The role of sentinel node biopsy in the treatment of women with early stage vulval cancer

June 2015
The role of sentinel node biopsy in the treatment of women with early stage vulval cancer was prepared and produced by:

Cancer Australia
 Locked Bag 3 Strawberry Hills NSW 2012 Australia
 Tel: +61 2 9357 9400  Fax: +61 2 9357 9477
 Website: www.canceraustralia.gov.au

© Cancer Australia (2014)

Copyright statements:

Paper-based publications
This work is copyright. You may reproduce the whole or part of this work in unaltered form for your own personal use or, if you are part of an organisation, for internal use within your organisation, but only if you or your organisation do not use the reproduction for any commercial purpose and retain this copyright notice and all disclaimer notices as part of that reproduction. Apart from rights to use as permitted by the Copyright Act 1968 or allowed by this copyright notice, all other rights are reserved and you are not allowed to reproduce the whole or any part of this work in any way (electronic or otherwise) without first being given the specific written permission from Cancer Australia to do so. Requests and inquiries concerning reproduction and rights are to be sent to the Publications and Copyright contact officer, Cancer Australia, Locked Bag 3, Strawberry Hills, NSW 2012.

Internet sites
This work is copyright. You may download, display, print and reproduce the whole or part of this work in unaltered form for your own personal use or, if you are part of an organisation, for internal use within your organisation, but only if you or your organisation do not use the reproduction for any commercial purpose and retain this copyright notice and all disclaimer notices as part of that reproduction. Apart from rights to use as permitted by the Copyright Act 1968 or allowed by this copyright notice, all other rights are reserved and you are not allowed to reproduce the whole or any part of this work in any way (electronic or otherwise) without first being given the specific written permission from Cancer Australia to do so. Requests and inquiries concerning reproduction and rights are to be sent to the Publications and Copyright contact officer, Cancer Australia, Locked Bag 3, Strawberry Hills, NSW 2012.

Copies of The role of sentinel node biopsy in the treatment of women with early stage vulvar cancer can be downloaded from the Cancer Australia website: www.canceraustralia.gov.au or ordered by telephone: 1800 624 973.

Recommended citation
Contents

Executive summary .......................................................................................................................... 6

1 Background .................................................................................................................................. 9
  1.1 Vulval cancer in Australia ........................................................................................................... 9

2 Methods ........................................................................................................................................ 10
  2.1 Inclusion criteria ........................................................................................................................... 11
  2.2 Literature search ........................................................................................................................... 11
  2.3 Quality assessment ....................................................................................................................... 12

3 Results .......................................................................................................................................... 15
  3.1 Sentinel lymph node identification ............................................................................................... 15
  3.2 Outcome measures of SLNB ......................................................................................................... 51

4 Conclusions .................................................................................................................................... 54

Appendix A Contributors ............................................................................................................... 56

Appendix B FIGO staging Carcinoma of the Vulva ........................................................................... 57

Abbreviations ................................................................................................................................... 58

Glossary ............................................................................................................................................ 59

References ......................................................................................................................................... 60
Tables

Table 1 All 42 studies identified (included/excluded) ................................................................. 13
Table 2 Study Characteristics, primary evidence based (29 studies from level III-1 to IV). .......................................................................................................................... 16
Table 3 Number of patients with Sentinel Lymph Node (SNL) detected (29 relevant studies) by technique................................................................. 32
Table 4 Identification of the sentinel lymph node (SLN) .......................................................... 34
Table 5 Studies with Blue Dye and Blue Dye plus Radio Isotope (R-I) ........................................... 34
Table 6 Overall outcomes measured and results from the primary evidence (29 relevant) studies. .................................................................................................................. 36
Table 7 False negative sentinel lymph node (%)........................................................................ 50
Table 8 Effect of immunohistochemistry on detection of positive sentinel lymph node........ 50
Acknowledgments

Funding

Funding for the development of this guide was provided by the Australian Government Department of Health and Ageing.

Contributors

Cancer Australia gratefully acknowledges the support of the individuals who contributed to the development of this report.

See Appendix A for more information.
Executive summary

Cancer of the vulva was the fourth most commonly diagnosed gynaecological cancer with 282 new cases in Australia in 2008, accounting for 0.6 per cent of all new cancers in women.\(^1\) In 2007, cancer of the vulva was the fourth most common cause of gynaecological cancer death in Australia, with 65 deaths, accounting for 0.4 per cent of all cancer deaths in women. Between 2006 and 2010, five-year relative survival was 71.3 per cent for vulval cancer in Australia.\(^1\)

There are no national Australian clinical practice guidelines for the management of women with cancer of the vulva.

- There are guidelines from the UK, Royal College of Obstetricians and Gynaecologists (2014)\(^2\) In unifocal tumours of less than 4 cm maximum diameter where there is no clinical suspicion of lymph node involvement, patients can be safely managed by removal of the identified sentinel lymph nodes.
  (Grade B. Based on other robust experimental or good observational studies).

- Sentinel lymph node biopsy should be offered to all eligible women with squamous carcinoma of the vulva.
  (Grade B. Based on other robust experimental or good observational studies).

However, no other statements were identified regarding the place of sentinel lymph node biopsy (SLNB) in the management of early vulval cancer by any international or national gynaecology or cancer organisation.

This systematic review was undertaken by Cancer Australia in order to assess the evidence for the use of sentinel node biopsy in the treatment of women with early-stage cancer of the vulva. A search of the literature published in the English language between September 1992 and February 2013 was undertaken using electronic databases. Forty-two studies were retrieved of which 29 were included in the review. Limited high level evidence was available. Many studies included small patient numbers, with heterogeneous patient populations. Furthermore, the variables that may influence the detection of the sentinel node, such as size of lesion, clinically suspicious lymph nodes, prior vulval or inguinal surgery and operator experience, are variably defined in the studies reviewed.

Summary of results

Diagnostic accuracy of sentinel lymph node identification and biopsy

Twenty-two studies\(^3\)\(^-\)\(^24\) were identified that reported the results of inguinal-femoral lymph node dissection after sentinel lymph node biopsy when the sentinel node was negative for tumour. Across those studies that reported the false negative rate, it ranged from 0% to 14.3%, with a weighted average rate of 10.9%. (N=1,456).
Based on twenty-three studies, the identification of the sentinel lymph node was enhanced by combined radio-isotope (R-I) and blue dye when compared to either used alone. The false negative rate observed in the fourteen studies was 2.6% (0-8.8%). In comparison, eight studies reported false negative rates of 4.5% (0-14.3%) for R-I alone, and a false negative rate of 9% (2-18%) was observed in seven studies using blue dye alone.

