techniques (blue dye 9%, 95% CI 0%-27%; radiocolloid 10%, 95% CI 1%-23%; combined 7%, 95% CI 4%-9%). The pooled rate of groin recurrence after a negative SLNB result was 3% (95% CI 2%-5%) and after a negative complete IFLD result was 1% (95% CI 0%-3%). As well, the rate of complications was higher with complete IFLD for wound infection (28%, 95% CI 17%-40%), wound breakdown (23%, 95% CI 18%-28%), lymphocysts (18%, 95% CI 11%-25%), and lymphedema of greater than six months' duration (25%, 95% CI 18%-33%) compared with SLNB (wound infection 4%, 95% CI 1%-9%; wound breakdown 6%, 95% CI 2%-12%; lymphocysts 4%, 95% CI 0%-10%; lymphedema 2%, 95% CI 0%-7%).

One paper by van der Zee et al. 2008 included in the Reade et al. review found that women with multifocal disease had higher recurrence rates after SLNB (11.8%, 2/17) compared with women with unifocal disease (2.3%, 6/259) (1,2). Also, most studies that assessed patient outcomes after SLNB selected women with tumours that were <4 cm (2). Therefore, very little information is available to assess the safety of SLNB in women with larger tumours.

Justification for Recommendations for Patient Selection

The Working Group considered the benefits of SLNB (lower rates of wound infection, wound breakdown, formation of lymphocysts, and long-term lymphedema) outweighed the potential increased risk of death in 90% of patients with missed metastatic spread to the lymph nodes (2). There is emerging data that SLNB with ultrastaging, a technique that examines more sections than routine pathology, is more sensitive at detecting lymph node metastases than conventional lymphadenectomy for other cancers (3,4). If this is the case for vulvar cancer, then SLNB will potentially have fewer missed metastases. The Working Group also concluded that the evidence suggested that the rate of recurrence of vulvar cancer was similar for SLNB and IFLD.

The Working Group chose to recommend SLNB for patients with unifocal disease based on the large GROningen INternational Study on Sentinel nodes in Vulvar cancer (GROINSS-V) by van der Zee et al. in 2008 (1). Also, since most studies included patients with tumours that were <4 cm, the Working Group recommended SLNB for this subgroup of patients. SLNB was not recommended for patients with clinically suspicious groin nodes because of the potential elevated false-negative rate and because this subgroup of patients were not included in many of the studies.

RECOMMENDATIONS FOR APPROPRIATE TECHNIQUES AND PROCEDURES

Vulvar cancer is a rare condition and the recommended procedure is technically challenging. Appropriate surgical training (i.e., supervised experiences with SLNB procedures followed by complete IFLD without any false negatives and ongoing annual experience with cases to maintain competence) is recommended to optimize patient outcomes and safety.

- This procedure should be performed by gynecologic oncologists in Gynecologic Oncology Centres. For more information on organization of gynecologic oncology services in Ontario, including a recommendation for centralization of services for vulvar cancer, please refer to EBS #4-11: Organization of Gynecologic Oncology Services in Ontario (5). Although volume has not been explicitly studied, the Working Group agrees that successful experience with SLNB followed by IFLD in at least 10 patients per centre is recommended.
- Radiocolloid tracers should be used alone or with blue dye. In patients where lymphoscintigraphy did not identify a sentinel node in the groin(s) of interest, the addition of blue dye should be used.
- Blue dye alone should be discouraged because of its low detection rate.
- There is insufficient evidence to make a recommendation for or against the use of near-infrared tracers.
- There is insufficient evidence to make recommendations regarding lymphoscintigraphy, although it may facilitate the surgical procedure by identifying the presence, location (unilateral vs. bilateral), and the number of sentinel nodes.
- Four quadrant intradermal injections into normal tissue at the margins of the tumour are recommended.
- Radiocolloids can be injected 30 minutes to 24 hours before the surgical procedure. The timing depends on the size of the radiocolloid. The directions in the manufacturer package insert should be followed.
- Blue dye should be injected in the same location as the radiocolloid after induction of anesthesia.
- A node with five times more than the background radioactivity should be used to identify a sentinel lymph node.
- To help identify blue nodes, surgeons should look for and follow blue lymphatic channels.
- There is insufficient evidence to make a recommendation for or against the use of frozen-section analysis.
- Ultrastaging should be used to assess for metastatic tumour(s) in the sentinel lymph nodes.

Qualifying Statements for Recommendations for Appropriate Techniques and Procedures

For squamous cell carcinoma only, after trimming the fat, the sentinel lymph node should be subjected to ultrastaging by serially sectioning the lymph nodes into 3-mm blocks. At

least two sections from each block, located 40 μm apart, should be examined to determine whether they contain tumour cells. If routine hematoxylin and eosin staining tests negative for metastatic disease on the first slide, immunohistochemical cytokeratin staining should be performed on the second slide.

Summary of Key Evidence for Recommendations for Appropriate Techniques and Procedures

Only one study by Levenback from the Reade et al. review (2) examined the impact of the learning curve on detection rates of SLNB (6). They found a 36% failure rate to detect a sentinel node in groin dissections in the first two years, and a 15% failure rate afterward.

The pooled detection rate per groin was substantially higher with the combination of blue dye and radiocolloid (87%, 95% CI 81%-92%) compared with blue dye alone (63%, 95% CI 49%-77%). The radiocolloid (Tc99) alone group had higher pooled detection rates (84%, 95% CI 74%-93%) than the blue dye alone group (63%, 95% CI 49%-77%). There were similar detection rates for the combined technique (87%, 95% CI 81%-92%) and the radiocolloid alone group (84%, 95% CI 74%-93%). All three techniques (blue dye 9%, 95% CI 0%-27%; radiocolloid 10%, 95% CI 1%-23%; combined 7%, 95% CI 4%-9%) had similar false-negative rates. No evidence was found for infrared tracers.

The Reade et al. review included three studies that reported on the diagnostic accuracy of frozen-section analysis (2). A large study found low sensitivity (48%) but high specificity (100%) for frozen-section analysis (7), whereas two older and smaller studies found sensitivities and specificities of >90% (8,9).

Eight of 12 studies included in the Reade et al. review found that ultrastaging increased the detection of metastases in sentinel lymph nodes previously found to be negative and four studies found no difference with additional ultrastaging (2). Two studies suggested that immunohistochemistry increased the detection rate beyond routine pathology (7,10) and one study did not (11). Furthermore, although one study did not find a correlation between occult lymph node metastases and survival rate ($p>0.05$) (12), a recent, large study found that the five-year disease-specific survival rate was significantly higher for women with positive sentinel lymph nodes detected by ultrastaging (92.1%) versus the survival rate for women identified by routine pathology (64.9%, $p<0.0001$) (7).

Justification for Recommendations for Appropriate Techniques and Procedures

The Working Group agreed upon a minimum of at least 10 correlated procedures per centre with full-node dissection based on the van der Zee study (1). This large study had a low recurrence rate after a negative SLNB result (2%) and centres needed to have completed at least 10 successful procedures to participate.

From the evidence, using radiocolloid tracer with or without blue dye had the highest detection rates. Therefore, the Working Group recommended radiocolloid tracers should be used either alone or with blue dye routinely; for patients in which lymphoscintigraphy does not identify a sentinel node in the groin(s) of interest, the addition of blue dye should be used. The recommended techniques in administering the tracers were based on the standard practice of the Working Group. The qualifying statements for the minimum number of sections were based on the standard practice of the Working Group and were used by the Gynecologic Oncology Group study by Levenback et al. 2012 (10).

The Working Group believed there was insufficient evidence to make a recommendation for or against the use of frozen-section analysis. The advantage of analyzing frozen sections is that it avoids a potential second procedure. The disadvantage is that processing the specimen for frozen section may reduce the amount of available tissue for permanent section analysis. There was also insufficient evidence to make a recommendation for lymphoscintigraphy.

Ultrastaging examines more sections than usual in addition to immunohistochemical staining and was recommended because the evidence suggested it may increase the detection of metastases in sentinel lymph nodes previously found to be negative and may have a

positive effect on survival rate. The Working Group believed the benefit of increased detection of metastases using ultrastaging outweighed the harms, including potential overtreatment of patients with micrometastases and the unclear clinical significance for patients with isolated tumour cells. The Working Group also believed the benefit of increased detection of metastases using ultrastaging outweighed its disadvantages of being time-consuming and costly.

Other Considerations

The Working Group believes that it is reasonable to omit a lymph node dissection in the contralateral side of a positive node when the sentinel node has tested negative in that contralateral side, although there are no data to make a recommendation for or against this statement. The Working Group expects the incidence of metastases on the contralateral side would be low because of the relatively low false-negative rate (~7% with combined technique, ~10% with radiocolloid only) and the two sides are biologically independent of each other. Also, performing a complete lymphadenectomy would increase morbidity.

FUTURE RESEARCH

GROINSS-V II http://public.ukcrn.org.uk/search/StudyDetail.aspx?StudyID=4971 is accruing patients until the end of 2015. This is a large observational study in which patients with positive sentinel lymph nodes will receive radiotherapy without undergoing a complete bilateral lymphadenectomy.

Funding

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Updating

All PEBC documents are maintained and updated
as described in the PEBC Document Assessment and Review Protocol.

Contact Information

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Evidence-Based Series #4-17: Section 2

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Sentinel Lymph Node Biopsy in Vulvar Cancer: Evidentiary Base

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Report Date: July 17, 2014

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INTRODUCTION

Vulvar cancer is a rare gynecologic malignant neoplasm that is diagnosed in approximately 1/100,000 women per year in Canada, accounting for approximately 4% of gynecologic malignant tumours (1,2); however, the incidence may be rising due to increased human papillomavirus infections (3). The overall survival rate is approximately 46% (4), but this varies from 19% to 94% depending on the stage of the disease (5). Traditionally, treatment has involved removal of the primary tumour and inguinofemoral lymph node dissection (IFLD). IFLD involves removal of the inguinal lymph nodes from the femoral triangle bordered by the inguinal ligament and the sartorius and adductor longus muscles. Significant morbidity is associated with the procedure, including a high incidence of long-term lymphedema and other complications. Sentinel lymph node biopsy (SLNB) has been proposed as an alternative to IFLD for patients with early-stage vulvar cancer. Only 25% to 35% of patients with early-stage vulvar cancer actually have lymph node metastases (6) and would benefit from full lymphadenectomy. Determination of the location of the sentinel lymph node is accomplished using dye and/or radiocolloids, which are injected prior to the procedure. Visualization may be accomplished using lymphoscintigraphy. If the sentinel lymph node tests negative for cancerous cells, then the assumption is that the rest of the lymph nodes in the lymphatic basin will also test negative for cancerous cells, thereby eliminating the need for IFLD and its associated morbidity. The detection of positive nodes in SLNB is also used to guide treatment decisions.

The Working Group for this guideline is aware that SLNB is already being practiced at some centres in Canada. Assessment of the studies comparing SLNB with IFLD will be the focus of this systematic review and specific aspects of clinical practice will also be addressed.
The research questions for this guideline, which were derived from the Working Group's objectives, are outlined in the following section.

RESEARCH QUESTIONS

For patients with stage I or II vulvar cancer and using IFLD as the reference standard:

1. What are the detection and false-negative rates of SLNB?
2. What is the recurrence rate after a negative SLNB test compared with the recurrence rate after a negative IFLD test?
3. What are the complication rates after SLNB compared with the complication rates after IFLD?
4. Which patient characteristics affect detection or false-negative rates of SLNB or recurrence or complication rates after SLNB?
5. What is the impact of the learning curve on detection or false-negative rates of SLNB or recurrence or complication rates after SLNB?
6. What is the diagnostic accuracy of frozen-section analysis of SLNB?
7. What is the diagnostic accuracy of SLNB using ultrastaging?
8. What social and ethical issues are associated with SLNB?

METHODS

This evidentiary base was developed using a planned three-stage method, summarized here and described in more detail in subsequent sections.

1. Search of existing guidelines that could be endorsed or adapted.
2. Search and evaluation of existing systematic reviews: If one or more existing systematic reviews are identified that address the research questions and are of reasonable quality, then those systematic reviews would form the core of the evidentiary base.
3. Systematic review of the primary literature: This review would focus on those areas not covered by existing reviews if any are located and accepted.

The Program in Evidence-Based Care (PEBC) is supported by the Ontario Ministry of Health and Long-Term Care (MOHLTC). All work produced by the PEBC is editorially independent of the MOHLTC.

Literature Search Strategy

Search for Existing Guidelines

In order to identify existing guidelines related to the research questions, a search was conducted of the Inventory of Cancer Guidelines (CancerView.ca). The purpose of this search was to identify existing guideline documents that could be adapted or adopted by the Working Group, or that were based on a systematic review that could be used as part of the evidentiary base for the development of recommendations.

Existing Systematic Reviews

The Working Group was aware of a completed systematic review and health technology assessment (HTA) with a search that was current to October 2011 that addressed the safety, effectiveness, feasibility, and cost of SLNB in the Canadian healthcare context to determine whether SLNB should be the standard of care for patients with early-stage vulvar cancer (7). Other than cost-effectiveness, which is outside the scope of the PEBC review, the questions from the Reade HTA (7) aligned very closely with our research questions. Data relevant to our study objective included detection rates and false-negative test rates for SLNB, determined by comparing SLNB to IFLD in the same patients, comparing recurrence and complication rates for the procedures, and assessing SLNB methods, such as the use of blue dye, technetium-99 (Tc99), or lymphoscintigraphy. Social and ethical issues were also explored. Given its comprehensiveness and relevance, the Working Group agreed to adopt the evidence base of

the Reade et al. HTA, and to conduct an additional search to bring the evidence base current to March 2013.

Search of Electronic Databases

A search of the electronic databases MEDLINE and EMBASE (OVID: October 2011 to March 2013) for articles published in English was conducted using the search terms outlined in Reade et al.'s systematic review (Appendix I) (7). The Cochrane Database of Systematic Reviews was searched for topic-specific reviews published up to March 2013. The Cochrane Database of Randomized Trials was not searched because the Working Group was aware *a priori* that there are no existing randomized trials on this topic due to feasibility problems given the small number of patients who are diagnosed with vulvar cancer. Reference lists of included articles were scanned for additional citations. A review of the titles and abstracts that resulted from the search was done by EV. For those items that warranted full-text review, EV reviewed each item independently. Results of this review are presented in Appendix II.

Study Selection Criteria

In order to maintain consistency, Reade et al.'s study selection criteria were adopted and only full-text articles that reported quantitative data were considered for inclusion. Because cost-effectiveness of the intervention was beyond the scope of this guideline, cost-related inclusion criteria were omitted. A primary screen of the abstract and title was conducted to confirm that the studies:

1. Included patients with stage I or II vulvar cancer who underwent either IFLD or SLNB;
2. Contained the outcomes of interest, including sensitivity, specificity, false-positive or -negative rates, groin recurrence rates, or complication rates; or
3. Included a discussion of organizational, implementation, social, or ethical aspects of SLNB.

Articles meeting the primary screening criteria were retained for full-text screening and were excluded according to the following criteria:

- Case reports with fewer than five patients
- Reports of only en-block ("butterfly incision") radical vulvectomy with concurrent bilateral lymphadenectomy
- Studies where patients underwent vulvar/groin reconstructive procedures
- Studies using coverings/foreign materials in the groin in all patients
- Studies of only stage 1A or clinically advanced/recurrent disease (clinical stage 3 or 4, or clinically involved lymph nodes)
- Studies with pregnant patients only or with a specific focus on treatment of vulvar cancer in pregnancy
- Studies on vulvar melanoma only
- Data that were published in duplicate (same patients also included in a later study)

Studies were included if they contained at least one of the following:

- Reports of complications related to surgical evaluation of inguinofemoral lymph nodes by SLNB or separate groin incisions for complete IFLD (wound infection or breakdown, lymphocysts, lymphedema)
- Reports of groin recurrence rates after negative lymphadenectomy or SLNB testing
- Reports of overall survival rates after SLNB
- Reports of sensitivity, specificity, negative or positive predictive values for the SLNB procedure, or ability to detect a sentinel lymph node

Data Extraction and Assessment of Study Quality and Potential for Bias

Data were extracted independently by EV. All extracted data and information were audited by an independent auditor.