The assumption in managing vulval cancer has been that midline tumours are likely to spread to either right and/or left inguinal-femoral lymph node groups, and bilateral assessment of the lymph nodes is essential in managing midline tumours. Based on ten studies, similar rates of false negative sentinel node biopsies (3.5%) were observed among women with a midline vulvar tumour, compared to the entire cohort of women undergoing sentinel node biopsy.

The potential for previous excisional surgery on the vulva to affect the lymphatic drainage pattern and the identification of SLN was not adequately addressed in the four studies that addressed this topic. A small study showed similar rates of identification of the sentinel lymph node in women who had previous excisional biopsy compared to women who had not. Across the cohort of 90 patients in the remaining three studies, the sentinel lymph node was identified in 92% of cases, increasing to 94% when both R-I and blue dye were used as the detector agent.

The use of serial sectioning for ultrastaging and immuno-histochemistry in the assessment of SLN has been shown to increase the detection rate of tumour in excised SLN in the treatment of both breast cancer and melanoma. Fifteen studies were identified that investigated ultrastaging and immuno-histochemistry examination of the sentinel lymph node with negative nodes subjected to ultrastaging and immuno-histochemistry examination. Seven studies reported on routine sectioning and staining with haematoxylin eosin (H&E) with negative nodes subjected to ultrastaging and immuno-histochemistry examination. Eight studies described ultrastaging and routine H&E of the excised sentinel node, with immuno-histochemistry examination of a negative sentinel node.

The range of increased detection according to individual publications was 0–41%. The results of these studies support the addition of ultrastaging and immuno-histochemistry examination for sentinel lymph nodes identified as negative on routine H&E, to increase accuracy of tumour detection in the sentinel lymph node.

Efficacy and safety of sentinel node biopsy vs complete inguinofemoral lymphadenectomy

This systematic review also included studies that reported the outcome measures of a negative SLNB compared to standard treatment (IFLN dissection) in vulval cancer where SLNB was the only treatment or SLNB was compared to complete IFLN dissection with negative nodes. Similar rates of recurrence in the groin were observed among women who had sentinel node biopsy and complete inguinal-femoral lymph node (IFLN) dissection, with lower rates of adverse event observed for SLNB. A systematic review that included three studies with a study cohort limited to early stage vulval cancer reported a mean groin recurrence rate of 2.0% (range 0-2.3%). The groin recurrence rate reported in all eleven studies in the Reade et al systematic review was 3.6% (range 0-22%). By comparison, the recurrence rate in a groin following complete IFLN dissection is reported to be 1.3% (range 0-
SLNB showed a higher recurrence rate compared to IFLN, however it is not possible to ascertain whether the difference is statistically significant.

Potential adverse effects of inguinal-femoral lymph node dissection include lymphoedema, lymphocyst formation, and cellulitis and wound complications. Eight studies were identified that had some assessment of postoperative complications, however the information provided is often limited and of poor quality.\textsuperscript{15, 25-28, 33-35}

Acute complications such as infection or wound collection were more frequently observed among patients undergoing inguinal-femoral lymph node dissection compared to those having sentinel node biopsy (23.5% compared to 14.5% of patients).\textsuperscript{15, 25-28, 33-35} The frequency of longer-term adverse effects such as lymphoedema and recurrent cellulitis was lower for patients who had sentinel node biopsy compared to patients who had complete lymph node dissection.\textsuperscript{15, 25-28, 33-35}

**Quality of life and patient satisfaction measures**

Two studies\textsuperscript{34, 35} were identified that provided quality of life assessment using the EORTC QLQ-C30, for women undergoing sentinel lymph node procedures for vulval cancer. Novackova et al. (2012) reported a non-significant trend towards improved quality of life in patients having sentinel node biopsy compared to patients having complete lymph node dissection. However, it is noted that the study was small (n=29), and the use of post-operative radiotherapy limits interpretation of the results. Oonk et al. (2009) reported reduced treatment-related morbidity in patients having sentinel node biopsy, however there was no difference in quality of life outcomes when compared to patients having complete lymph node dissection. Overall, there is no evidence that a statistically significant or clinically meaningful difference exists between SLNB and IFLND on quality of life.
1 Background

1.1 Vulval cancer in Australia

Vulval cancer in Australia is uncommon, making up 6.2% of all gynaecological cancers. Among 82.6% cases of vulval cancer have squamous cell histology.\(^1\) As it an uncommon malignancy, data that clearly define best practice outcomes are difficult to obtain and interpret. For the purpose of this review, only publications dealing with early squamous cell cancer of the vulva were evaluated. The International Federation of Gynaecology and Obstetrics (FIGO) categorises vulval cancer into stages (see Appendix A).\(^36\) Stage I vulval cancer is defined as being confined to the vulva. Studies that did not distinguish between results for stage I and II cancers were excluded from the review, as involvement of the urethra or anus (stage II and above) implies alternative lymphatic pathways.

Complete inguino-femoral lymph node (IFLN) dissection is part of standard treatment for early stage vulval cancer but is associated with a high incidence of post-operative groin wound complications and lymphoedema of the leg. Lymphoedema has been reported in up to 62% of patients undergoing complete IFLN dissection.\(^37\) Sentinel lymph node biopsy (SLNB) aims to remove the lymph node(s) that act as the primary drainage point for vulval cancer. As fewer than 20% of early vulval cancer cases will have lymph node involvement, the identification of a sentinel node free of tumour means that approximately 80% of women with vulval cancer can avoid the potential complications and long term morbidity associated with complete IFLN dissection.

The rationale for performing SLNB in early vulval cancer is aimed at reducing the morbidity associated with full lymphadenectomy without compromising the ability to cure this malignancy. Such an approach has been successfully implemented in the management of melanoma and breast cancer. However previous attempts at treatment modification to reduce morbidity in vulval cancer have resulted in unacceptable levels of recurrence in the inguino-femoral lymph nodes.\(^30\)

Standard treatment of early stage vulval cancer entails radical resection of the primary vulval tumour and depending on the site of tumour, either unilateral or bilateral IFLN dissection. This treatment is associated with a high chance of cure if the IFLN are negative for tumour.

Recurrence of tumour in undissected IFLN has a mortality that may be as high as 90%.\(^31\) In order to consider SLNB as an alternative to complete IFLN dissection outcome measures of groin recurrence, survival and morbidity need to be ascertained to ensure that the survival of women undergoing SLNB instead of IFLN is not compromised.
2 Methods

The questions addressed in this review were developed in consultation between Cancer Australia and the clinicians undertaking the review. The questions that were considered to be critical in the assessment of the role of SLNB in the management of women with early stage cancer of the vulva were:

1. What is the sensitivity/negative predictive value of sentinel lymph node identification and biopsy in relation to:
   - size of the lesion
   - site of lesion on the vulva
   - unifocal vs multifocal disease
   - previous excisional vulvar surgery
   - the presence or absence of lympho-vascular invasion
   - type of histological assessment of sentinel lymph node
     o standard processing
     o ultrassectioning +/- Immunohistochemistry (IHC)
   - the technique used for identification of the SLN
     o Tissue dye agents
     o Radio-labelled nanocolloid
     o Combined technique

2. What are the outcomes measures of a negative SLNB compared to standard treatment (IFLN dissection) in vulvar cancer where SLNB was the only treatment or SLNB was compared to complete IFLN dissection with negative nodes with respect to:
   - Survival
     o Overall and disease free
   - Patterns of recurrence
     o Inguinal vs systemic
   - Complications of treatment
     o lymphoedema
     o lymphocyst formation
     o cellulitis
     o wound complications

3. What is the impact on quality of life and patient satisfaction measures?
2.1 Inclusion criteria

2.1.1 Participants

For all questions, participants were women with early-stage, squamous cell cancer of the vulva.

2.1.2 Intervention/Comparison

In order to assess the quality of data presented in the publications reviewed, the following variables had to be clearly described.

- The agent used for identification of the SLN
- Timing of injection
- Location of injections
- Technique used to detect and remove SLN
- Definition of what constitutes a SLN
- Number of lymph nodes present in a SLNB
- Number of patients and groins dissected
- Method of histological assessment of SLN
- Length of follow up of patients undergoing the procedure

2.2 Literature search

A systematic literature search was undertaken using the search terms:

- Vulvar cancer/carcinoma
- squamous cell cancer vulva
- sentinel lymph node identification
- sentinel lymph node biopsy.

The procedure of SLN identification in vulvar cancer was initially described by Barton in 1992. A complete list of publications available from September 1992 until February 2013 was identified using nine databases.

- MEDLINE/PubMed
- EMBASE
- Health Economic Evaluations Database (HEED)
- Cochrane Central Register of Controlled Trials (CENTRAL)
- Cochrane Database of Systematic reviews.
- Health Services Technology Assessment Texts (HSTAT)
Proceedings of scientific meetings of Society of Gynaecologic Oncologists (SGO), International Gynaecological Cancer Society (IGCS) and European Society Gynaecological Oncology (ESGO)

Two hundred and forty five (245) studies were initially identified, from these forty two (42) search results were identified for full screening of which 29 publications were considered relevant, and 23 were suitable for inclusion in the final analysis.

2.2.1 Exclusion criteria

Studies were excluded if they met any of the following criteria:

- no distinction between stage 1 (early stage cancer of the vulva) and stage II
- articles including data that:
  - reported cases other than squamous cell cancer of the vulva except where the final data analysis excluded these cases
  - reported on clinically advanced squamous cancers except where the final data analysis excluded these cases
- review articles
- publications in a language other than English
- case reports of fewer than five patients
- editorial and opinion publications
- abstracts of oral presentations

2.3 Quality assessment

All publications were independently assessed for suitability to include in the final analysis by two members of the review team. These studies were allocated levels of evidence according to NHMRC guidelines.  

Table 1 summarises all of the 42 studies identified in the literature search. The studies highlighted in bold are those included in this systematic review.
Table 1 All 42 studies identified (included/excluded)