As an initial screen, guidelines were evaluated to determine whether they were based on a systematic review in which the relevant literature was searched in at least one electronic database. Guidelines not based on a systematic review were excluded from further consideration. If systematic review methodology was used, then an assessment of the guideline quality was conducted using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument (8). Systematic reviews identified in the search of electronic databases were assessed using the Assessment of Multiple SysTemAtic Reviews (AMSTAR) tool (9).

For individual studies, the quality of observational studies was assessed by a modified Newcastle-Ottawa Scale (see Appendix III) (10). Evidence was selected and reviewed by a PEBC methodologist and the three other members of the guideline development Working Group. Data extraction was verified by a project research assistant. Strengths and weaknesses were evaluated with the aim of characterizing the quality of the evidence base as a whole, without the use of a scoring system or cut-offs, according to the policy of the PEBC.

Synthesizing the Evidence

When clinically homogenous results from two or more studies were available, a meta-analysis was conducted using the MetaXL version 1.3 software provided by EpiGear International Pty Ltd. (11). For all outcomes, pooled prevalence with random effects using a double arcsine transformation to stabilize the variance in MetaXL was used.

Statistical heterogeneity was calculated using the x^2 test for heterogeneity and the I^2 percentage. A probability level for the x^2 statistic ≤10% ($p \leq 0.10$) and/or an I^2 >50% would be considered indicative of statistical heterogeneity.

RESULTS

Search for Existing Guidelines

Two guidelines were found that addressed the topic of sentinel lymph node biopsy in vulvar cancer (12,13). One was published in 2006 by the Society of Obstetricians and Gynaecologists of Canada and expressed the opinion that until there are more clinical trials conducted, SLNB in vulvar cancer should be considered an experimental procedure (13). A second guidance document addressing the management of squamous cell carcinoma of the vulva, which was released in 2011 by the Alberta Health Services, stated that there may be a role for SLNB in vulvar cancer, but results of a trial comparing methods of locating the sentinel lymph node were needed before making a recommendation (12). Neither of these guidelines was based on a systematic review of the literature; therefore, they were not considered further in this guideline development process.

Search for Existing Systematic Reviews

No systematic reviews other than the Reade et al. review described previously were found (7).

Literature Search Results

A total of 270 nonduplicate records were found in the search of MEDLINE and EMBASE. After primary screening, 165 articles were excluded and 45 articles were retained for full-text review. The reasons for exclusion can be found in Appendix I. Five of these articles met the inclusion criteria and were retained after full-text review (14-18). These studies addressed complications with lymphadenectomy and/or various aspects of the clinical practice of SLNB that related to the research questions.

Study Design and Quality

Systematic Review

Table 1 includes the scores for each of the 11 AMSTAR items for the Reade et al. 2012 systematic review (7). There are no randomized controlled trials on these topics due to the very low incidence of vulvar cancer; therefore, the studies included in the Reade et al. review were observational and the evidence generally rated as lower quality because of study design and low numbers of patients (studies with as few as five patients met the inclusion criteria for this existing review). Results were pooled across studies without a meta-analysis to determine overall mean rates for the outcomes of interest. Pooled recurrence and complication rates reported in this systematic review were heavily weighted by the findings of GROningen INternational Study on Sentinel nodes in Vulvar cancer (GROINSS-V), a study conducted in the Netherlands on 403 patients who underwent SLNB followed by IFLD or follow-up in cases that tested negative (19). They used the combined technique of radioactive tracer and blue dye in women with early-stage squamous cell carcinoma of the vulva. The review was assessed for quality with the AMSTAR tool (9). It received a high rating for quality on items that were considered relevant (Table 1).

Table 1. Evaluation of included publications using AMSTAR.

ITEM	Reade et al. 2012 (7)
1. Was an *a priori* design provided?	Yes
2. Was there duplicate study selection and data extraction?	No
3. Was a comprehensive literature search performed?	Yes
4. Was the status of publication (i.e., grey literature) used as an inclusion criterion?	Yes
5. Was a list of studies (included and excluded) provided?	Yes
6. Were the characteristics of the included studies provided?	Yes
7. Was the scientific quality of the included studies assessed and documented?	Yes
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes
9. Were the methods used to combine the findings of the studies appropriate?	Yes
10. Was the likelihood of publication bias assessed?	No
11. Was the conflict of interest stated?	Yes
TOTAL AMSTAR POINTS (Yes = 1, No = 0, Maximum possible points = 11))	9

Primary Studies

In addition to the Reade et al. review, five studies met the inclusion criteria (14-18). Four of these studies were rated very low on the Newcastle-Ottawa Scale mainly because there was no comparison group and no learning curve assessment (Table 2) (14-16,18). Only the Soliman et al. 2012 study scored higher because it included follow-up of patients (17).

Table 2. Results of modified Newcastle-Ottawa Scale for included studies.

ITEM	Garcia-Iglesias et al. 2012 (14)	Levenback et al. 2012 (15)	Novackova et al. 2012 (16)	Soliman et al. 2012 (17)	Zekan et al. 2012 (18)
1. Representativeness of cohort	0	0	0	0	1
2. Selection of the comparison group	0	0	1	0	0
3. Learning curve requirement before study participation	0	0	0	0	0
4. Demonstration that outcome of interest was not present at the start of the study	0	1	0	1	1
5. Comparability of cohorts on the basis of design or analysis	1	1	0	2	1
6. Assessment of outcome	1	0	0	1	0
7. Was follow-up at least one year for the outcome of lymphedema and two years before assessment of groin recurrence rate?	NA	NA	0	1	NA
8. Adequacy of follow-up of cohorts	NA	NA	1	1	NA
TOTAL NEWCASTLE-OTTAWA POINTS (max = 9 points)	2	2	2	6	3

Abbreviations: NA, not applicable. Total of nine points possible, one point each for questions 1-4 and 6-8 and two possible points for question 5.

Outcomes

1. What are the detection and false-negative rates of SLNB using IFLD as the reference standard?

Three additional studies beyond the Reade et al. 2012 systematic review were included (Figures 1 and 2) (7,14,15,18). Although there was significant heterogeneity among studies (blue dye alone I^2=73%, p=0.03; Tc99 only I^2=74%, p<0.001; combined I^2=87%, p<0.001), the pooled detection rate per groin was substantially higher with the combination of blue dye and radiocolloid (87%, 95% confidence interval [CI] 81%-92%) compared with blue dye alone (63%, 95% CI 49%-77%). The radiocolloid (Tc99) alone group had higher pooled detection rates (84%, 95% CI 74%-93%) than the blue dye alone group (63%, 95% CI 49%-77%); however, the confidence intervals overlapped slightly. There were similar detection rates for the combined technique (87%, 95% CI 81%-92%) and the radiocolloid alone group (84%, 95% CI 74%-93%). For false-negative rates, the studies were more homogenous but the confidence intervals overlapped for all three groups (blue dye 9%, 95% CI 0%-27%; radiocolloid 10%, 95% CI 1%-23%; combined 7%, 95% CI 4%-9%); therefore, we do not know if they are different. The benefit of the addition of lymphoscintigraphy to the procedure could not be assessed with the data provided.

Figure 1. Detection rates for SLNB using IFLD as reference standard.

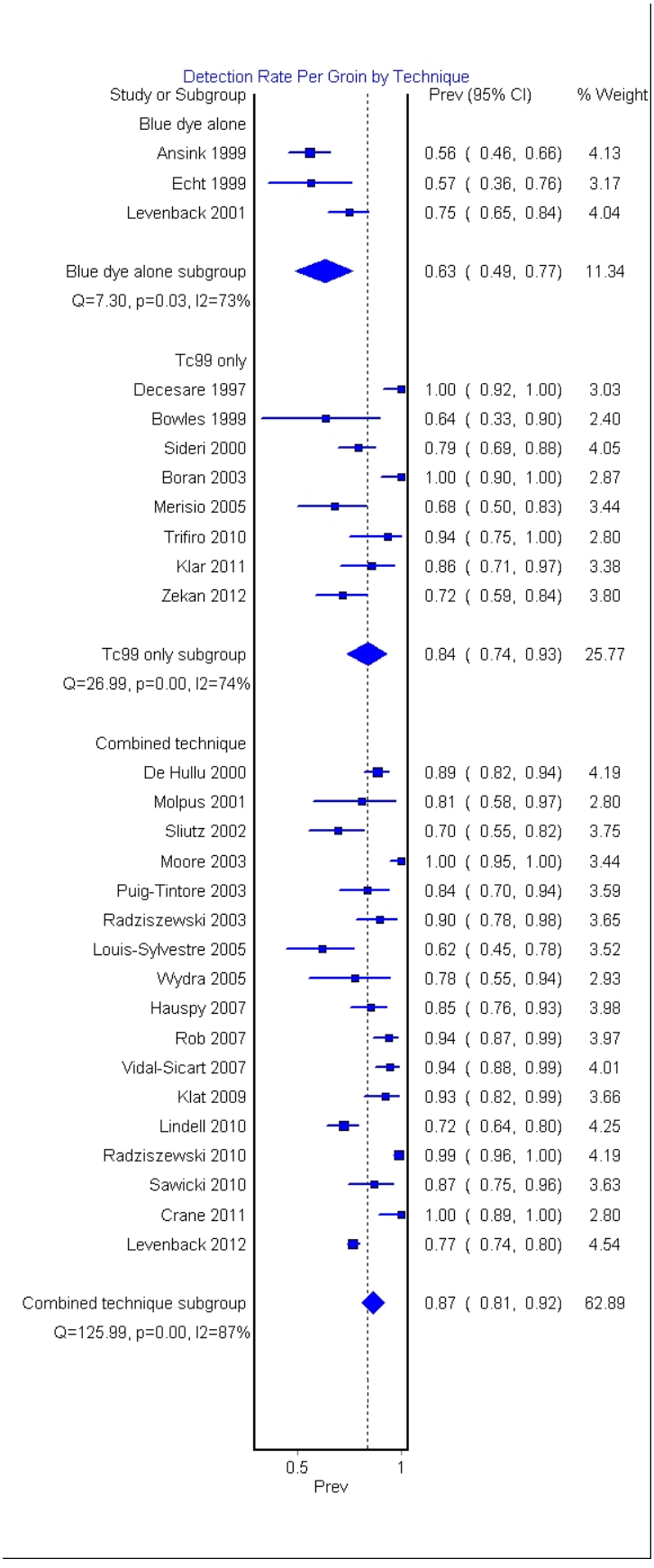
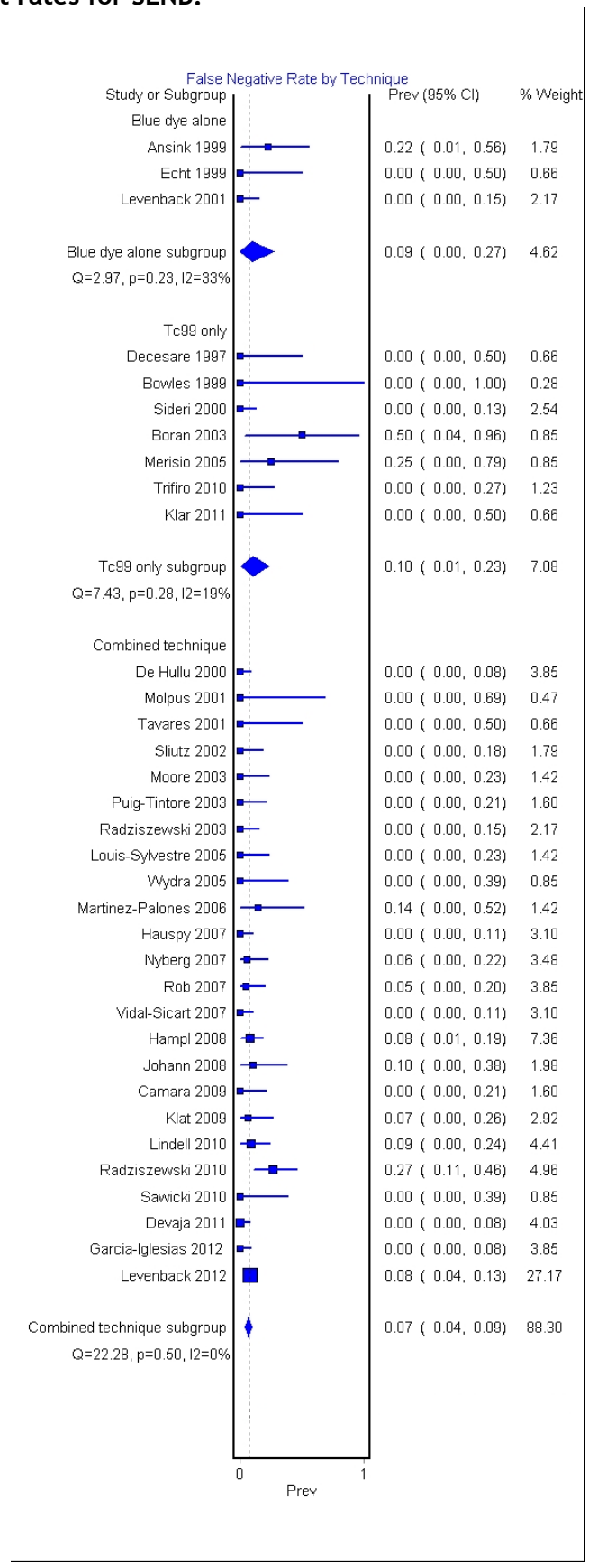


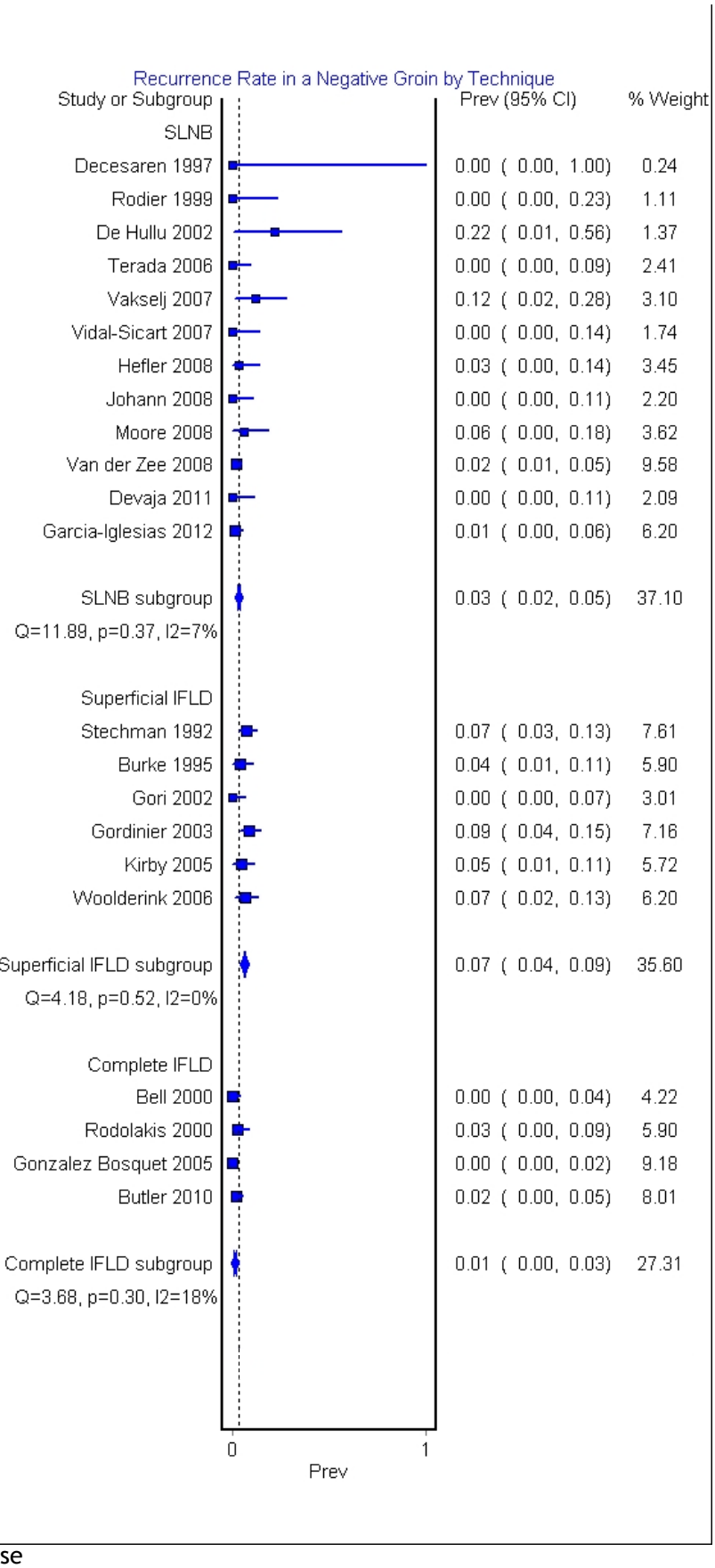
Figure 2. False-negative test rates for SLNB.