<table>
<thead>
<tr>
<th>Author</th>
<th>Study design</th>
<th>N</th>
<th>Follow up (months)</th>
<th>Level</th>
<th>Quality</th>
<th>Primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Included for accuracy of SLN identification</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rob 2007</td>
<td>diagnostic accuracy</td>
<td>59</td>
<td>NR</td>
<td>III-2</td>
<td>Moderate</td>
<td>Identification of SLN with blue dye &amp; radio-isotope</td>
</tr>
<tr>
<td>Levenback 2001</td>
<td>case series</td>
<td>52</td>
<td>N/A</td>
<td>IV</td>
<td>low</td>
<td>sensitivity of blue dye to identify SLN</td>
</tr>
<tr>
<td>Hampi 2008</td>
<td>observational</td>
<td>127</td>
<td>NR</td>
<td>III-2</td>
<td>moderate</td>
<td>Detect SLN with blue dye and R-I</td>
</tr>
<tr>
<td>Johann 2008</td>
<td>case series</td>
<td>39</td>
<td>111</td>
<td>IV</td>
<td>low</td>
<td>sensitivity to detect SLN by R-I</td>
</tr>
<tr>
<td>de Hullu 2000</td>
<td>case series</td>
<td>41</td>
<td></td>
<td>III-2</td>
<td>moderate</td>
<td>Sentinel node identified</td>
</tr>
<tr>
<td>Martinez-Palones 2006</td>
<td>diagnostic accuracy, case series</td>
<td>28</td>
<td>22.5</td>
<td>IV</td>
<td>low</td>
<td>False negative SLN (R-I and blue dye)</td>
</tr>
<tr>
<td>Merisio 2005</td>
<td>case series</td>
<td>20</td>
<td>NR</td>
<td>III-2</td>
<td>moderate</td>
<td>False negative rate of SLN biopsy using radio-isotope</td>
</tr>
<tr>
<td>Moore and Pasquale 2003</td>
<td>case series</td>
<td>21</td>
<td>N/A</td>
<td>III-2</td>
<td>high</td>
<td>Blue Dye vs Radio-isotope identification of SLN</td>
</tr>
<tr>
<td>Sideri 2000</td>
<td>case series</td>
<td>44</td>
<td>NR</td>
<td>III-2</td>
<td>high</td>
<td>False negative rate of SLN biopsy</td>
</tr>
<tr>
<td>Ansink 1999</td>
<td>diagnostic accuracy</td>
<td>51</td>
<td>N/A</td>
<td>IV</td>
<td>low</td>
<td>Detection of SLN with blue dye</td>
</tr>
<tr>
<td>Vakselj 2007</td>
<td>case series</td>
<td>35</td>
<td>32</td>
<td>IV</td>
<td>low</td>
<td>NPV of negative SLN</td>
</tr>
<tr>
<td>Zekan 2012</td>
<td>case series</td>
<td>25</td>
<td>0</td>
<td>III-2</td>
<td>moderate</td>
<td>Accuracy of SLN</td>
</tr>
<tr>
<td>Aktivos 2011</td>
<td>case series</td>
<td>34</td>
<td></td>
<td>IV</td>
<td>moderate</td>
<td>Detection of SLN with dye and/or colloid</td>
</tr>
<tr>
<td>Achimas-Cadariu 2009</td>
<td>case series</td>
<td>56</td>
<td>25</td>
<td>IV</td>
<td>low</td>
<td>Sentinel node detection (R-I and blue dye)</td>
</tr>
<tr>
<td>Ennik 2011</td>
<td>diagnostic accuracy</td>
<td>65</td>
<td>N/A</td>
<td>IV</td>
<td>low</td>
<td>SLN detection in patients with prior excisional biopsy c/w no excision</td>
</tr>
<tr>
<td>Slutz 2002</td>
<td>case series</td>
<td>26</td>
<td>NR</td>
<td>III-2</td>
<td>moderate</td>
<td>False negative rate of SLN (R-I only)</td>
</tr>
<tr>
<td>Levenback 2012</td>
<td>observational</td>
<td>452</td>
<td>0</td>
<td>III-2</td>
<td>high</td>
<td>Negative predictive value of a negative Sentinel LN</td>
</tr>
<tr>
<td>Crosbie 2010</td>
<td>diagnostic accuracy</td>
<td>32</td>
<td>62</td>
<td>IV</td>
<td>low</td>
<td>SLN detection / excisional biopsy incisional biopsy</td>
</tr>
<tr>
<td>Lindell 2010</td>
<td>diagnostic accuracy</td>
<td>77</td>
<td>N/A</td>
<td>III-3</td>
<td>moderate</td>
<td>SLN identification/ SN mapping preoperatively</td>
</tr>
<tr>
<td>Devaja 2011</td>
<td>diagnostic accuracy</td>
<td>60</td>
<td>24</td>
<td>IV</td>
<td>low</td>
<td>Detection of SLN</td>
</tr>
<tr>
<td>Radziszewski 2010</td>
<td>diagnostic accuracy, Case series</td>
<td>56</td>
<td></td>
<td>N/A</td>
<td>III-2</td>
<td>Low Detection of SLN</td>
</tr>
<tr>
<td>Included for QOL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Novackova 2012</td>
<td>case -control cohort</td>
<td>29</td>
<td>6</td>
<td>IV</td>
<td>low</td>
<td>Prevalence of lymphoedema (circumference/MFBIA)</td>
</tr>
<tr>
<td>Oonk 2009</td>
<td>questionnaire</td>
<td>62</td>
<td>33</td>
<td>III-2</td>
<td>high</td>
<td>QOL</td>
</tr>
<tr>
<td>Heffer 2008</td>
<td>case series</td>
<td>75</td>
<td>35.5</td>
<td>III-3</td>
<td>low</td>
<td>Inguinal post op morbidity, seroma, abscess, wound breakdown</td>
</tr>
<tr>
<td>de Hullu 2001</td>
<td>questionnaire</td>
<td>106</td>
<td></td>
<td>IV</td>
<td>moderate</td>
<td>Acceptable false neg patient</td>
</tr>
<tr>
<td>Included for technique</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beneder 2008</td>
<td>pilot study</td>
<td>10</td>
<td></td>
<td>IV</td>
<td>low</td>
<td>Number of sentinel LN</td>
</tr>
<tr>
<td>Huftheman 2012</td>
<td>case series</td>
<td>9</td>
<td>0</td>
<td>IV</td>
<td>low</td>
<td>Feasibility and accuracy of SLN using indocyanine green</td>
</tr>
<tr>
<td>Klar 2011</td>
<td>case series</td>
<td>16</td>
<td>N/A</td>
<td>III-3</td>
<td>moderate</td>
<td>Identification of SLN by R-I</td>
</tr>
<tr>
<td>Crane 2011</td>
<td>pilot study</td>
<td>10</td>
<td>N/A</td>
<td>IV</td>
<td>low</td>
<td>SLN identification using immuno fluorescence</td>
</tr>
<tr>
<td>Included for Recurrence</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Van der Zee 2008</td>
<td>observational</td>
<td>403</td>
<td>35</td>
<td>III-1</td>
<td>high</td>
<td>Groin recurrence in neg SLN</td>
</tr>
<tr>
<td>Study</td>
<td>Study Type</td>
<td>n</td>
<td>Stage</td>
<td>Grade</td>
<td>Risk</td>
<td>Outcome</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>---------------------</td>
<td>-----</td>
<td>-------</td>
<td>-------</td>
<td>------</td>
<td>---------------------------------------</td>
</tr>
<tr>
<td>Terada 2006</td>
<td>case series</td>
<td>21</td>
<td>S5</td>
<td>III-3</td>
<td>low</td>
<td>Recurrence in negative SLN</td>
</tr>
<tr>
<td>Moore 2008</td>
<td>observational</td>
<td>31</td>
<td>29</td>
<td>IV</td>
<td>moderate</td>
<td>groin recurrence</td>
</tr>
<tr>
<td>Included for pathology assessment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moore and Granai 2003</td>
<td>diagnostic accuracy</td>
<td>29</td>
<td>NR</td>
<td>III-2</td>
<td>Moderate</td>
<td>Sensitivity of IHC vs Ultrastaging for negative SLN</td>
</tr>
<tr>
<td>Molpus 2001</td>
<td>case series</td>
<td>11</td>
<td>N/A</td>
<td>IV</td>
<td>low</td>
<td>false neg rate of standard histology</td>
</tr>
<tr>
<td>Brunner 2008</td>
<td>case series</td>
<td>44</td>
<td>NR</td>
<td>III-2</td>
<td>moderate</td>
<td>false neg frozen</td>
</tr>
<tr>
<td>Terada 2000</td>
<td>case series</td>
<td>9</td>
<td>21</td>
<td>III-3</td>
<td>low</td>
<td>false neg SLN with routine histology vs ultrastaging</td>
</tr>
<tr>
<td>Regauer 2008</td>
<td>descriptive</td>
<td>38</td>
<td>39</td>
<td>IV</td>
<td>high</td>
<td>number identified with H&amp;E</td>
</tr>
<tr>
<td>Excluded</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oonk 2010</td>
<td>observational</td>
<td>135</td>
<td>III-2</td>
<td>low</td>
<td></td>
<td>size of sent met and risk non sent met</td>
</tr>
<tr>
<td>de Hullu 1998</td>
<td>Pilot, case series</td>
<td>10</td>
<td>III-2</td>
<td>low</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nyberg 2007</td>
<td>diagnostic accuracy</td>
<td>47</td>
<td>NR</td>
<td>III-3</td>
<td>low</td>
<td>Identification of SLN with Blue and R-I (40 of 47 patients had both)</td>
</tr>
<tr>
<td>García-Iglesias 2012</td>
<td>retrospective</td>
<td>76</td>
<td>36</td>
<td>IV</td>
<td>low</td>
<td>Groin recurrence after negative SLNB</td>
</tr>
<tr>
<td></td>
<td>observational</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: NR, not reported; N/A, not applicable; H&E: hematoxylin eosin; IHC: immunohistochemistry; LN: lymph node; R-I: radio isotope; SLN: sentinel lymph node; SN: sentinel node; SLNB: sentinel lymph node biopsy.
3 Results

The standard initial management of inguino-femoral lymph nodes in the treatment of early stage vulvar cancer is:

- Ipsilateral complete inguino femoral lymphadenectomy (IFLN) for lateral vulvar lesions
- Bilateral complete inguino femoral lymphadenectomy (IFLN) for vulvar lesions encroaching upon or crossing the midline

3.1 Sentinel lymph node identification

The reviewed studies describe three techniques for the identification of SLN (see Table 3):

1. Peri-tumoural injection of blue dye
2. Peri-tumoural injection of fluorescent agent and visualization using fluorescent imaging system.
3. Peri-tumoural injection of Technetium 99m nanocolloid (Radio-Isotope R-I)

The number of patients with SLN detected across the studies is shown in Table 3. This table includes the percentage of SLN and the number of patients with false negatives detected per study. The false negative rate was calculated for this review using the data provided by each study (number of patients with false negatives/total number of patients for each study). Two studies did not report on the number of patients with SLN but the number of groins, these are noted under their respective entries.

In many reports combined techniques for SLN identification were used. Two studies reported on fluorescent imaging techniques which are not in common clinical use in the Australian setting, and so were excluded from further analysis.\textsuperscript{38, 39}

The studies that examined the detection rate of SLN report results according to:

- number of patients with SLN identified/ number of patients having the procedure
- number of groins with SLN identified/ number of groins needing to be evaluated

All studies are observational studies of test accuracy and some include a very heterogeneous patient/pathology population (See Table 2). The variables that may influence the detection of SLN, such as size of lesion, clinically suspicious lymph nodes, prior vulvar or inguinal surgery and operator experience, are inconsistently defined in the studies reviewed. In particular, there was very little information provided about who performed the peri-tumoural injection and the experience of the operator, therefore no comment can be made about any learning curve phenomena in SLN identification for vulvar cancer.
### Table 2: Study Characteristics, primary evidence based (29 studies from level III-1 to IV).