2. What is the recurrence rate after a negative SLNB test compared to the recurrence rate after a negative IFLD test?

Recurrence in a groin is usually a fatal event; therefore, it is an important outcome to evaluate. One additional study was included beyond the Reade et al. 2012 review (Figure 3) (7,14). The IFLD studies were divided into two groups: superficial and complete according to the Reade et al. 2012 definitions. "Complete dissection" was used to describe IFLD plus an attempt to remove the deep femoral lymph nodes, whereas "superficial dissection" was used to describe procedures in which no attempt was made to remove the deep femoral lymph nodes. Within each group, the studies were fairly homogenous with I^2 <19%. The pooled recurrence rates were low in all groups. Each of the IFLD groups (complete 1%, 95% CI 0%-3%; superficial 7%, 95% CI 4%-9%) had overlapping confidence intervals with the pooled recurrence rate in the SLNB group (3%, 95% CI 2%-5%).

Figure 3. Recurrence rates in a groin negative for after SLNB or IFLD.



3. What are the complication rates after SLNB compared with the complication rates after IFLD?

Complications of interest in vulvar cancer surgery include wound infection, wound breakdown, formation of lymphocysts (fluid collections in the groin), and long-term lymphedema. Two studies were found in addition to the studies included in the Reade et al. 2012 review (7,16,17). The data from Novackova et al. 2012 were included in the meta-analysis, but the data from Soliman et al. 2012 were not included because it could not be determined whether they used a complete or superficial IFLD technique (Figures 4 to 7) (16,17).

There was substantial heterogeneity among studies within groups of different techniques. Only three groups had I^2 <50%. These included SLNB for wound infection rates, superficial IFLD for wound breakdown rates, and SLNB for rates of lymphocysts. For all four complications evaluated (wound infection, wound breakdown, formation of lymphocysts, and long-term lymphedema), the rate of complications was always higher (the confidence intervals did not overlap) for patients who received complete IFLD compared to patients who received SLNB only. Furthermore, there was a higher rate (without overlapping confidence intervals) of lymphedema for patients who had superficial IFLD (15%, 95% CI 10%-21%) compared to patients who had SLNB only (2%, 95% CI 0%-7%).

Figure 4. Wound infection rates after SLNB or IFLD.

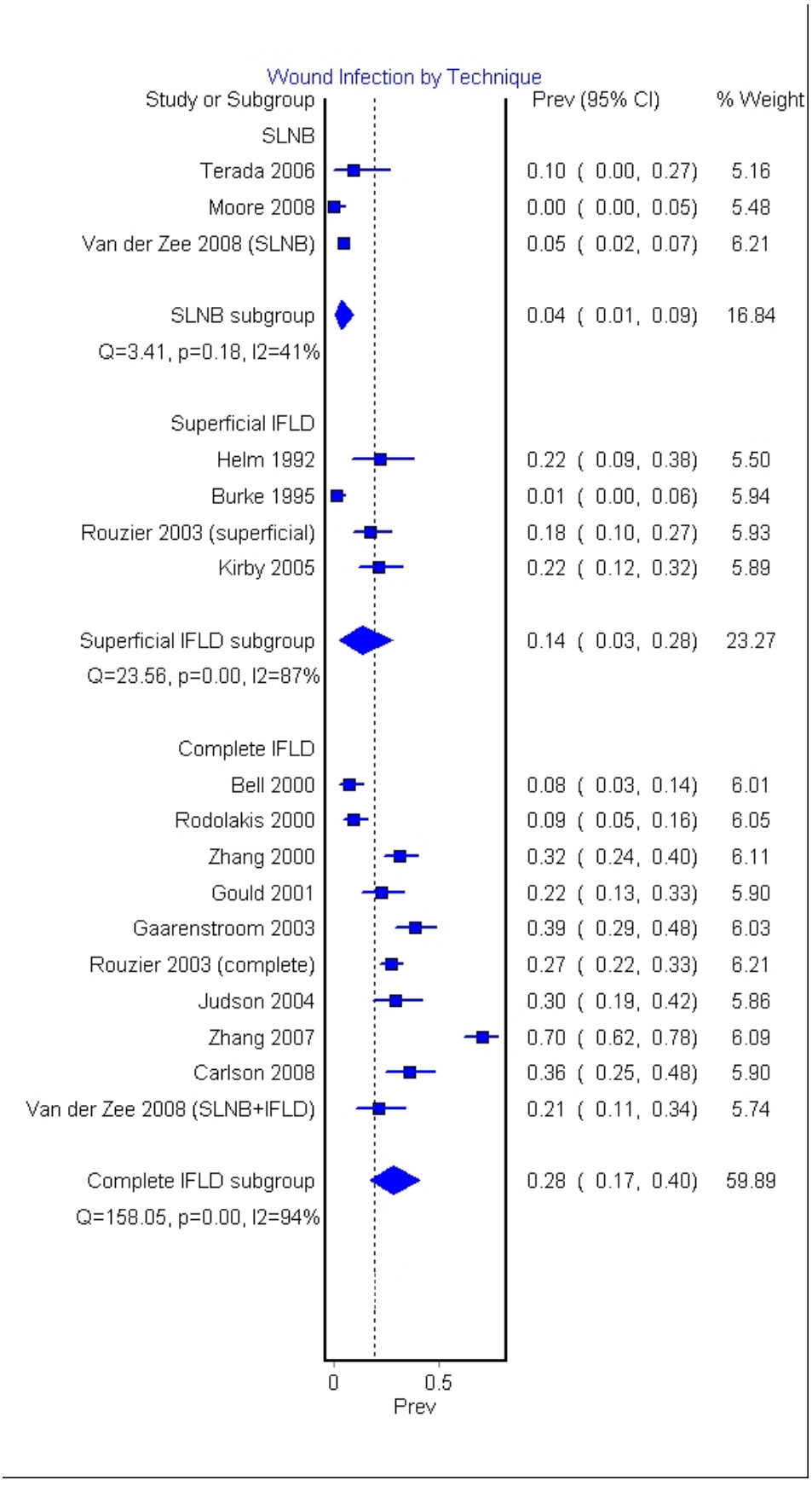


Figure 5. Wound breakdown rates after SLNB or IFLD.

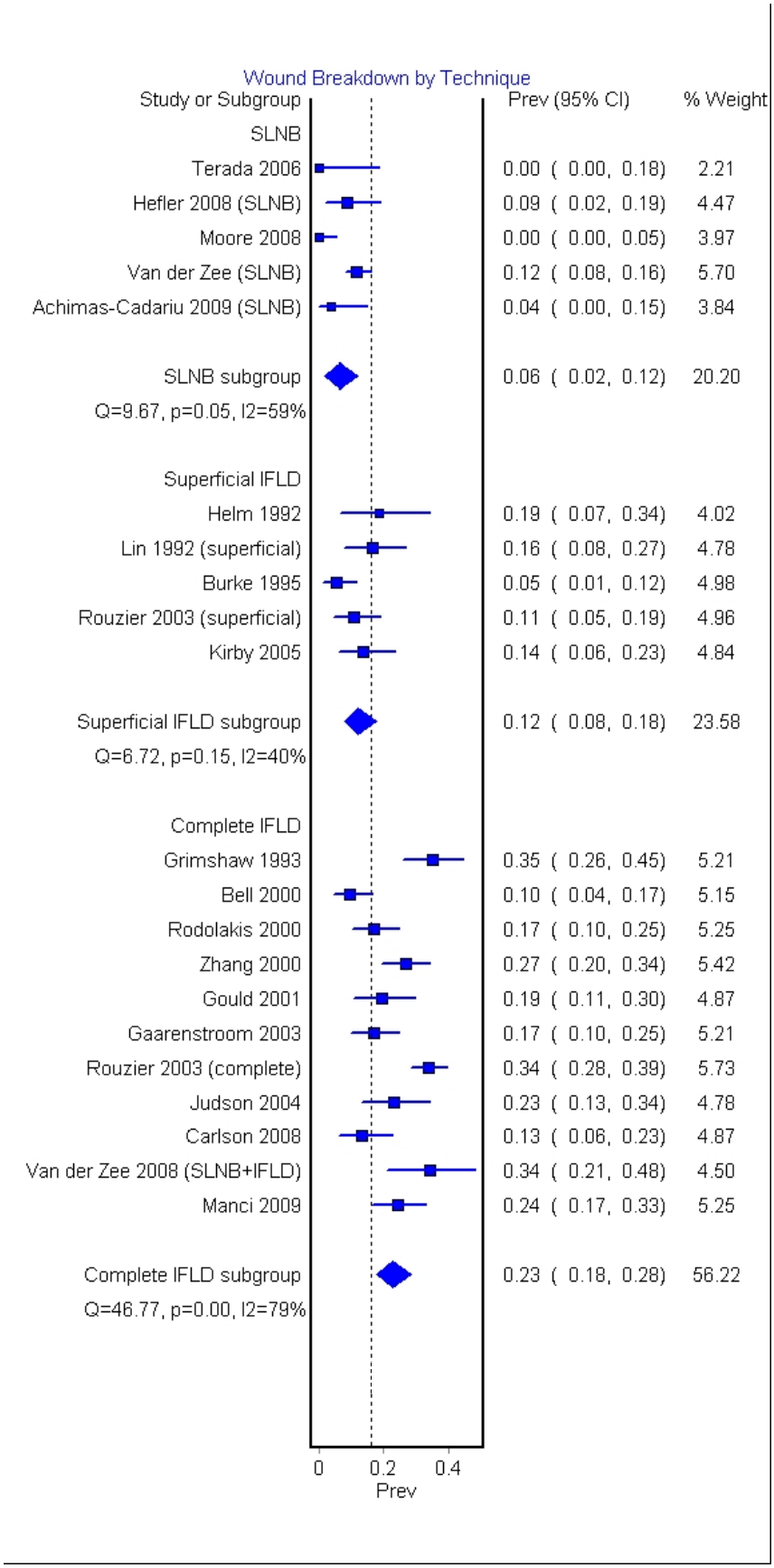


Figure 6. Rates of lymphocysts after SLNB or IFLD.

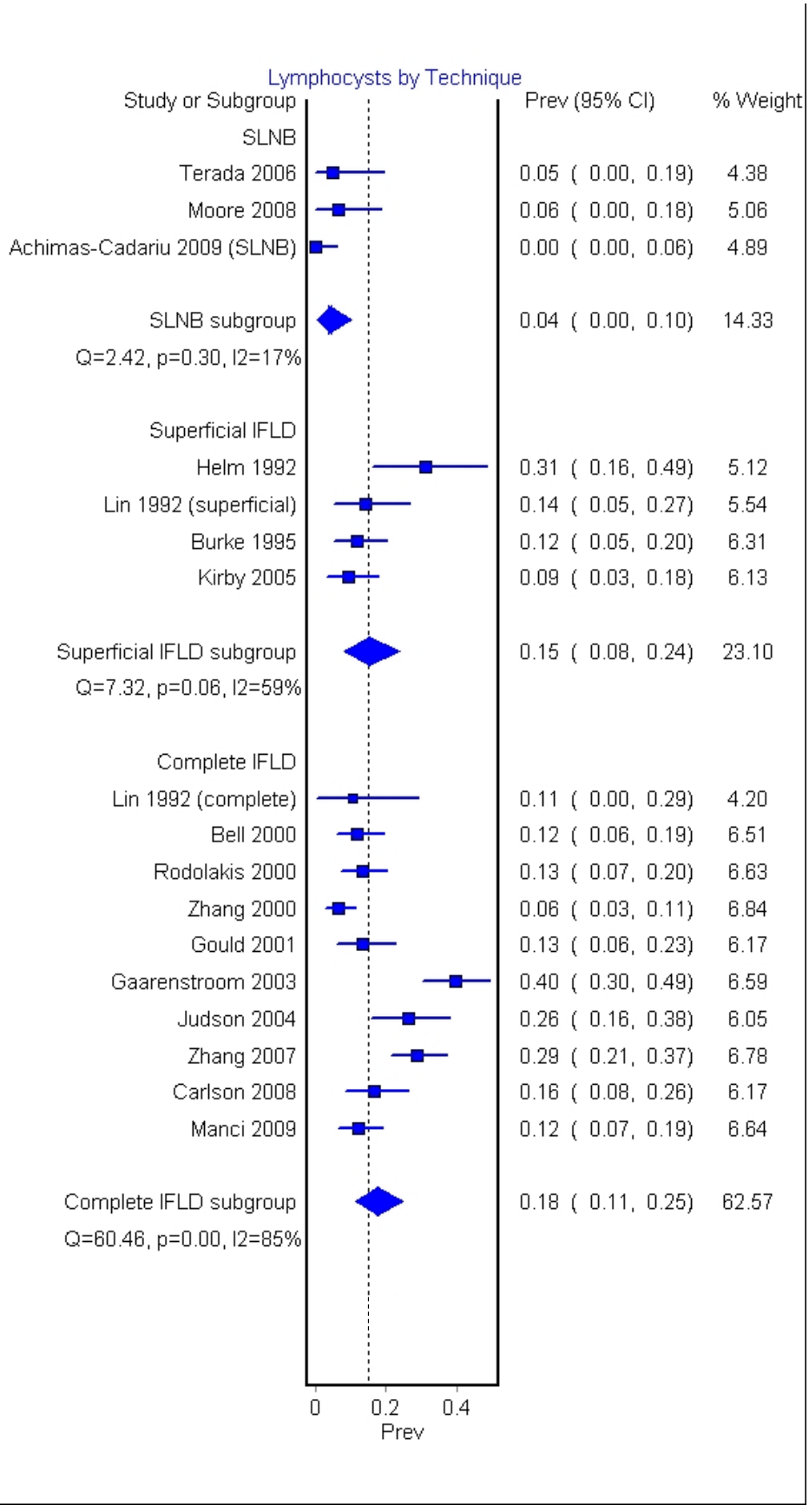
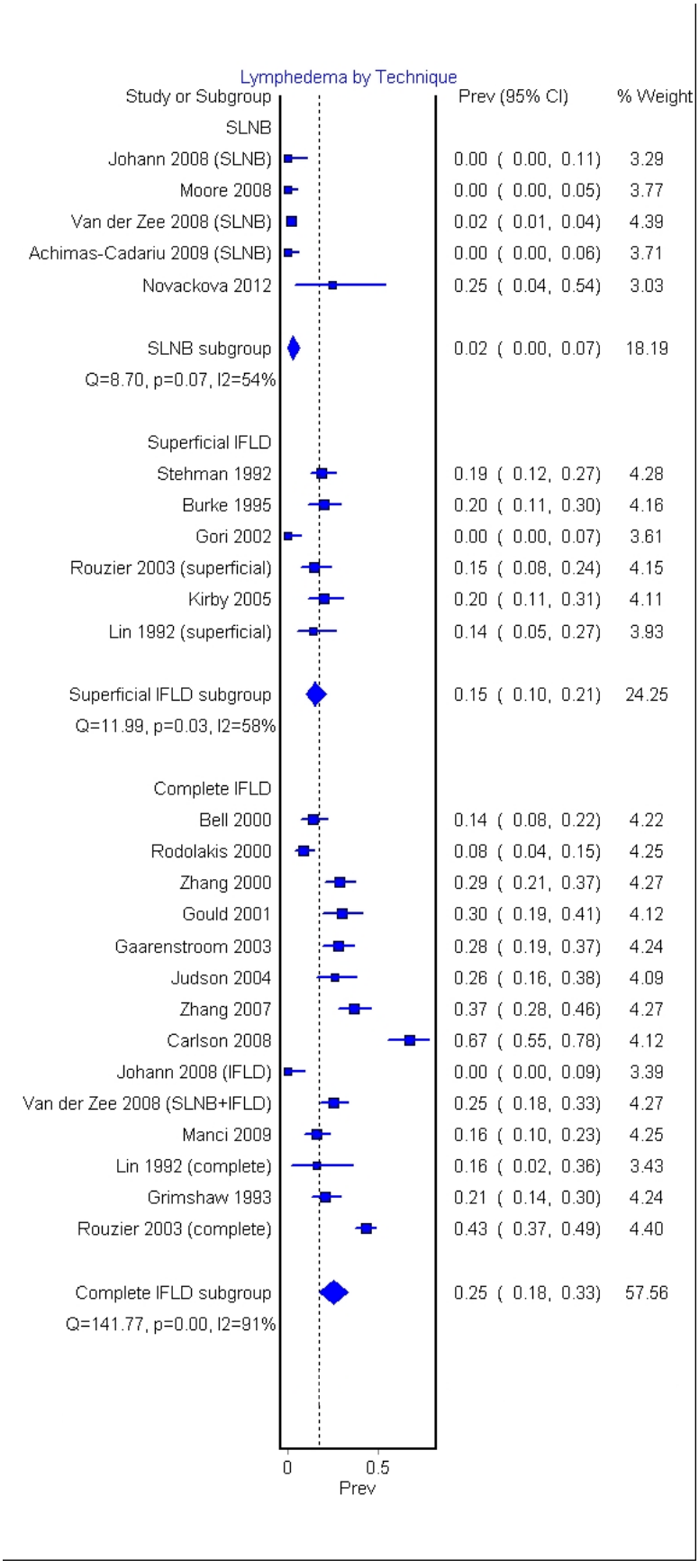


Figure 7. Rates of lymphedema after SLNB or IFLD.