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study design; location</th>
<th>Patient number (N), Age, Study duration</th>
<th>Patient status</th>
<th>Follow up (months)</th>
<th>Outcomes measured</th>
<th>Technique</th>
<th>Level / Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Accuracy of SLN identification</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ansink et al 1999</td>
<td>Diagnostic accuracy; The Netherlands</td>
<td>N=51, Age=701 (mean), Study duration=3 years</td>
<td>Patients with histologically confirmed SCC of the vulva without clinically suspicious lymph nodes or other signs of metastatic disease.</td>
<td>NR</td>
<td>Negative predictive value of SLN detection with blue dye</td>
<td>“Patent blue V was injected intradermally shortly before surgery. Routine groin lymph node dissection and radical vulvectomy were performed. During the surgery, blue lymph vessels and lymph nodes were identified, and the blue lymph nodes were sent separately for histologic examination. In case of a medial or midline tumor, the aim was to identify a blue lymph node bilaterally (midline tumor as a tumor with a medial margin &lt;1 cm from the midline). The negative predictive value of the blue lymph nodes for the absence of metastases was assessed by histologic examination of the groin lymph node specimens.”</td>
<td>III-2 / High</td>
</tr>
<tr>
<td>de Hullu et al 2000</td>
<td>Case series; Amsterdam, the Netherlands</td>
<td>N=59, Age=69 (median), Study duration=3 years</td>
<td>Patients with primary vulval cancer, with T1 (≤ 2 cm) or T2 (&gt; 2 cm) tumors.</td>
<td>NR</td>
<td>Negative predictive value of SLN and detection of false negative SLN</td>
<td>“The day before operation 0.2 to 0.6 mL of 60-MBq technetium-99m-labeled nanocolloid was injected circumferentially intradermally around the tumour”</td>
<td>III-1 / High</td>
</tr>
<tr>
<td>Author, Year</td>
<td>Study design; location</td>
<td>Patient number (N), Age, Study duration</td>
<td>Patient status</td>
<td>Follow up (months)</td>
<td>Outcomes measured</td>
<td>Technique</td>
<td>Level / Quality</td>
</tr>
<tr>
<td>--------------</td>
<td>------------------------</td>
<td>----------------------------------------</td>
<td>----------------</td>
<td>-------------------</td>
<td>-------------------</td>
<td>-----------</td>
<td>----------------</td>
</tr>
<tr>
<td>Sideri et al 2000</td>
<td>Case series; Milan, Italy</td>
<td>N=44, Age=NR, Study duration=3 years</td>
<td>Patients with early invasive squamous cell vulval cancer (20 with T1 and 23 T2 vulval lesions, 1 with vaginal cancer)</td>
<td>NR</td>
<td>Detection of SN using lymphoscintigraphy and gamma detecting probe.</td>
<td>Lymphoscintigraphy (technetium-99m human albumin administered perilesionally) was done a day before surgery to establish lymphatic drainage and identify SN location. After complete ILND was performed.</td>
<td>III-2 / High</td>
</tr>
<tr>
<td>Levenback et al 2001</td>
<td>Case series; Texas, USA</td>
<td>N=52, Age=58 (median), Study duration=2 years</td>
<td>Patients undergoing primary surgical treatment for vulval cancer (87% with T1 and T2 lesions, 92% suspicious lymph nodes, 67% squamous cell carcinoma, remaining with</td>
<td>NR</td>
<td>Effectiveness of intraoperative lymphatic with blue dye alone to identify sentinel nodes</td>
<td>“Isosulfan blue dye was injected intradermally at the edge of the primary tumour closest to the adjacent groin. Bilateral dye injections and groin dissections were performed if the tumour was within 2 cm of the midline.”</td>
<td>IV / Low</td>
</tr>
<tr>
<td>Author, Year</td>
<td>Study design; location</td>
<td>Patient number (N), Age, Study duration</td>
<td>Patient status</td>
<td>Follow up (months)</td>
<td>Outcomes measured</td>
<td>Technique</td>
<td>Level / Quality</td>
</tr>
<tr>
<td>-------------</td>
<td>------------------------</td>
<td>----------------------------------------</td>
<td>----------------</td>
<td>-------------------</td>
<td>-------------------</td>
<td>-----------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Sliutz et al 2002[^17]</td>
<td>Case series; Germany</td>
<td>N=26, Age=40-89, Study duration=2 years</td>
<td>Patients with early vulvar cancer, planned for local wide excision or vulvectom including groin dissection</td>
<td>NR</td>
<td>SNL detection with gamma probe</td>
<td>“Two to 3h before the planned procedure technetium99 m-labeled micro-colloid intradermally was injected at four locations around the tumor. In the operating theatre SLNs were identified at the beginning of the procedure using a handheld gamma-detection probe. After resection of suspected SLNs a standard unilateral or bilateral grain dissection was performed, subsequently followed by local wide excision or, if indicated, radical vulvectomy. SN detection using technetium99 m-labeled microcolloid was compared with final histopathological and immunohistochemical results.”</td>
<td>III-2 / Moderate</td>
</tr>
<tr>
<td>Moore et al 2003[^10]</td>
<td>Case series; USA</td>
<td>N=21, Age=79 (median), Study duration=NR</td>
<td>Patients with primary squamous cell carcinoma of the vulval</td>
<td>NR</td>
<td>SLN detection with blue dye and Technetium-99m sulfur colloid radio-isotope.</td>
<td>“Technetium-99m sulfur colloid was injected intradermally at the tumor margins 90–180 min preoperatively followed by a similar injection of isosulfan blue dye 5–10 min before the groin dissection.”</td>
<td>III-2 / High</td>
</tr>
<tr>
<td>Author, Year</td>
<td>Study design; location</td>
<td>Patient number (N), Age, Study duration</td>
<td>Patient status</td>
<td>Follow up (months)</td>
<td>Outcomes measured</td>
<td>Technique</td>
<td>Level / Quality</td>
</tr>
<tr>
<td>--------------</td>
<td>------------------------</td>
<td>----------------------------------------</td>
<td>----------------</td>
<td>-------------------</td>
<td>-------------------</td>
<td>-----------</td>
<td>----------------</td>
</tr>
<tr>
<td>Merisio et al 2005⁹</td>
<td>Case series; Parma, Italy</td>
<td>N=20, Age=75 (mean), Study duration=4 years</td>
<td>Patients with stage T1 (9), and T2 (11), N0, M0 squamous cell carcinoma of the vulval were included in the study.</td>
<td>NR</td>
<td>SLN detection by preoperative lymphoscintigraphy with technetium-99 m-labeled nanocolloid and radio guided intraoperative detection</td>
<td>dissection. A handheld collimated gamma counter was employed to identify Tc-99m-labeled sentinel nodes. Lymphatic tracts that had taken up blue dye and their corresponding sentinel node were also identified and retrieved. A completion inguinal dissection was then performed.”</td>
<td>III / 2 / Moderate</td>
</tr>
<tr>
<td>Martinez-Palones et al 2006¹⁰</td>
<td>Diagnostic accuracy.</td>
<td>N=55, Age=70 (mean), Study</td>
<td>Patients with early stage vulval cancer</td>
<td>22.5 (median, with SLN)</td>
<td>SLN identification; recurrence after</td>
<td>“SLN detection was done by lymphoscintigraphy 16 h before surgery. The procedure was performed using human serum albumin nanocolloid particles radioactively labeled with technetium-99 m pertechnetate. The tracer was injected subcutaneously, and views were obtained using gamma cameras. Lymphadenectomy was preceded by radio guided sentinel lymph node detection using a ScintiProbe MR 100 surgical probe.”</td>
<td>IV / Low</td>
</tr>
<tr>
<td>Author, Year</td>
<td>Study design; location</td>
<td>Patient number (N), Age, Study duration</td>
<td>Patient status</td>
<td>Follow up (months)</td>
<td>Outcomes measured</td>
<td>Technique</td>
<td>Level / Quality</td>
</tr>
<tr>
<td>--------------</td>
<td>------------------------</td>
<td>-----------------------------------------</td>
<td>----------------</td>
<td>-------------------</td>
<td>-------------------</td>
<td>-----------</td>
<td>----------------</td>
</tr>
<tr>
<td>Hauspy et al 2007</td>
<td>Case series; Ontario, Canada</td>
<td>N=41, Age=65 (mean), Study duration=2 years</td>
<td>Patients with surgically managed vulval cancer of clinical stages T1 and T2.</td>
<td>NR</td>
<td>SLN detection with technetium sulfur colloid and/or lymphazurin blue</td>
<td>“2–4 hours preoperatively, 0.1–0.2 mci of filtered sulfur colloid technetium injected intradermally. Early on both technetium and lymphazurin blue dye were used in all patients. Later on, if no lymph nodes were identified with technetium, up to 4 mci of lymphazurin blue dye were used.”</td>
<td>III-2 / Moderate</td>
</tr>
<tr>
<td></td>
<td>case series; Barcelona, Spain</td>
<td>duration=10 years</td>
<td>(52 with SCC and 3 with melanoma).</td>
<td>60 (median, without SLN identification)</td>