4. Which patient characteristics affect detection or false-negative rates of SLNB or recurrence or complication rates after SLNB?

The largest prospective study by van der Zee et al. 2008 published about the SLNB procedure in early vulvar cancer was included in the Reade et al. 2012 review (7,19). The van der Zee et al. 2008 study reported that patients with multifocal disease had a higher recurrence rate after SLNB (11.8%, 2/17) compared to patients with unifocal disease (2.3%, 6/259) (19). Furthermore, most studies assessing patient outcomes of SLNB selected patients with tumours that were <4 cm (7). Therefore, very little information is available to assess the safety of SLNB in patients with larger tumours.

5. What is the impact of the learning curve on detection or false-negative rates of SLNB or recurrence or complication rates after SLNB?

Only one study included in the Reade et al. 2012 review reported the impact of the learning curve on detection rates of SLNB (7). Levenback et al. 2001 found a failure to detect sentinel lymph nodes in 36% of groin dissections in the first two years and a 15% failure rate in detecting sentinel lymph nodes afterward (20). No other studies were found.

6. What is the diagnostic accuracy of frozen-section analysis of SLNB?

Three studies included in the Reade et al. review reported on the diagnostic accuracy of frozen-section analysis intraoperatively (7). Oonk et al. 2010 performed frozen-section analysis on 315 patients and found a sensitivity of 48% (95% CI 38–57), a specificity of 100% (98%–100%), a negative predictive value of 78%, and a positive predictive value of 100% (21). Hauspy et al. 2007 found a sensitivity, specificity, and positive predictive and negative predictive values of 94%, 100%, 100%, and 96%, respectively, for frozen-section analysis (22). Rob et al. 2007 found a diagnostic accuracy of 98% for frozen-section analysis in which 2 of 98 nodes were falsely negative (23).

7. What is the diagnostic accuracy of SLNB using ultrastaging?

From the Reade et al. review, eight studies suggested that ultrastaging increased the detection of metastases in sentinel lymph nodes previously found to be negative without ultrastaging (19,21,24-29), whereas four other studies found no difference with additional ultrastaging (Table 3) (30-33). Furthermore, one study suggested the addition of immunohistochemistry to ultrastaging did not increase the detection of metastases in lymph nodes (34). However, two studies found that immunohistochemistry increased detection of metastases beyond routine hematoxylin and eosin staining (21) and ultrastaging with hematoxylin and eosin staining (15,21).

One study did not find a correlation between occult lymph node metastases detected by ultrastaging and survival rate ($p>0.05$) (35). However, a more recent and larger study by Oonk et al. 2010 found that the five-year disease-specific survival rate was significantly higher for women with positive sentinel lymph nodes detected by ultrastaging (92.1%) versus the survival rate for women identified by routine pathology (64.9%, $p<0.0001$) (21).

Table 3. Detection of metastases using ultrastaging.

Reference	Ultrastaging among negatives, # of positives per total negatives from routine examination	Ultrastaging only, # of positives per all positives found	Ultrastaging with immunohistochemistry
Levenback 2012 (15)			28 metastases detected in 200 women (14%) when ultrastaging

Reference	Ultrastaging among negatives, # of positives per total negatives from routine examination	Ultrastaging only, # of positives per all positives found	Ultrastaging with immunohistochemistry
			with hematoxylin and eosin staining did not reveal metastatic disease
Oonk 2010 (21)	36/304 women	55/135 women	SLN metastases found by routine hematoxylin and eosin in 80/135 (59%) positive patients, by ultrastaging with hematoxylin and eosin in an additional 55/135 (41%) positive patients, and by ultrastaging with immunohistochemistry in an additional 36/304 (12%) patients with negative SLN
Moore 2003 (34)			No difference for the detection of micrometastases with the use of hematoxylin and eosin (2 positive, 89 negative) staining and immunohistochemistry (2 positive, 89 negative) staining
Devaja 2011 (24)	5/72 SLN, 4/34 women		
Lindell 2010 (29)		2/20 groins	
van der Zee 2008 (19)		68/163 groins	
Louis-Sylvestre 2005 (28)	1/16 groins		
Puig-Tintore 2003 (27)		3/8 women	
Molpus 2001 (26)	2/18 SLN		
de Hullu 2000 (25)	4/102 SLN		
Klar 2011 (30)		0/3 women	
Boran 2003 (32)	0/26 SLN	0/4 women	
Sliutz 2002 (33)		0/18 SLN	
de Hullu 2002 (31)	0% SLN		

Abbreviations: SLN, sentinel lymph node.

8. What social and ethical issues are associated with SLNB?

Although one study included in the Reade et al. review found that patients who underwent SLNB alone had higher rates of satisfaction with their treatment and had fewer symptoms from complications than patients who underwent IFLD, there was no difference in overall quality of life in this study (7,36). Another study by Novackova et al. 2012, found that six months after the surgical procedure, patients who received IFLD scored worse on social functioning, fatigue, and dyspnea compared to patients who received SLNB (16).

Furthermore, from the Reade et al. review, one study found that patients who received SLNB were more likely than those who received IFLD to recommend this procedure to a friend, regardless of the false-negative rates (36). One study found that for patients who received IFLD, if the false-negative rate was 5%, 34% of patients preferred SLNB over IFLD (37); another study found that if the false-negative rate was 10%, then 48% would recommend SLNB (36). Also, physicians seemed more likely to accept higher false-negative rates than patients when recommending SLNB (37).

ONGOING TRIALS

The GROINSS-V II study http://public.ukcrn.org.uk/search/StudyDetail.aspx?StudyID=4971 is accepting patients until the end of 2015. The aims of this study are to investigate the safety of replacing complete IFLD by adjuvant radiotherapy in patients with early-stage vulvar cancer with a sentinel node metastasis of <2 mm; to evaluate the short- and long-term morbidity associated with the sentinel lymph node procedure and adjuvant (chemo)radiotherapy; to further establish the safety of omitting complete IFLD in patients with a negative sentinel node; and to explore the efficacy, safety and short- and long-term morbidity of IFLD and radiotherapy in patients with sentinel node metastasis >2 mm.

DISCUSSION

The SLNB detection rate for vulvar metastases was highest when radiocolloid tracer with or without blue dye was used compared to when blue dye was used alone. The false-negative rates appear similar across techniques. These results need to be interpreted with caution because they are derived from observational studies. Stronger conclusions could be made if randomized controlled trials were available; however, because the prevalence of vulvar cancer is low, it is unlikely that these types of studies will be performed.

Since SLNB does not accurately predict the reference standard (i.e., IFLD) with 100% certainty, the major concern is that the missed cancers could lead to higher recurrence rates, a fatal event for vulvar cancer. The rate of recurrence is similar for SLNB and IFLD, although this finding should be interpreted with caution because the evidence is derived mainly from noncomparative observational studies. The rate of recurrence was very low for both techniques suggesting that SLNB does not substantially elevate the rate of recurrence compared with IFLD.

Because SLNB is a less-invasive procedure, it is reasonable to assume there would be less morbidity with SLNB compared with IFLD. Again, the evidence was derived from noncomparative observational studies and suggested complete IFLD had higher rates of wound infection, wound breakdown, formation of lymphocysts (fluid collections in the groin), and long-term lymphedema. Therefore, one of the main benefits of SLNB would be fewer complications associated with this procedure compared with IFLD. Further studies are needed to assess the impact of SLNB compared with IFLD on quality of life and patient satisfaction.

There were very few studies that assessed patient characteristics, learning curve, and frozen-section analysis for the detection of metastases using SLNB. Therefore, strong conclusions could not be made. Because most of the studies included patients with tumours <4 cm in size, the generalizability of these results to other patient populations is limited.

Ultrastaging appears to increase the detection of metastases in sentinel lymph nodes previously found to be negative without ultrastaging. One study detected a survival benefit for patients with positive tumours found by ultrastaging compared to routine pathology, but another smaller study did not find a benefit. Even though ultrastaging is more time-consuming and costly than routine pathology, it may potentially increase the detection rate and decrease the number of false positives. These benefits should be weighed against the potential harm of overtreatment of patients with micrometastases and the costs of the procedure when developing recommendations.

CONCLUSIONS

The SLNB detection rate was most favourable with radiocolloid tracer with or without blue dye. The false-negative rates were similar using a combination of radiocolloid tracer with blue dye or either one alone. The recurrence rates after a negative SLNB compared to the recurrence rates after a negative IFLD were similar. The rates of complications were higher

with complete IFLD compared to SLNB for complications of vulvar cancer surgery, including wound infection, wound breakdown, formation of lymphocysts, and long-term lymphedema. Also, the evidence suggested ultrastaging may increase the detection of metastases in sentinel lymph nodes that previously tested negative and may have a positive effect on survival rate.

CONFLICT OF INTEREST

Information regarding conflict of interest declarations can be found at the end of Section 3.

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A complete list of the members of the Gynecologic Cancer DSG and the Working Group, with their affiliations and conflict of interest information, is provided in Section 3, Appendix IV.

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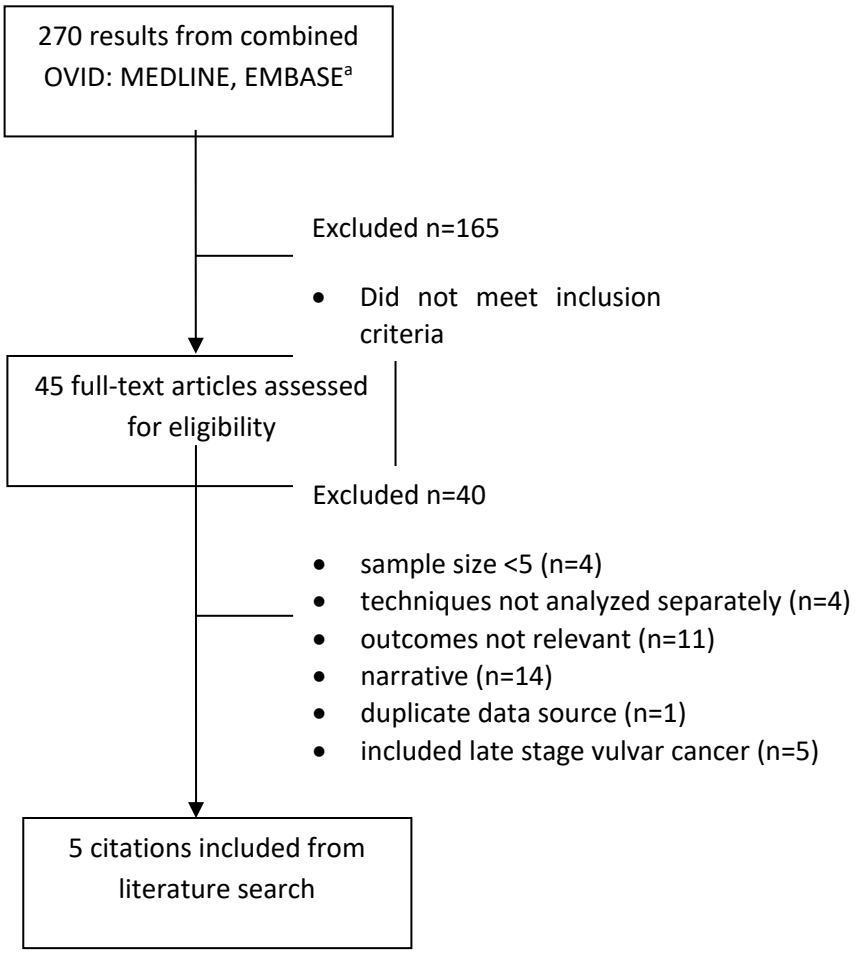
Appendix I. Flow diagram of results from literature search strategies.



[a] Online search strategy available in Appendix II.

Appendix II. Literature search strategies.

	Ovid Search Strategy (MEDLINE Search)
#	**Search terms**
1	exp Vulvar Neoplasms/
2	vulvar cancer.mp
3	vulvar carcinoma.mp
4	(squamous cell carcinoma and vulva*).mp
5	(vulva* and tumour).mp
6	(vulva* and tumor).mp
7	(vulva* and malignan*).mp
8	or/1-7
9	exp Sentinel Lymph Node Biopsy/
10	sentinel lymph node*.mp
11	sentinel node*.mp
12	ultrastaging.mp
13	exp Lymph Node Excision/
14	lymphadenectomy.mp
15	lymph node dissection.mp
16	lymph node excision.mp
17	exp Technetium Compounds/ or exp Technetium/ or exp Technetium Tc 99m Sulfur Colloid/
18	(scintigraph* or scintigram* or scintiphotograph* or gamma camera? or lymphoscintigraph* or lympho-scintigraph*).mp
19	exp Radionuclide Imaging/
20	or/9-19
21	8 and 20

	Ovid Search Strategy (EMBASE Search)
#	**Search terms**
1	exp vulva carcinoma/
2	exp vulva tumor/
3	exp vulva cancer/
4	vulvar cancer.mp
5	vulvar carcinoma.mp
6	(squamous cell carcinoma and vulva*).mp
7	(vulva* and tumour).mp
8	(vulva* and tumor).mp
9	(vulva* and malignan*).mp
10	or/1-9
11	exp sentinel lymph node/
12	sentinel lymph node*.mp
13	sentinel node*.mp
14	ultrastaging.mp

15	exp lymphadenectomy/
16	lymphadenectomy.mp
17	lymph node dissection.mp
18	lymph node excision.mp
19	exp technetium 99m/ or exp technetium sulfur colloid tc 99m/ or exp technetium/
20	technetium.mp
21	(scintigraph* or scintigram* or scintiphotograph* or gamma camera? or lymphoscintigraph* or lympho-scintigraph*).mp
22	exp scintiscanning/
23	or/11-22
24	10 and 23

	Cochrane Library Search Strategy
#	**Search terms**
1	MeSH descriptor **Vulvar Neoplasms** explode all trees
2	(vulvar cancer):ti,ab,kw
3	(vulvar carcinoma):ti,ab,kw
4	(squamous cell carcinoma and vulva*):ti,ab,kw
5	(vulva* and tumour):ti,ab,kw
6	(vulva* and tumor):ti,ab,kw
7	(vulva* and malignan*):ti,ab,kw
8	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)
9	MeSH descriptor **Sentinel Lymph Node Biopsy** explode all trees
10	(sentinel lymph node):ti,ab,kw
11	(sentinel node):ti,ab,kw
12	(ultrastaging):ti,ab,kw
13	MeSH descriptor **Lymph Node Excision** explode all trees
14	(lymphadenectomy):ti,ab,kw
15	(lymph node dissection):ti,ab,kw
16	(lymph node excision):ti,ab,kw
17	MeSH descriptor **Technetium Tc 99m Sulfur Colloid** explode all trees
18	MeSH descriptor **Technetium** explode all trees
19	(lymphoscintigra*):ti,ab,kw or (lympho-scintigra*):ti,ab,kw or (scintigra*):ti,ab,kw or (scintiphotograph*):ti,ab,kw or (gamma camera*):ti,ab,kw
20	MeSH descriptor **Radionuclide Imaging** explode all trees
21	(#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20)
22	(#8 AND #21)

Appendix III. Newcastle-Ottawa Scale for quality of observational studies.

	Modified Newcastle-Ottawa Scale, Cohort studies
	Total of nine stars possible: one for each numbered question in the selection and outcome categories, and two possible stars in the comparability category.
	Selection
1	Representativeness of cohort: a) Reported consecutive patients ✸ b) Invited consecutive patients to participate ✸ c) Selected group/volunteers d) Not stated if consecutive and/or no description of the cohort
2	Selection of the comparison group: a) From same community as the study group ✸ b) From a different source and/or time period c) No description d) No comparison group (patients served as own controls)
3	Learning curve requirement before study participation? a) Statement that surgeon or team had to complete a specified number of SLNBs prior to participating in the study ✸ b) No learning curve requirement
4	Demonstration that outcome of interest was not present at the start of the study a) Yes, explicitly stated no pre-existing lymphedema ✸ b) Yes, ensured only patients with clinically nonpalpable groins were included ✸ c) No explicit statement
	Comparability
1	Comparability of cohorts on the basis of design or analysis a) Study controlled for radiation treatment postoperatively (for lymphedema) ✸ b) Study controlled for age of patients ✸ c) One star may be given if patients served as own controls d) No stars if no control group and patients did not serve as own controls
	Outcome
1	Assessment of outcome: a) Independent blinded assessment ✸ b) Medical records; records linkage ✸

c) For studi es of feasibility (no reported patient outcomes), was there central/specialized pathology review or dual pathology review? ✸

c) Self-report

d) No description

2 Was follow-up at least one year for the outcome of lymphedema and two years before assessment of groin recurrence?

a) Yes ✸

b) No and/or not stated when assessment was made

c) No stars given for short-term feasibility studies

3 Adequacy of follow-up of cohorts:

a) Complete follow-up of all subjects accounted for ✸

b) Patients lost to follow-up unlikely to introduce bias (<10% lost or description provided of those lost), or response rates in surveys was >80% ✸

c) Follow-up rate <90% and no description of those lost to follow-up

d) No statement of adequacy of follow-up

e) No stars for short-term feasibility studies without patient follow-up

Appendix IV. Members of the Working Group and Expert Panel.

Working Group

- **Dr. Al Covens**, Gynecologic Oncologist, Sunnybrook Health Sciences Centre, Toronto, Ontario
- **Dr. Clare Reade**, Gynecologic Oncology Fellow, University of Toronto, Toronto, Ontario
- **Erin B. Kennedy**, Health Research Methodologist, Program in Evidence-Based Care, Cancer Care Ontario/McMaster University, Hamilton, Ontario
- **Dr. Emily Vella**, Health Research Methodologist, Program in Evidence-Based Care, Cancer Care Ontario/McMaster University, Hamilton, Ontario
- **Dr. Waldo Jimenez**, Gynecologic Oncologist, Juravinski Cancer Centre/McMaster University, Hamilton, Ontario
- **Dr. Tien Le**, Gynecologic Oncologist, The Ottawa Hospital, General Campus, Ottawa, Ontario

Expert Panel

- **Dr. Michael Fung Kee Fung** (chair), Gynecologic Oncologist, Ottawa General Hospital, Ottawa, Ontario
- **Dr. Laurie Elit,** Gynecologic Oncologist, Juravinski Cancer Centre, Hamilton, Ontario
- **Dr. Barry Rosen**, Gynecologic Oncologist, University Health Network (Princess Margaret Hospital), Toronto, Ontario
- **Dr. Julie Ann Francis**, Gynecology Oncologist, Kingston General Hospital, Kingston, Ontario
- **Dr. Michel Prefontaine**, Gynecology Oncologist, London Health Sciences Centre, London, Ontario
- **Dr. Jason Dodge**, Gynecologic Oncologist, University Health Network, Toronto, Ontario
- **Dr. Joan Murphy**, Gynecologic Oncologist, University Health Network, Toronto, Ontario
- **Dr. Anthony Fyles**, Radiation Oncologist, Princess Margaret Hospital, Toronto, Ontario
- **Dr. Hal Hirte**, Medical Oncologist, Juravinski Cancer Centre, Hamilton, Ontario
- **Dr. Elizabeth Strevel**, Medical Oncologist, Trillium Health Partners Credit Valley Site, Mississauga, Ontario
- **Dr. Helen MacKay**, Medical Oncologist, University Health Network (Princess Margaret Hospital), Toronto, Ontario
- **Dr. Bojana Djordjevic**, Gynecologic Pathologist, Division of Anatomical Pathology, Eastern Ontario Regional Laboratory, Ottawa, Ontario
- **Dr. Nadia Ismiil**, Anatomical Pathologist, Sunnybrook Health Sciences Centre, Toronto, Ontar

Evidence-Based Series 4-17: Section 3

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Sentinel Lymph Node Biopsy in Vulvar Cancer: Development Methods, Recommendations Development, and External Review Process

A Covens, C Reade, EB Kennedy, E Vella, W Jimenez, T Le, and the Gynecologic Cancer Disease Site Group

Report Date: July 17, 2014

These guideline recommendations have been ENDORSED, which means that the recommendations are still current and relevant for decision making. Please see Section 4: Document Assessment and Review for a summary of updated evidence published between 2013 and 2017, and for details on how this Clinical Practice Guideline was ENDORSED.

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, termed Disease Site Groups (DSGs), as well as other groups or panels called together for a specific topic, all mandated to develop the PEBC products. These panels comprise clinicians, other healthcare providers and decision makers, methodologists, and community representatives from across the province.

The PEBC produces evidence-based and evidence-informed guidelines, known as Evidence-Based Series (EBS) reports, using the methods of the Practice Guidelines Development Cycle (1,2). The EBS report consists of an evidentiary base (typically a systematic review), an interpretation of and consensus agreement based on that evidence by our Groups or Panels and the resulting recommendations, and an external review by Ontario clinicians and other stakeholders in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each document through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original guideline information.

This EBS comprises the following sections:

- *Section 1: Guideline Recommendations*. Contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation

by the Group or Panel involved and a formalized external review by review participants in Ontario.

- *Section 2: Evidentiary Base*. Presents the comprehensive evidentiary/systematic review of the clinical and scientific research on the topic and the conclusions reached by the Group or Panel.
- *Section 3: Development Methods, Recommendations Development, and External Review Process*. Summarizes the EBS development process, the recommendations development process, and the results of the formal external review of the draft version of the EBS.

FORMATION OF WORKING GROUP

The Gynecologic Cancer DSG asked the PEBC to develop a guideline for sentinel lymph node biopsy (SLNB) in vulvar cancer. The Gynecologic Cancer DSG identified individuals within and outside the Gynecologic Cancer DSG to participate as Working Group members. This Working Group consisted of four gynecologic oncologists and two methodologists. The Gynecologic Cancer DSG and two pathologists provided feedback on the guideline as it was being developed and acted as Expert Panel for the document at Internal Review by reviewing the document and outlining which changes needed to be made before the document could be approved.

OBJECTIVES

This Working Group developed the following objective(s) for this guideline in consultation with the Gynecologic Cancer DSG.

1. To determine whether SLNB can safely and effectively identify women with node-negative, early-stage vulvar cancer.
2. To provide guidance with respect to the appropriate techniques and procedures in SLNB for women with early-stage vulvar cancer. These include:

- Selecting appropriate patients
- Determining the appropriate technique
    - learning curve and maintenance
    - what tracer to inject
    - whether lymphoscintigraphy should be used
    - where and when to inject
    - role of intraoperative frozen-section analysis
    - role of ultrastaging and the use of immunohistochemistry
- Management of patients with positive sentinel lymph nodes

RESEARCH QUESTIONS

From these objectives, the following research questions were derived to direct the search for available evidence to inform recommendations to meet the objectives.

For patients with stage I or II vulvar cancer and using inguinofemoral lymph node dissection (IFLD) as the reference standard:

1. What are the detection and false-negative rates of SLNB?
2. What is the recurrence rate after a negative SLNB test compared with the recurrence rate after a negative IFLD test?
3. What are the complication rates after SLNB compared with the complication rates after IFLD?
4. Which patient characteristics affect detection or false-negative rates of SLNB or recurrence or complication rates after SLNB?

5. What is the impact of the learning curve on detection or false-negative rates of SLNB or recurrence or complication rates after SLNB?
6. What is the diagnostic accuracy of frozen-section analysis of SLNB?
7. What is the diagnostic accuracy of SLNB using ultrastaging?
8. What social and ethical issues are associated with SLNB?

EVIDENTIARY BASE DEVELOPMENT

Using the preceding research questions, a search for existing guidelines, systematic reviews, and a systematic review of the primary literature was conducted, as described in Section 2 of this EBS.

INITIAL RECOMMENDATIONS

Using the evidentiary base in Section 2, the Working Group developed a set of initial recommendations. These initial recommendations were developed through consideration of the aggregate evidence quality, the potential for bias in the evidence, and the likely benefits and harms of SLNB in vulvar cancer. The Working Group considered the values they used in weighing benefits compared to harms, and then made a considered judgment. This process is described in detail in the following section for each topic area.

RECOMMENDATIONS FOR PATIENT SELECTION

Key Evidence for Benefits and Harms

The studies found in the literature were of low level because of the observational and mainly noncomparative study designs and a lack of randomized controlled trials. There were similar detection rates for the combined technique (87%, 95% confidence interval [CI] 81%-92%) and the radiocolloid alone group (84%, 95% CI 74%-93%). The pooled detection rate per groin was higher with the combination of blue dye and radiocolloid (87%, 95% CI 81%-92%) or radiocolloid (technetium-99, Tc99) alone (84%, 95% CI 74%-93%) compared with blue dye alone (63%, 95% CI 49%-77%). The false-negative rates were similar for the three techniques (blue dye 9%, 95% CI 0%-27%; radiocolloid 10%, 95% CI %1-23%; combined 7% 95% CI 4%-9%). The pooled rate of groin recurrence after a negative result for SLNB was 3% (95% CI 2%-5%) and after a complete IFLD tested negative was 1% (95% CI 0%-3%). As well, the rate of complications was higher with complete IFLD for wound infection (28%, 95% CI 17%-40%), wound breakdown (23%, 95% CI 18%-28%), lymphocysts (18%, 95% CI 11%-25%), and lymphedema with greater than six months' duration (25%, 95% CI 18%-33%) compared with SLNB (wound infection 4%, 95% CI 1%-9%; wound breakdown 6%, 95% CI 2%-12%; lymphocysts 4%, 95% CI 0%-10%; lymphedema 2%, 95% CI 0%-7%).

One paper by van der Zee et al. 2008 included in the Reade et al. review found that women with multifocal disease had higher recurrence rates after SLNB (11.8%, 2/17) compared with women with unifocal disease (2.3%, 6/259) (3,4). Also, most studies assessing patient outcomes of SLNB selected women with tumours that were <4 cm (4). Therefore, very little information is available to assess the safety of SLNB in women with larger tumours.

Aggregate Evidence Quality and Potential for Bias

The studies found in the literature were of low quality because the study designs were observational and noncomparative, and were not randomized control trials.

Values of the Working Group

Because IFLD is the current reference standard, SLNB would have to demonstrate clear advantages over IFLD in order to replace it. The Working Group was concerned with the potential risk of mortality for patients with a false-negative SLNB. They weighed this risk against

the benefit of a decrease in morbidity and complications with SLNB compared with IFLD. They also took into consideration the similar recurrence rates for patients with a negative SLNB compared to patients with a negative IFLD suggesting that the effect of these procedures on mortality rates would be similar for these patient groups.

Considered Judgment

The Working Group considered the benefits of SLNB (lower rates of wound infection, wound breakdown, formation of lymphocysts, and long-term lymphedema) outweighed the potential increased risk of death associated with a false-negative SLNB. There is emerging data that SLNB with ultrastaging is more sensitive at detecting lymph node metastases than conventional lymphadenectomy for other cancers (5,6). If this is the case for vulvar cancer, then SLNB will potentially have fewer missed metastases. They also believed the evidence suggested the rate of recurrence of vulvar cancer was similar for SLNB and IFLD.

The Working Group chose to recommend SLNB for patients with unifocal disease based on the large van der Zee study (3). Also, since most studies included patients with tumours that were <4 cm, the Working Group recommended SLNB for this subgroup of patients. SLNB was not recommended for patients with clinically suspicious groin nodes because of the potentially elevated false-negative rate and because this subgroup of patients was not included in many of the studies.

RECOMMENDATIONS FOR PATIENT SELECTION

- SLNB is recommended for women with unifocal tumours <4 cm and clinically nonsuspicious nodes in the groin.
- There is insufficient evidence to make a recommendation for or against SLNB for women with tumours >4 cm or women with multifocal disease.
- SLNB is not recommended when there are clinically suspicious groin nodes.

RECOMMENDATIONS FOR APPROPRIATE TECHNIQUES AND PROCEDURES

Key Evidence for Benefits and Harms

Only one study by Levenback from the Reade et al review examined the impact of the learning curve on detection rates of SLNB (7). They found a 36% failure rate to detect SLNB in groin dissections in the first two years and a 15% failure rate afterward.

The pooled detection rate per groin was substantially higher with the combination of blue dye and radiocolloid (87%, 95% CI 81%-92%) compared with blue dye alone (63%, 95% CI 49%-77%). The radiocolloid (Tc99) alone group had higher pooled detection rates (84%, 95% CI 74%-93%) than the blue dye alone group (63%, 95% CI 49%-77%). There were similar detection rates for the combined technique (87%, 95% CI 81%-92%) and the radiocolloid alone group (84%, 95% CI 74%-93%). For false-negative rates all three groups (blue dye 9%, 95% CI 0%-27%; radiocolloid 10%, 95% CI 1%-23%; combined 7%, 95% CI 4%-9%) had similar false-negative rates. No evidence was found for infrared tracers.

The Reade et al review included three studies that reported on the diagnostic accuracy of frozen-section analysis (4). The recent and largest study found low sensitivity (48%) but high specificity (100%) for frozen-section analysis (8), whereas two other older and smaller studies found sensitivities and specificities of greater than 90% (9,10).

Eight of 12 studies included in the Reade et al. review found that ultrastaging increased the detection of metastases in sentinel lymph nodes previously found to be negative and four studies found no difference with additional ultrastaging (4). Two studies suggested that immunohistochemistry increased the detection rate beyond routine pathology (8,11) and one study did not (12). Furthermore, although one study did not find a correlation between occult

lymph node metastases and survival rate ($p>0.05$) (13), a large, recent study found that the five-year disease-specific survival rate was significantly higher for women with positive sentinel lymph nodes detected by ultrastaging (92.1%) versus women identified by routine pathology (64.9%, $p<0.0001$) (8).

Aggregate Evidence Quality and Potential for Bias

Studies included in the Reade et al. review were of low quality due to the observational design of the studies and the low samples sizes in many of the studies (4).

Values of the Working Group

The Working Group chose techniques they believed would maximize the sensitivity of SLNB and minimize the false-negative rate.

Considered Judgment

The Working Group agreed upon a minimum of at least 10 correlated procedures with full-node dissection based on the van der Zee study (3). This large study had a low recurrence rate after a negative SLN test (2%) and centres needed to have completed at least 10 successful procedures without any false-negative lymph nodes identified to participate. The Working Group chose a caseload of three to four per year based on their expert opinion and experience in clinical practice.