<td>surgical treatment with or without SN identification</td>
<td>injected in each quadrant around the tumor with depots of technetium 99-m labeled nanocolloid. Immediately after injection, dynamic lymphoscintigraphy was performed using a gamma camera. Additional static images were taken about 2–3 h after injection to identify the sentinel node. At the time of surgery and before induction of anaesthesia, approximately 2–4 ml of isosulfan blue dye was injected superficially around the tumor at the same locations as the tracer. The sentinel node was detected before opening groin skin using a handheld gamma probe.”</td>
<td></td>
</tr>
<tr>
<td>Author, Year</td>
<td>Study design; location</td>
<td>Patient number (N), Age, Study duration</td>
<td>Patient status</td>
<td>Follow up (months)</td>
<td>Outcomes measured</td>
<td>Technique</td>
<td>Level / Quality</td>
</tr>
<tr>
<td>--------------</td>
<td>------------------------</td>
<td>----------------------------------------</td>
<td>---------------</td>
<td>------------------</td>
<td>------------------</td>
<td>-----------</td>
<td>----------------</td>
</tr>
<tr>
<td>Rob et al 2007</td>
<td>Diagnostic accuracy; Prague, Czech Republic</td>
<td>N=59, Age=NR, Study duration=4 years</td>
<td>Women with squamous cell vulval cancers &lt; 4 cm (T1b and T2 tumours).</td>
<td>NR</td>
<td>SLNs in vulval cancer using blue dye and 99mTc radiocolloid</td>
<td>mL of lymphazurin blue dye was injected intradermal at the leading edge(s) of the lesion at the beginning of surgery.”</td>
<td>III-2 / NA</td>
</tr>
<tr>
<td>Vakselj et al 2007</td>
<td>Case series; Ljubljana, Slovenia</td>
<td>N=35, Age=65.8 (mean), Study duration=3 years</td>
<td>Patients with vulval cancer (32 with SCC, 1 with melanoma, 1 BCC, 1 with adeno-squamos cell carcinoma)</td>
<td>32</td>
<td>Detection of SLN using 99mTc, dynamic lymphoscintigraphy, and blue dye before surgery; NPV of negative SLN.</td>
<td>“Optimum timing of preoperative scintigraphy scans and its contribution to 99mTc SLN detection over that of the intraoperative handheld gamma probe. Blue dye alone was used in the first 16 women (group A) and the combination of 99mTc and blue dye was used on 43 women (group B).”</td>
<td>IV / Low</td>
</tr>
<tr>
<td>Hampl et al 2008</td>
<td>Observational; Germany</td>
<td>N=127, Age=61.4 (mean), Study duration= 3 years</td>
<td>Women with primary T1–T3 vulval cancer (44.8% had T1, 49.6% had T2, 5.6% had</td>
<td>NR</td>
<td>Detection of SLN after application of 99mTechnetium labeled nanocolloid</td>
<td>“Patients had a SLN removal after application of 99mTcTechnetium labeled nanocolloid and/or blue dye. Subsequently, in all women a</td>
<td>III-2 / Moderate</td>
</tr>
<tr>
<td>Author, Year</td>
<td>Study design; location</td>
<td>Patient number (N), Age, Study duration</td>
<td>Patient status</td>
<td>Follow up (months)</td>
<td>Outcomes measured</td>
<td>Technique</td>
<td>Level / Quality</td>
</tr>
<tr>
<td>-------------</td>
<td>------------------------</td>
<td>----------------------------------------</td>
<td>---------------</td>
<td>-------------------</td>
<td>-----------------</td>
<td>-----------</td>
<td>----------------</td>
</tr>
<tr>
<td>Johann et al 2008(1)</td>
<td>Case series (retrospective study); Bern, Switzerland</td>
<td>N=63, Age=68.4 (median for group 1) and 62.8 (median for group 2), Study duration=17 years</td>
<td>T3(1), Patients who underwent SLNB and/or ILND for vulval SCC in the years 1990–2007.</td>
<td>111 for ILND and median of 24 for SLNB</td>
<td>and/or blue dye.</td>
<td>complete inguinofemoral lymphadenectomy and the adequate vulval operation were performed. SLN were examined by routine pathologic examination (H&amp;E), followed by step-sectioning and immunohistochemistry if negative.”</td>
<td>IV / Low</td>
</tr>
<tr>
<td>Achimas-Cadariu et al 2009(2)</td>
<td>Retrospective: Wiesbaden,</td>
<td>N=59, Age=66 (median), Study</td>
<td>Patients with vulvar cancer (56 with</td>
<td>25</td>
<td>Sensitivity to detect SLN with Tc(99m) Radioisotope.</td>
<td>“Four aliquots of 15 MBq Tc(99m) labeled nanocolloids were injected intradermally adjacent to the tumour. Surgery, radical vulvectomy, hemi-vulvectomy or wide excision, respecting tumour diameter and localization. Surgical SLNB, 18 to 24 h after sentinel lymph node scintigraphy; 2–10 minutes prior to the first incision, blue dye was injected into the superficial margins of the tumour. SNs were localized transcutaneously with a handheld gamma-probe. Followed by surgery.”</td>
<td>IV / NA</td>
</tr>
<tr>
<td>Author, Year</td>
<td>Study design; location</td>
<td>Patient number (N), Age, Study duration</td>
<td>Patient status</td>
<td>Follow up (months)</td>
<td>Outcomes measured</td>
<td>Technique</td>
<td>Level / Quality</td>
</tr>
<tr>
<td>--------------</td>
<td>------------------------</td>
<td>----------------------------------------</td>
<td>---------------</td>
<td>------------------</td>
<td>-----------------</td>
<td>-----------</td>
<td>----------------</td>
</tr>
<tr>
<td>Germany</td>
<td>duration=8 years</td>
<td>SCC, 3 with melanoma</td>
<td></td>
<td>Technetium-99m</td>
<td>Technetium-99m colloid albumin injection subcutaneously around the tumor on the day before surgery. The lymph node locations were marked on the skin surface. In addition, an intraoperative mapping with isosulfan blue dye was performed about 15–30 minutes before start of surgery. Intraoperative identification used both visual identification of the stained lymph vessels and nodes and radiation measured by a handheld probe.”</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crosbie et al 2010</td>
<td>Diagnostic accuracy: UK</td>
<td>N=32, Age=67 (median) , Study duration=4 years</td>
<td>Patients with clinical stage I and II squamous cell carcinoma of the vulva</td>
<td>SLN detection with 99mTc and blue dye</td>
<td>“The day before surgery, 40 MBq 99mTc-labelled HAS nano-colloid in a total volume of 0.2 ml, was injected intradermally at four locations around the primary tumour or scar. An intra-operative gamma probe was then used to confirm the lymphoscintigraphy-marked area(s) in the groin. A small skin incision was made at the marked spot and a sentinel node excision biopsy performed, assisted by the gamma probe and visual identification of blue-</td>
<td>IV / Low</td>
<td></td>
</tr>
<tr>
<td>Author, Year</td>
<td>Study design; location</td>
<td>Patient number (N), Age, Study duration</td>
<td>Patient status</td>
<td>Follow up (months)</td>
<td>Outcomes measured</td>
<td>Technique</td>
<td>Level / Quality</td>
</tr>
<tr>
<td>-------------------</td>
<td>------------------------</td>
<td>-----------------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
<td>--------------------</td>
<td>-----------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Lindell et al 2010</td>
<td>Diagnostic accuracy (retrospective); Stockholm, Sweden</td>
<td>N=77, Age=71.2 (mean), Study duration=7 years</td>
<td>Patients with invasive squamous cell carcinoma in vulva (76 patients with invasive vulvar cancer T1–T2 and one T3, with invasion to the vagina)</td>
<td>SN detection rate with radioactive tracer and blue dye</td>
<td>“The patients underwent SN mapping preoperatively with radioactive tracer and blue dye (n = 60) or only blue dye (n = 17). The SN was removed separately followed by complete inguinofermal lymphadenectomy.”</td>
<td>III-3 / Moderate</td>
<td></td>
</tr>
<tr>
<td>Radziszewski et al 2010</td>
<td>Diagnostic accuracy and Case series; Poland</td>
<td>N=62 (excluded 6, N=56), Age=68-9 (median), Study duration=4 years</td>
<td>Patients with vulval cancer (SCC)</td>
<td>NR</td>
<td>SLN detection (Tc-99m and blue dye)</td>
<td>“The SLN was identified intraoperatively using lymphoscintigraphy with technetium-99m as well as patent blue V staining. The resected lymph nodes (LN) were submitted for histological examination by haematoxylin–eosin staining (H–E) and cytokeratin immunohistochemistry (IHC) and examined by the reverse transcriptase-polymerase chain reaction (RT-PCR) assay.”</td>
<td>III-2 / Low</td>
</tr>
<tr>
<td>Akrivos et al 2011</td>
<td>Case series; Athens, Greece</td>
<td>N=34, Age=69.1 (mean), Study duration=4 years</td>
<td>Patients with vulval cancer (all with SCC)</td>
<td>No</td>
<td>SLN detection with Tc99m-nanocolloid and methylene blue.</td>
<td>“27 patients underwent four intradermal peritumoral injections of 99m-Tc-nanocolloid 24 h before surgery. Thirty minutes after injection, lymphoscintigraphy”</td>
<td>IV / Moderate</td>
</tr>
</tbody>
</table>
The role of sentinel node biopsy in the treatment of women with early stage vulvar cancer