From the evidence, using radiocolloid tracer with or without blue dye had the highest detection rates. Therefore, the Working Group recommended radiocolloid tracers should be used either alone or with blue dye routinely or in patients where lymphoscintigraphy does not identify a sentinel node on the groin(s) of interest, the addition of blue dye should be used. The recommended techniques in administering the tracers were based on the standard practice of the Working Group. The qualifying statements for the minimum number of sections were based on the standard practice of the Working Group and were used by the Gynecologic Oncology Group study by Levenback et al. 2012 (11).

The Working Group believed there was insufficient evidence to make a recommendation for or against the use of frozen-section analysis. The advantage of analyzing frozen sections is that it avoids a potential second procedure. The disadvantage is that processing the specimen for frozen section may reduce the amount of available tissue for permanent section analysis.

Ultrastaging examines more sections than usual in addition to immunohistochemical staining and was recommended because the evidence suggested it may increase the detection of metastases in sentinel lymph nodes previously testing negative and may have a positive effect on survival rate. The Working Group believed the benefit of increased detection of metastases using ultrastaging outweighed the harms, including potential overtreatment of patients with micrometastases and the unclear clinical significance for patients with isolated tumour cells. The Working Group also believed the benefit of increased detection of metastases using ultrastaging also outweighed its disadvantages of being time-consuming and costly.

RECOMMENDATIONS FOR APPROPRIATE TECHNIQUES AND PROCEDURES

- It is preferred that surgeons participate in at least 10 successful SLNB procedures followed by complete IFLD without any false negatives prior to performing SLNB alone. A minimum of three to four cases per year are preferred to maintain competence.
- Radiocolloid tracers should be used alone or with blue dye. In patients where lymphoscintigraphy did not identify a sentinel node on the groin(s) of interest, the addition of blue dye should be used.
- Blue dye alone should be discouraged because of the low detection rate.

- There is insufficient evidence to make a recommendation for or against the use of near-infrared tracers.
- Four quadrant intradermal injections into normal tissue at the margins of the tumour are recommended.
- Radiocolloids can be injected a minimum of 30 minutes to 24 hours before the surgical procedure. This depends on the size of the radiocolloid, and manufacturer package inserts should be followed.
- Blue dye should be injected in the same location as the radiocolloid after induction of anesthesia.
- A node that has >5 times the background radioactivity should be used as a cut-off to identify a sentinel lymph node.
- To help identify blue nodes, one should look for and follow blue lymphatic channels.
- There is insufficient evidence to make a recommendation for or against the use of frozen-section analysis.
- Ultrastaging should be used.

Qualifying Statements for Recommendations for Appropriate Techniques and Procedures

For squamous cell carcinoma only, after trimming the fat, the sentinel lymph node should be subjected to ultrastaging by serially sectioning them into 3 mm blocks. At least two sections from each block, 40 μm apart, should be examined to determine whether they contain tumour cells. If routine hematoxylin and eosin staining tests negative for metastatic disease on the first slide, immunohistochemical cytokeratin staining should be performed on the second slide.

RECOMMENDATION FOR PATIENTS WITH POSTIVE SENTINEL LYMPH NODES

Key Evidence for Benefits and Harms

There were no studies that provided evidence for this recommendation.

Values of the Working Group

Even though there was no evidence for this recommendation, the Working Group believed it was important to include this recommendation as a consensus statement with agreement from internal and external reviewers.

Considered Judgment

The Working Group believes that it is reasonable to omit a lymph node dissection in the contralateral side of a positive node when the sentinel node has tested negative in that contralateral side, although there is no data to make a recommendation for or against this statement. The Working Group expects the incidence of metastases on the contralateral side would be low because of the relatively low false-negative rate (~7% with combined technique, ~10% with radiocolloid only) and because the two sides are biologically independent of each other. Also, performing a complete lymphadenectomy would increase morbidity.

RECOMMENDATION FOR PATIENTS WITH POSITIVE SENTINEL LYMPH NODES

Women with a positive sentinel lymph node should receive a complete bilateral node dissection unless there was a negative sentinel lymph node on the contralateral side. In this case, they would receive a unilateral node dissection.

INTERNAL REVIEW

Almost all PEBC documents undergo internal review. This review is conducted by the Expert Panel and the Report Approval Panel (RAP). The Working Group was responsible for

incorporating the feedback and required changes of both of these panels, and both panels had to approve the document before it could be sent to External Review.

Expert Panel Review and Approval

The Gynecologic Cancer DSG (and two pathologists) acted as the Expert Panel for this document. The members of this group were required to submit conflict of interest declarations prior to reviewing the document. These declarations are described in Appendix I. The document must be approved by formal vote. To be approved, 75% of the Gynecologic Cancer DSG membership must cast a vote or abstain, and 75% of voters must approve the document. At the time of the voting, Gynecologic Cancer DSG members could suggest changes to the document and possibly make their approval conditional on those changes. In those cases, the Working Group was responsible for considering the changes; if those changes could be made without substantially altering the recommendations, the altered draft would not need to be resubmitted.

The Gynecologic Cancer DSG reviewed the document in January 2014 via email and also at a Gynecologic Cancer DSG meeting on March 4, 2014. Of the 13 members of the Gynecologic Cancer DSG, 10 members casted votes and three abstained, for a 77% response rate. Of those who casted votes, 10 of 10 approved the document (100%). During this review, the Gynecologic Cancer DSG provided the following feedback and the Working Group made the following changes.

A statement should be made regarding the necessity, or lack thereof, of a preoperative computed tomography (CT) scan as a "screen" for suspicious nodes prior to SLNB.

- The Working Group believed this was outside the scope of this guideline and it would be up to the discretion of the treating physician.

The staging system being referred to (stage I and II) should be clarified.

- This was clarified as T1 or T2, <4 cm, squamous cell cancer of the vulva.

One member recommended against the use of frozen-section analysis.

- The Working Group members disagreed with this because there was insufficient evidence to support a recommendation against frozen-section analysis.

One member requested an explanation of the improved five-year survival rate for women with positive sentinel nodes identified by ultrastaging versus those identified by routine staging.

- The Working Group believed it was most likely due to volume of disease, but did not want to specifically state a reason.

One member requested information regarding whether patients who had SLNB only and then are treated with chemotherapy only have inferior outcomes than those who had IFLD?

- This is currently being investigated, but there is no evidence yet.

Report Approval Panel Review and Approval

The purpose of the RAP review is to ensure the methodological rigour and quality of PEBC documents. The RAP consists of nine clinicians with broad experience in clinical research and guideline development, and the Director of the PEBC. For each document, three RAP members review the document: the Director and two others. RAP members must not have had any involvement in the development of the guideline prior to Internal Review. All three RAP members must approve the document, although they may do so conditionally. If there is a conditional approval, the Working Group is responsible for ensuring the necessary changes are made, with the Assistant Director of Quality and Methods, PEBC, making a final determination that the RAP's concerns have been addressed.

In March 2014, the RAP reviewed this document. One RAP member approved the document on March 10, 2014, and two conditionally approved the document on March 4 and

March 21, 2014. Key issues raised by the RAP and changes made by the Working Group included the following:

If SLNB is recommended to replace IFLD, this should be stated.

- The objective was restated as "To determine whether sentinel lymph node biopsy (SLNB) can safely and effectively identify women with node-negative, early-stage vulvar cancer and be used as an alternative to inguinofemoral lymph node dissection (IFLD)."

If the volume required before performing SLNB alone will change the organization of care in Ontario (e.g., who is doing it or where it is being done), then we need better evidence for this recommendation. There is no evidence for a volume–outcome relationship.

- The Working Group reworded the recommendations as "Vulvar cancer is a rare condition and the recommended procedure is technically challenging. Appropriate surgical training, that is supervised experiences with SLNB procedures followed by complete IFLD without any false-negatives, as well as on-going annual experience with cases to maintain competence, is recommended to optimize patient outcomes and safety. While volume has not been explicitly studied, successful SLNB experience with at least ten patients has been used in the large GROINSS-V multicentre study used to support the preceding recommendation. The Working Group believes this is reasonable to guide practice."

For the last recommendation, include it under a heading of 'other considerations' and combine the justification and summary under this heading. Do not include it as a separate recommendation, because there is not enough evidence to support it.

- The Working Group moved this recommendation under the title 'other considerations'.

External Review by Ontario Clinicians and Other Experts

The PEBC external review process is two-pronged and includes a targeted peer review that is intended to obtain direct feedback on the draft report from a small number of specified content experts as well as a professional consultation that is intended to facilitate dissemination of the final guidance report to Ontario practitioners.

Following approval of the document at Internal Review, the draft document with the recommendations modified as suggested by reviewers was circulated to external review participants for review and feedback.

Methods

Targeted Peer Review: During the guideline development process, several targeted peer reviewers considered to be clinical and/or methodological experts on the topic were identified by the Working Group. Several weeks before completion of the draft report, the nominees were contacted by email and asked to serve as reviewers. Four reviewers agreed, and the draft report and a questionnaire were sent via email for their review. The questionnaire consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a guideline. Written comments were invited. The questionnaire and draft document were sent out on May 8, 2014. Follow-up reminders were sent via email at two weeks and at by telephone call at four weeks where necessary. The Working Group reviewed the results of the survey.

Professional Consultation: Feedback was obtained through a brief online survey of healthcare professionals who are the intended users of the guideline. Participants were asked to rate the overall quality of the guideline (Section 1) and whether they would use and/or recommend it. Written comments were invited. Participants were contacted by email and directed to the

survey website where they were provided with access to the survey, the guideline recommendations (Section 1), and the evidentiary base (Section 2). The notification email was sent on May 20, 2014. The consultation period ended on June 16, 2014. The Working Group reviewed the results of the survey.

Results

Targeted Peer Review: Three of four reviewers provided a response. One reviewer was from the province of Québec, Canada, one from Texas, USA, and the third was from The Netherlands. Key results of the feedback survey are summarized in Table 1.

Table 1. Responses to the first eight items on the targeted peer reviewer questionnaire.

	Reviewer Ratings (N=3)				
Question	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. **Rate the guideline development methods.**	0	0	0	0	3
2. **Rate the guideline presentation.**	0	0	0	1	2
3. **Rate the guideline recommendations.**	0	0	0	0	3
4. Rate the completeness of reporting.	0	0	0	0	3
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?	0	0	0	0	3
6. Rate the overall quality of the guideline report.	0	0	0	0	3
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. I would make use of this guideline in my professional decisions.	0	0	0	0	3
8. I would recommend this guideline for use in practice.	1	0	0	0	2

9. What are the barriers or enablers to the implementation of this guideline report?

The targeted peer reviewers commented that vulvar cancer is a rare diesease; therefore, there is a potentially limited number of cases per surgeon per year to maintain skills. This was expressed as a major concern by one reviewer who suggested that a clear statement should be made that this procedure is only allowed by surgeons with certified experience in centres for gynecologic oncology with sufficient numbers (this comment was the reason for the "strongly disagree" rating associated with question #8 in Table 1). Another targeted peer reviewer expressed a similar concern with the comment "I do not foresee any barriers if surgery is performed at a tertiary centre with gyne-oncology support. The decision should be multidisciplinary and surgery must be performed by trained gynecology surgeon." Access to equipment such as a gamma probe was also listed as a potential barrier.

Table 2. Summary of written comments by targeted peer reviewers and modifications/actions taken.

Written Comment	Modifications/Actions/Comments
1. Page 40, point 5: Is it really chemotherapy that is meant or radiation therapy?	This was a question posed by an Internal Reviewer of the guideline; therefore, we are

	not sure whether they were referring to chemotherapy or radiation therapy.
2. There were some concerns about the adequate time to inject (30 minutes before surgery seems too short (especially when these patients are old and in some circumstances lymphatic flow can be delayed. Otherwise, in midline tumors the guideline is not clear)	The Working Group took this comment under advisement and concluded that the recommendation to follow manufacturer's instructions was sufficient. Therefore, no modification was made.
3. Evidence with regards to whether lymphoscintigram should be used or not is not clearly stated.	There was insufficient evidence to make such a recommendation and the recommendations section has been modified to reflect our inability to make a recommendation regarding lymphoscintigraphy.
4. Social/ethical issues are not fully addressed.	The Working Group did not include social/ethical issues within the scope of this guideline.
5. Needs for sufficient centralization and expertise for performance of this procedure.	NA

Professional Consultation: The professional consultation resulted in replies from 19 participants from Ontario (n=12), Québec (n=1), British Columbia (n=3), Los Angeles, USA (n=1), and the European Union (n=2). Key results of the feedback survey are summarized in Table 3.

Table 3. Responses to three items on the professional consultation survey.

	Number (%)				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.	0	1 (5%)	2 (11%)	9 (47%)	5 (26%)
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.	0	1 (5%)	2 (11%)	7 (37%)	9 (47%)
3. I would recommend this guideline for use in practice.	0	0	2 (11%)	7 (37%)	10 (53%)

4. What are the barriers or enablers to the implementation of this guideline report?

The professional consultation elicited the following comments from respondents regarding barriers and enablers:

Comfort with the procedure/learning curve:

It is unlikely that all staff members will have completed 10 procedures; therefore, several respondents to the professional consultation suggested that performance of the procedure be limited to appointed individuals at tertiary centres. It was suggested that a reference to PEBC EBS #4-11 Organization of Gynecologic Oncology Services in Ontario be provided in this document. That guideline addresses the issue of centralization of gynecologic oncology services for the Ontario population, including vulvar cancer patients. A further

suggestion was made that the procedure only be conducted by surgeons whose focus is vulvar cancer.

Other requirements:

To carry out these recommendations, a high-quality sentinel lymph node program needs to be in place, including nuclear medicine, pathology (including capacity for ultrastaging), and surgeons who are working together to ensure high-quality results. If that is not in place with adequate numbers, a service should track their outcomes when using the technique.

Description of the procedure:

Methodology to perform SLN approach is not fully described There are some concerns about the adequate time to inject (30 min before surgery seems too short (especially when these patients are old and in some circumstances lymphatic flow can be delayed. Otherwise, in midline tumors the guideline is not clear).

Other barriers/concerns:

- A reluctance to change established practice
- Concerns regarding the evidence that SLNB is therapeutic rather than purely staging
- Concerns over the plausibility of false negatives
- Perceptions regarding cost of the procedure
- Patients may not want to risk a slightly higher false-negative rate of SLNB (given the importance of nodal status in prognosis and treatment) for surgical morbidity
- What to do in case of a nuclear isotope shortage?
- Difficulty in convincing those who believe in complete IFLD given the paucity of data as well as the "poor quality" of observational data
- Disseminating the guideline to gynecologists and pathologists
- Technical support from institutions for procedure
- Reimbursement schedule for procedure

Enablers:

- Where there is a full-service pathology lab, ultrastaging can be carried out easily and inexpensively.
- EBS #4-11 Organization of Gynecologic Oncology Services in Ontario: reference to this guideline would enhance the message that vulvar cancer, in general, and SLNB specifically needs to be managed by specialists.

Responses to comments and suggestions that were received through the professional consultation are described in Table 4.

Table 4. Summary of written comments by professional consultants and modifications and actions taken.

Summary of Written Comments	Modifications/Actions/Comments
• Include reference to EBS #4-11.	EBS #4-11 referenced
• In the report, not clear when you are talking about the number of procedures done whether it is per institution or surgeon. With the low volume of vulvar	The recommendation is per insititution.

cancer, unlikely to have 10 cases of SLNB per year per surgeon.	
• Add Qualifying Statements about limitations of the data regarding the primary recommendations. Suggestion to grade the recommendations as expert-opinion only.	At this time, formal grading is not part of the recommendations development process.

Conclusion

This EBS report reflects the integration of feedback obtained through the external review process with final approval given by the Gynecologic Oncology DSG and the RAP of the PEBC. Updates of the report will be conducted in accordance with the PEBC Document Assessment and Review Protocol.

Conflict of Interest

In accordance with the PEBC Conflict of Interest (COI) Policy, the guideline authors, Gynecologic Cancer DSG members, and internal and external reviewers were asked to disclose potential conflicts of interest.

Four authors declared no conflicts. Two authors, AC and WJ, declared conflicts. AC is planning on joining a Groins Study as a principal investigator and has published his opinion of this topic in peer-reviewed journals. WJ has received a grant from the Juravinski Cancer Foundation for a study on sentinel nodes in uterine cancer and has been a principal investigator in an ongoing trial on sentinel node biopsy in uterine cancer.

For the Expert Panel, all 13 members reported that they had no conflicts of interest.

One targeted peer reviewer reported receiving related grant or research support and a second reported expertise in sentinel node mapping in cervical and endometrial cancer. The third targeted peer reviewer did not report any COI.

The declared COI did not disqualify any individuals from performing their designated role in the development of this guideline in accordance with the PEBC COI Policy. To obtain a copy of the policy, please contact the PEBC office by email at ccopgi@mcmaster.ca

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Evidence-Based Series 4-17 Version 2: Section 4

Sentinel Lymph Node Biopsy in Vulvar Cancer

Document Assessment and Review

C. Reade, D. Sivajohanathan, and Members of the Expert Panel on Sentinel Lymph Node Biopsy in Vulvar Cancer

January 26, 2018

The 2014 guideline recommendations are

ENDORSED

This means that the recommendations are still current and relevant for decision making

OVERVIEW

The original version of this guidance document was released by Cancer Care Ontario's Program in Evidence-based Care in 2014. In 2016, this document was assessed in accordance with the PEBC Document Assessment and Review Protocol and was determined to require a review. As part of the review, a PEBC methodologist conducted an updated search of the literature. A clinical expert (CR) reviewed and interpreted the new eligible evidence and proposed the existing recommendations could be endorsed. The Expert panel on Sentinel Lymph Node Biopsy in Vulvar Cancer endorsed the recommendations found in Section 1 (Practice Guideline Report) on January 26, 2018.

DOCUMENT ASSESSMENT AND REVIEW RESULTS

Question Considered

For patients with stage I or II vulvar cancer and using IFLD as the reference standard:

1. What are the detection and false-negative rates of SLNB?
2. What is the recurrence rate after a negative SLNB test compared with the recurrence

rate after a negative IFLD test?
3. What are the complication rates after SLNB compared with the complication rates after IFLD?
4. Which patient characteristics affect detection or false-negative rates of SLNB or recurrence or complication rates after SLNB?
5. What is the impact of the learning curve on detection or false-negative rates of SLNB or recurrence or complication rates after SLNB?
6. What is the diagnostic accuracy of frozen-section analysis of SLNB?
7. What is the diagnostic accuracy of SLNB using ultrastaging?
8. What social and ethical issues are associated with SLNB?

Literature Search and New Evidence

The new search (2013 to August 2017) yielded five practice guidelines, six systematic reviews, one RCT, and nine. An additional search for ongoing studies on clinicaltrials.gov yielded three potentially relevant ongoing trials. Brief results of these publications are shown in the Document Summary and Review Tool.

Impact on Guidelines and Its Recommendations

The use of SLNB in the case of previous excision of the primary tumour, or in recurrent disease was identified as an area not covered by the current recommendations and guideline. However, the Working Group felt there is currently no adequate evidence to warrant a review of this literature at this time.

The new data supports existing recommendations. Hence, the Expert Panel ENDORSED the 2014 recommendations on sentinel lymph node biopsy.

cancer care ontario | action cancer ontario
program in evidence-based care | programme de soins fondé sur des preuves

Number and Title of Document under Review	Guideline 4-17: Sentinel Lymph Node Biopsy in Vulvar Cancer
Original Report Date	July 17, 2014
Clinical Expert	Dr. Clare Reade
Research Coordinator	Duvaraga Sivajohanathan
Date Assessed	November 29, 2016
Approval Date and Review Outcome (once completed)	January 26, 2018

Original Question(s):

For patients with stage I or II vulvar cancer and using IFLD as the reference standard:

1. What are the detection and false-negative rates of SLNB?
2. What is the recurrence rate after a negative SLNB test compared with the recurrence rate after a negative IFLD test?
3. What are the complication rates after SLNB compared with the complication rates after IFLD?
4. Which patient characteristics affect detection or false-negative rates of SLNB or recurrence or complication rates after SLNB?
5. What is the impact of the learning curve on detection or false-negative rates of SLNB or recurrence or complication rates after SLNB?
6. What is the diagnostic accuracy of frozen-section analysis of SLNB?
7. What is the diagnostic accuracy of SLNB using ultrastaging?
8. What social and ethical issues are associated with SLNB?

Target Population:

This practice guideline applies to women in Ontario with early-stage (T1 or T2, <4 cm) squamous cell cancer of the vulva are the target population.

Study Selection Criteria:

Inclusion Criteria

1. Included patients with stage I or II vulvar cancer who underwent either IFLD or SLNB;
2. Contained the outcomes of interest, including sensitivity, specificity, false-positive or negative rates, groin recurrence rates, or complication rates; or
3. Included a discussion of organizational, implementation, social, or ethical aspects of SLNB.

Studies were included if they contained at least one of the following:

1. Reports of complications related to surgical evaluation of inguinofemoral lymph nodes by SLNB or separate groin incisions for complete IFLD (wound infection or breakdown, lymphocysts, lymphedema)
2. Reports of groin recurrence rates after negative lymphadenectomy or SLNB testing

3. Reports of overall survival rates after SLNB
4. Reports of sensitivity, specificity, negative or positive predictive values for the SLNB procedure, or ability to detect a sentinel lymph node

Exclusion Criteria

1. Case reports with fewer than five patients
2. Reports of only en-block ("butterfly incision") radical vulvectomy with concurrent bilateral lymphadenectomy
3. Studies where patients underwent vulvar/groin reconstructive procedures
4. Studies using coverings/foreign materials in the groin in all patients
5. Studies of only stage 1A or clinically advanced/recurrent disease (clinical stage 3 or 4,
   or clinically involved lymph nodes)
6. Studies with pregnant patients only or with a specific focus on treatment of vulvar cancer in pregnancy
7. Studies on vulvar melanoma only
8. Data that were published in duplicate (same patients also included in a later study)

Search Details:

- 2013 to August 30th, 2017 (MEDLINE, EMBASE)
- 2013 to August 30th, 2017 (clinicaltrials.gov)

Summary of New Evidence:

Of 573 total hits from MEDLINE and EMBASE + 11 hits from clinicaltrials.gov, 21 references representing five practice guidelines, six systematic reviews, one RCT, and nine observational studies (five prospective and four retrospective) met the inclusion criteria. There were three ongoing trials identified.

Details from the included trials are summarized in the tables below.

Clinical Expert Interest Declaration:

None

1. Does any of the newly identified evidence contradict the current recommendations? (i.e., the current recommendations may cause harm or lead to unnecessary or improper treatment if followed)	No
2. Does the newly identified evidence support the existing recommendations?	Yes
3. Do the current recommendations cover all relevant subjects addressed by the evidence? (i.e., no new recommendations are necessary)	Yes. The clinical expert noted the following questions are not covered by the current recommendations; however, there is currently no adequate literature to provide evidence-based recommendations in this area.

	1. If a patient recurs in the vulva – can they have repeat SLNB (if they only had SLNB the first time around)? 2. If a patient has had previous vulvar surgery (incomplete resection from non-radical excision, previous cancer surgery, etc.), can they safely undergo SLNB? What is the detection rate and what is the groin recurrence rate?
Review Outcome as recommended by the Clinical Expert	ENDORSE
If outcome is UPDATE, are you aware of trials now underway (not yet published) that will impact recommendations?	N/A
DSG/GDG Commentary	

Guidelines

Reference	Recommendations
Diagnosis, Therapy and Follow-up Care of Vulvar Cancer and its Precursors. Guideline of the DGGG and DKG [1]	Consensus: The following conditions must be met for sentinel lymph node biopsy to be indicated: • maximum tumor diameter at skin level < 4cm • unifocal tumor • inguinofemoral lymph nodes must be clinically and sonographically unremarkable • team must be experienced in marking sentinel lymph nodes • ultrastaging of the lymph nodes must be done with additional immunohistochemical examination by a pathologist • the patient must be informed in detail about the benefits and possible oncologic risks of the method • the patient must be followed up regularly (good patient compliance)
Recommendations of the Polish Gynecological Oncology Society for the diagnosis and treatment of vulvar cancer [2]	Please refer to **Figure 2. Guidelines for early stage of disease (without clinically suspicious lymph nodes)** in publication.
New NCCN Guidelines for Vulvar Cancer [3]	SLNB is advisable only in selected patients. Criteria for patient selection include unifocal tumor less than 4cm, clinically nonsuspicious nodes in the groin, no previous vulvar surgery, and adequate surgical experience and resources for the physician to perform the procedure properly. Microinvasion, defined as tumors smaller than 1 mm, should be treated with wide local resection and observation. Tumors larger than 1 mm are treated according to site. Both vulvar midline lesions and lateral lesions (>2 cm from vulvar midline) are treated with lateral local resection or modified radical vulvectomy; vulvar midline lesions require bilateral inguinofemoral node evaluation and SLNB or bilateral inguinofemoral LND. Lateral lesions should have ipsilateral groin node evaluation plus SLNB or ispsilateral groin LND. LND is performed through a separate incision.
Vulvar Cancer, Version 1.2017, NCCN Clinical Practice Guidelines in Oncology [4]	For T1 tumors with ≤1mm depth of invasion (pT1A), the NCCN Guidelines Panel recommends wide local resection or radical local resection; IFLN evaluation is not required due to the low risk of lymph node metastasis in these patients.45,66,72–75 Patients should be observed following resection. If surgical pathology reveals >1mm invasion, additional surgery may be indicated.

	For patients with T1 or smaller T2 tumors with a depth of invasion >1 mm, primary treatment is dictated by tumor location. Patients with lateralized lesions (>1-mm invasion) located ≥2 cm from the vulvar midline should undergo radical local resection or modified radical vulvectomy accompanied by ipsilateral groin node evaluation. Groin evaluation can be performed through SLN biopsy or ipsilateral IFLN dissection. Dissection should be performed if no SLNs are detected. Adjuvant therapy is informed by primary tumor and nodal surgical pathology. Patients with midline vulvar lesions (>1-mm invasion) should undergo radical local resection or modified radical vulvectomy accompanied by bilateral groin node evaluation consisting of SLN biopsy or ipsilateral IFLN dissection. Groin dissection is required on sides for which SLNs are not detected. Adjuvant therapy is informed by primary tumor and nodal surgical pathology.
European Society of Gynaecological Oncology Guidelines for the Management of Patients With Vulvar Cancer [5]	The SLN procedure is recommended in patients with unifocal cancers of less than 4 cm, without suspicious groin nodes (grade B). Use of radioactive tracer is mandatory; use of blue dye is optional (grade B). Lymphoscintigram is advised to enable the preoperative identification, location, and number of SLNs (grade C). Intraoperative evaluation and/or frozen sectioning of the SLN can be performed in an attempt to prevent a second surgical procedure. Caution is warranted because of an increased risk of missing micro metastases on final pathology due to the loss of tissue arising from processing for frozen-section assessment (grade C). When an SLN is not found (method failure), inguinofemoral lymphadenectomy should be performed (expert agreement). Where metastatic disease is identified in the SLN (any size): inguinofemoral lymphadenectomy in the groin with the metastatic SLN should be performed (grade C). For tumors involving the midline, bilateral SLN detection is mandatory. When only unilateral SLN detection is achieved, an inguinofemoral lymphadenectomy in the contralateral groin should be performed (expert agreement). Pathological evaluation of SLNs should include serial sectioning at levels of at least every 200 Km. If the hematoxylin eosin sections are negative, immunohistochemistry should be performed (grade C).

Abbreviations: DGGG - Guidelines programme of the German Society of Gynaecology and Obstetrics; DKG - German Cancer Society; IFLN - inguinofemoral lymph node; LND - lymph node dissection; NCCN – National Comprehensive Cancer Network; SLN - sentinel lymph node; SLNB - sentinel lymph node biopsy

Systematic Reviews

Author, year, reference	Inclusion criteria	Methods	Intervention/ Comparison	Outcomes of interest	Brief results
Bacalbasa N et al. (2016) [6]	Literature that examines SLN biopsy in early-stage vulvar cancer patients regarding feasibility, oncological safety and clinical utility.	Searched for English articles in PubMed and Medline databases with no date limitations using the keywords, "vulvar cancer", "sentinel lymph node", and "dissection"	SLNB	False negatives Quality of life Sensitivity Negative predictive value	The authors did not report the total number of included studies or include a PRISMA flow diagram. The authors only present the most important studies (n=5) that reported the efficacy of the SLN technique in vulvar cancer. The authors concluded that SLNB provides important staging information and has a positive effect on the QoL in patients with vulvar cancer.
Lawrie TA et al (2015) [7]	Studies that evaluated the diagnostic accuracy of traceable agents for sentinel node assessment compared with histological examination of removed groin lymph nodes following complete inguinofemoral lymphadenectomy in women with vulval cancer, provided there were sufficient data for the construction of two-by-two tables.	We searched MEDLINE (1946 to February 2013), EMBASE (1974 to March 2013) and the relevant Cochrane trial registers.	Sentinel node assessment	Sensitivity Negative predictive value Detection rates	34 studies were included. • Pooled sensitivity estimate for studies using blue dye only was 0.94 (95% CI, 0.69-0.99); for mixed tests was 0.91 (95% CI, 0.71- 0.98), for Tc-99 only was 0.93 (95% CI, 0.89 -0.96) and for combined tests was 0.95 (95% CI, 0.89-0.97) • Negative predictive values (NPVs) for all index tests were 95%. • The mean detection rate for blue dye alone was 82%, compared with 95%, 96%and

					98%for mixed tests, Tc-99 and combined tests, respectively.
Tu H et al (2015) [8]	All patients underwent bilateral inguinal lymph node dissection. All patients were treated with bilateral inguinal lymph node dissection, and the patients were treated with SLNB to evaluate the lymph node metastasis of vulvar squamous cell carcinoma. The sensitivity and specificity of lymph node metastasis in patients with SLNB were taken as the observation index. Excluded: Studies of patients with vulvar melanoma, advanced vulvar cancer, total number of <10 studies, case reports, only studies of selective inguinal lymph node dissection, incomplete reporting or lack of necessary observational indicators	The Cochrane Library Clinical Trials Database, PubMed, EMBase, Wanfang Database, Chinese Biomedical Literature Database and Chinese Journal Full-text Database were searched from 1990 to 2014. Chinese search terms include: vulvar cancer, vulvar tumor, groin, outpost, lymph node biopsy, lymph drawing, lymphography, lymph node dissection. The search terms included: vulva * cancer, vulva * tumor, randomized controlled trial, inguinal lymph node dissection, sentinel node, inguinal node dissection, lymphadenectomy, lymphatic mapping, lymphoscintigraphy; the above search terms were separately and joint search.	Sentinel lymph node biopsy	Sensitivity Specificity SLN detection rate	29 studies were included. • Using a fixed effects model, combined sensitivity and specificity of SLNB were 0.94 (95% CI, 0.91-0.96) and 1.00 (95% CI, 0.99-1.00), respectively • Subgroup analysis showed that the sensitivity of SLNB using single tracer and combined tracer was 0.92 (95% CI, 0.85-0.97) and 0.94 (95% CI, 0.91-0.97), respectively. • In the case of "hyper-staging" the sensitivity of the combination was 0.93 (95% CI, 0.90-0.96) and 0.97 (95% CI, 0.90-1.00) , respectively
Meads C et al (2014) [9]	Women with early stages of vulval cancer: at least 75% of population with	Comprehensive searches from the inception of database to October	SLNB	Diagnostic accuracy, morbidity	29 studies were included.Of these, 24 studies reported results for SLN followed by IFL,

	FIGO stage I and II or TNM categories T1-2 N0 M0. Excluded: Patients with vulval melanomas, advanced caner – FIGO stage IV, inoperable tumours, tumours unsuitable for primary surgery, patients with clinical suspicion of metastases,	2013 were conducted in MEDLINE, Embase, Science Citation Index, the Cochrane Library, MEDION, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, the Health Technology Assessment Database, Clinical Trials.com as well as a search of internet to identify relevant published and unpublished studies and studies in progress. Both MESH terms and text words were used and included 'vulva cancer', 'sentinel lymph node biopsy' and 'lymphoscintigraphy'.		following SLN biopsy, mortality and disease-free survival, quality of life, and impact on surgeon's and team's skills and experience (learning curve).	and 5 reported clinical follow-up only for SLN negatives. • Mean SLN detection rates were 94.0% for 99mTc, 68.7% for blue dye and 97.7% for both. • SLN biopsy had pooled sensitivity of 95% (95% CI 92-98%) with NPV of 97.9% in studies using 99mTc/blue dye, ultrastaging and immunohistochemistry with IFL as reference. • Pooled sensitivity for SLN with clinical follow-up for SLN-negatives was 91% (85-95%) with NPV 95.6%. • Patients undergoing SLN biopsy experienced less morbidity than those undergoing IFL.
Hassanzade M et al (2013) [10]	Studies evaluating sentinel node mapping in vulvar cancer.	MEDLINE and SCOPUS databases were searched using "sentinel AND vulv" up to March 2013.	Sentinal node mapping	Detection rate, sensitivity,	47 studies were included. • Pooled patient basis sensitivity for inguinal node involvement was 92% [90-95] (Cochrane Q = 42.7; p=0.014; I^2=20.5%) • Pooled groin basis sensitivity for was 92% [89-94] (Cochrane Q = 33.36; p=0.15; I^2=22.1%)

					• Pooled NPV for patient basis, 97% [96-98] and for groin basis, 98% [97-99] • SN detection rate and sensitivity were related to mapping method and location of the tumour
Meads C et al (2013) [11]	Studies where at least 75% of women had been with diagnosed vulval cancer of FIGO stage IB or II or TNM categories T1–2, N0–2, M0. For the test accuracy reviews, any studies evaluating SLN biopsy with 99m-Tc or blue dye, or both, with reference standard of IFL for all, or for test positives with clinical follow-up for test negatives, were included. For the effectiveness reviews, randomized controlled trials, cohort, case–control or case series of surgical or radiotherapy treatment with outcomes including survival, recurrence, early and late complications and QoL were included.	Databases including MEDLINE, EMBASE, Science Citation Index, MEDION, The Cochrane Library, clinical trials, medical search gateways were searched from inception to January 2011, with no language restrictions.	SLNB IFL	Sensitivity False-positive rates Detection rates Quality of life	Test accuracy: 26 studies were included. • All of the point estimates of sensitivity were above 90% for studies with IFL for all or when using groin and distant recurrences only for clinical follow-up. • All of the point estimates of specificity were 100% because false-positive results were not possible. • 11 studies using 99m-Tc with blue dye, ultrastaging and immunohistochemistry had a pooled sensitivity of 95.6% (95% CI, 91.5%-98.1%) and a specificity of 100% (95% CI, 99.0%-100%). The mean SLN detection rates were 94.6% (90.9-97.1, range 76–100%) for Tc-99m only, 68.7% (63.1-74.0, range 53–88%) for blue dye only and 97.7% (96.6 -98.5, range 84–100%) for both. • One study measured QoL and found no difference between SLN biopsy and IFL

					groups for global health status.

Abbreviations: FIGO - International Federation of Gynecology and Obstetrics; ICG - indocyanine green; SLN – sentinel lymph node; SLNB – sentinel lymph node biopsy; QoL – quality of life; CI – confidence interval; Tc-99 – technetium-99; IFL - inguinofemoral lymphadenectomy; SN – sentinel node

Published Randomized Controlled Trials

Author, year, reference	Population	N	Median Follow-up	Intervention/ Comparison	Outcomes of interest	Brief results
Schaafsma BE et al (2013) [12]	Patients with FIGO stage I vulvar cancer with a unifocal squamous cell carcinoma measuring less than 4 cm in diameter, not encroaching on the vagina, anus or urethra and with negative inguinofemoral nodes as determined by palpation and ultrasonography participated in this double-blind, randomized, non-inferiority trial. Four participants with a tumour >4cm were scheduled to undergo SLN biopsy of the inguinofemoral nodes. Excluded: Patients who were pregnant, lactating, or were allergic to iodine or ICG.	24	NR	ICG:HAS Vs ICG	Detection rate Adverse events	• Of the 35 SLNs identified, 100% were radioactive, 100% were fluorescent and 77% were blue. • No adverse reactions associated with the use of ICG or ICG:HSA were reported • No significant difference was observed in the average number of in vivo identified fluorescent SLNs per groin between ICG:HSA and ICG alone (p = 0.06). • There was no significant difference in intraoperative detection rate (p = 0.27).

Abbreviations: FIGO - International Federation of Gynecology and Obstetrics; ICG - indocyanine green; SLN –sentinel lymph node; HAS – human serum albumin

Published Observational Studies

Author, year, reference	Population	N (pts)	Median Follow-up	Intervention/ Comparison	Outcomes of interest	Brief results
Prospective studies						
Boran N et al (2013) [13]	Patients with histologically confirmed SCC of the vulva between April 200 and October 2005 with T1 or T2 tumours that did not encroach in the urethra, vagina, or anus; have invasion greater than 1mm in depth and were candidates for ILND Exclusion: Patients with clinically palpable groin lymph nodes, and those with prior vulvar surgery that could disrupt lymphatic drainage	21 (12 , Tc-99M; 9, blue-dye)	NR	SLND using Tc-99 or Tc-99 with blue dye	False-negative rates	• SLN was detected in all patients in all patients using Tc-99 (n=12) or blue dye with Tc-99 (n=9) • The false negative rate for SLNs using Tc-99m was 15.4% per groin
Matheron HM et al (2013) [14]	Between April 2012 and February 2013 fourteen patients with early-stage SCC of the vulva and one	15	NR	SN biopsy using ICG-Tc99	Detection rates	• A total of 46 sentinel nodes were excised from 27 groins, yielding an average of 1.7

	patient with melanoma of the vulva were included.	(29 groins)				sentinel nodes (range 1–3) per groin. • In vivo, 98% of sentinel nodes were radioactive; with fluorescence imaging 96% of the sentinel nodes were intraoperatively visualized; ex vivo, all excised sentinel nodes were both radioactive and fluorescent; and with blue dye, only 65% of the sentinel nodes were visualized at the time of excision. All these nodes were both radioactive and fluorescent
Soergel P et al (2017) [15]	Patients with histologically proven cancer of the vulva in stage FIGO I-II, in which a unilateral or bilateral inguinal sentinel lymphadenectomy was planned during a radical local excision or a radical vulvectomy, were informed and, if they consented, included in this study.	27	NR	ICG vs 99Tc Vs Patent blue	Sensitivity Adverse events PPV False negative	• Sensitivity for ICG was 100% (95% CI, 96-100) when compared with 99Tc • Sensitivity for patent blue was 38.6% when compared with 99Tc • Minor local skin coloration of the vulva in half of the patients for up to 3 days • PPV for ICG was 91.9% (95% CI, 84.6-96.5) when compared with 99Tc • PPV for patent blue was 100% when compared with 99TC • One false negative sentinel lymph node for both ICG and 99Tc

Te Grootenhuis NC et al (2016) [16]	Patients with SCC of the vulva (T1, <4cm) with a depth of invasion >1mm and no palpable, clinically suspect or cytological proven inguinofemoral lymph node metastases between 2000 and 2006. Only looked at patients with unifocal disease.	377	105 mths (0-179)	SN procedure	Local recurrence rate Groin recurrence rate	• The overall local recurrence rate was 27.2% at 5 years and 39.5% at 10 years after primary treatment, while for SN-negative patients 24.6% and 36.4%, and for • SN-positive patients 33.2% and 46.4% respectively (p = 0.03). • In 15.4% SN-negative patients (15.4%) an inguinofemoral lymphadenectomy was performed, because of a local recurrence. • Isolated groin recurrence rate was 2.5% for SN-negative patients and 8.0% for SN-positive patients at 5 years.
Verbeek FPR et al (2015) [17]	Women who planned to undergo SLN biopsy for clinically International Federation of Gynecology and Obstetrics stage I vulvar cancer and with clinically negative inguinofemoral nodes.	12	NR	ICG-99Tc	Detection rates	• Position of SLN were located during preoperative lymphoscintigraphy in all 12 patients • 21 lymph nodes were resected
Retrospective						
Amavi AK (2016) [18]	Patients with SCC of the vulva, including early and advanced stages, managed by first surgery between 2007 and 2010.	38	19.4 mths (6-61.5)	Primary surgery	Overall survival	• Five-year OS rate for stage I, 71.4%; stage II, 70% and stage III, 46.7% (p=0.32)

	Tumour stage: I, 18.4%; II, 42.1%; III, 39.5%					
El Afandy AE et al (2013) [19]	Patients who had clinical and surgical stage I or II disease, where the depth of invasion was greater than 1 mm, the primary treatment was consisting of radical wide excision with 2 cm safety margin and superficial inguinal lymphadenectomy with multiple individual modification	41	63 mths (24-71)	Superficial inguinal lymphadenectomy	Groin recurrence rate	• Groin recurrence rate after negative SIND was 17% • Mean number of nodes resected per groin was eight (range 1–17)
Klapdor R et al (2017) [20]	Node negative vulvar cancer patients who had tumours smaller than 4 cm in diameter treated between 2008 and 2014 Tumour stage: pT1a , 13.3%; pT1b, 70%; pT2, 16.7% SLN imaging: planar lymphoscintigraphy, 93.3%; SPECT/CT, 86.7%; blue dye, 66.7% Excluded: Vulvovaginal melanomas	30	43.5 mths (4-75)	SLND Patients with midline tumours underwent tumour localization (>2cm from midline), unilateral SLND was performed if only unilateral drainage was preoperatively identified	Groin recurrence rate Perioperative complications	• 6.6% (95% CI, 1.9-21.3) isolated groin recurrences were identified – both patients had >2 cm midline tumours • 9.5% (95% CI, 2.7-28.9) isolated groin recurrence rate for stage pT1b • One patient developed a deep vein thrombosis, another developed postoperative bleeding, and lastly a wound breakdown occurred
Van Doorn HC et al (2016) [21]	Consecutive patients with recurrent vulvar SCC who underwent a repeat SLN procedure between 2006 and 2014. All patients underwent a local radical	27	NR	SLN procedure – 99Tc	Proportion of groins in which a SLN was identified during	• In 78% of patients and 84% of groins, the repeat SLN procedure was successful

	excision of the vulvar tumour and unilateral or bilateral SLN at initial surgery, followed by radiotherapy.				surgery for recurrent SCC	

Abbreviations: FIGO - International Federation of Gynecology and Obstetrics; ICG - indocyanine green; ILND - inguinal lymph node dissection; LND - lymph node dissection; CI – confidence interval; mths – months; Tc-99 – technetium-99; NR – not reported; PPV – positive predictive value; SCC – small cell carcinoma; SN – sentinel node; SLN - sentinel lymph node; SLND - sentinel lymph node dissection

Ongoing Trials

Protocol ID	Official Title	Intervention/ Comparison	Status	Estimated Study Completion Date	Last Updated
NCT00315159	Conservative Management With Isolated Sentinel Lymph Node Biopsy in Vulvar Cancer Patients With Sentinel Lymph Nodes Determined to be Negative for Metastatic Disease	Sentinel node biopsy	Completed	May 2014	January 12, 2015
NCT02969278	Study on the Prediction of Groin Lymphonodal Status Through 18FDG-PET/CT Combined With Sentinel Lymph Node Biopsy in Bulky a/o Multifocal a/o Pretreated Vulvar Cancer, N0 at Conventional Imaging (GRO-SNaPET Study)	18FDG-PET/TC vs. Sentinel node biopsy	Recruiting	July 2017	November 21, 2016
NCT01500512	GROningen INternational Study on Sentinel Nodes in Vulvar Cancer (GROINSS-V) II: An Observational Study	Sentinel lymph node dissection	Active, not recruiting	July 2015	August 24, 2017

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LITERATURE SEARCH STRATEGY

MEDLINE

1 exp Vulvar Neoplasms/
2 vulvar cancer.mp.
3 vulvar carcinoma.mp.
4 (squamous cell carcinoma and vulva*).mp.
5 (vulva* and tumour).mp.
6 (vulva* and tumor).mp.
7 (vulva* and malignan*).mp.
8 or/1-7
9 exp Sentinel Lymph Node Biopsy/
10 sentinel lymph node*.mp.
11 sentinel node*.mp.
12 ultrastaging.mp.
13 exp Lymph Node Excision/
14 lymphadenectomy.mp.
15 lymph node dissection.mp.
16 lymph node excision.mp.
17 exp Technetium Compounds/ or exp Technetium/ or exp Technetium Tc 99m Sulfur Colloid/
18 (scintigraph* or scintigram* or scintiphotograph* or gamma camera? Or lymphoscintigraph* or lympho-scintigraph*).mp.
19 exp Radionuclide Imaging/
20 or/9-19
21 8 and 20
22 limit 21 to yr="2013 -Current"

EMBASE

1 exp vulva carcinoma/
2 exp vulva tumor/
3 exp vulva cancer/
4 vulvar cancer.mp.
5 vulvar carcinoma.mp.
6 (squamous cell carcinoma and vulva*).mp.
7 (vulva* and tumour).mp.
8 (vulva* and tumor).mp.
9 (vulva* and malignan*).mp.
10 or/1-9
11 exp sentinel lymph node/
12 sentinel lymph node*.mp.
13 sentinel node*.mp.
14 ultrastaging.mp.
15 exp lymphadenectomy/
16 lymphadenectomy.mp.
17 lymph node dissection.mp.
18 lymph node excision.mp.
19 exp technetium 99m/ or exp technetium sulfur colloid tc 99m/ or exp technetium/
20 technetium.mp.

21 (scintigraph* or scintigram* or scintiphotograph* or gamma camera? Or lymphoscintigraph* or lympho-scintigraph*).mp.
22 exp scintiscanning/
23 or/11-22
24 10 and 23
25 limit 24 to yr="2013 -Current"

clinicaltrials.gov
Searched with keywords: ("vulvar cancer") AND ("sentinel node").

Members of the Expert Panel

Name	Affiliation	Conflict of Interest
Allan Covens Gynecologic Oncologist	Sunnybrook Health Sciences Centre Toronto, ON	No conflict of interest declared
Genevieve Bouchard-Fortier Gynecologic Oncologist	Princess Margaret Cancer Centre Toronto, ON	No conflict of interest declared
Laurie Elit Gynecologic Oncologist	Juravinski Cancer Centre Hamilton, ON	No conflict of interest declared
Sarah Ferguson Gynecologic Oncologist	Princess Margaret Cancer Centre Toronto, ON	No conflict of interest declared
Julie Ann Francis Gynecologic Oncologist	Kingston General Hospital Kingston, ON	No conflict of interest declared
Lilian Gien Gynecologic Oncologist	Sunnybrook Health Sciences Centre Toronto, ON	No conflict of interest declared
Waldo Jimenez Gynecologic Oncologist	Juravinski Cancer Centre Hamilton, ON	Has received a grant as a principal or co-investigator from Juravinski Cancer Centre for a protocol on sentinel node biopsy in endometrial cancer
Leah Jutzi Gynecologic Oncologist	Royal Victoria Regional Health Centre Barrie, ON	No conflict of interest declared
Jacob McGee Gynecologic Oncologist	London Health Sciences Centre London, ON	Has received $5000 or more in a single year to act in a consulting capacity (BRCA mutation testing practices at London Health Sciences Centre), to assist with publication costs and in travel support from AstraZeneca to conferences

DEFINITIONS OF REVIEW OUTCOMES

1. **ARCHIVE** –ARCHIVE means that a Clinical Expert and/or Expert Panel has reviewed new evidence pertaining to the guideline topic and determined that the guideline is out of date or has become less relevant. The document, however, may still be useful for education or other information purposes. The document is designated archived on the CCO website and each page is watermarked with the words "ARCHIVED."

2. **ENDORSE** – ENDORSE means that a Clinical Expert and/or Expert Panel has reviewed new evidence pertaining to the guideline topic and determined that the guideline is still useful as guidance for clinical decision making. A document may be endorsed because the Expert Panel feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. **UPDATE** – UPDATE means the Clinical Expert and/or Expert Panel recognizes that the new evidence pertaining to the guideline topic makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The Expert Panel advises that an update of the document be initiated. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making, unless the recommendations are considered harmful.