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study design; location</th>
<th>Patient number (N), Age, Study duration</th>
<th>Patient status</th>
<th>Follow up (months)</th>
<th>Outcomes measured</th>
<th>Technique</th>
<th>Level / Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Devaja et al 2011</td>
<td>Diagnostic accuracy; UK</td>
<td>N=60, Age=63 (median), Study duration=6 years</td>
<td>Women with invasive vulval carcinoma with a depth of invasion of more than 1 mm.</td>
<td>24</td>
<td>SLN detection (with Tc-99m and methylene-blue dye)</td>
<td>Followed and SNs as well as other nodes were demonstrated. The supposed to be sentinel nodes were marked on the skin of our patients with ink. The next day, after induction of general anaesthesia and 10 min before groin dissection, methylene blue dye was injected intradermally around the tumor in a similar manner to 99m-Tc-nanocolloid in all 34 patients. A handheld c-probe was used intraoperatively to identify the “hot” SNs.</td>
<td>IV / Low</td>
</tr>
<tr>
<td>Author, Year</td>
<td>Study design; location</td>
<td>Patient number (N), Age, Study duration</td>
<td>Patient status</td>
<td>Follow up (months)</td>
<td>Outcomes measured</td>
<td>Technique</td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>------------------------</td>
<td>----------------------------------------</td>
<td>----------------</td>
<td>------------------</td>
<td>-------------------</td>
<td>-----------</td>
<td></td>
</tr>
<tr>
<td>Ennik et al. 2011</td>
<td>Diagnostic accuracy (retrospective); Melbourne, Australia</td>
<td>N=64, Age=&lt;50, 50-70, &gt;70, Study duration=10 years</td>
<td>Patients with vulvar cancer who underwent sentinel node procedure</td>
<td>32.1</td>
<td>SNL detection with blue dye and Technetium-99m</td>
<td>&quot;Two to 4 injections of technetium 99m were given intradermally at the leading edge of the primary tumor or previous surgical scar. When dye was used to detect SNs, 2 injections (usually patent blue 5) were given after the patient had been prepared for surgery. The groin(s) in which an SN was expected to be found were opened surgically and checked for blue nodes. A handheld navigator gamma probe was used to identify ‘‘hot’’ nodes intraoperatively.”</td>
<td></td>
</tr>
<tr>
<td>Levenback et al. 2012</td>
<td>Observational; USA</td>
<td>N=452, Age=&lt;40, 40-81, &gt;81, Study duration=10 years</td>
<td>Women with invasive squamous cell carcinoma of the vulva</td>
<td>NR</td>
<td>Negative predictive value of SLN, SLNB sensitivity analysis</td>
<td>&quot;Women underwent intraoperative lymphatic mapping and SLNB with isosulfan blue dye. At the onset of the study, preoperative chemotherapy. During the last 2 years of the study, a selected group of women had an SLN dissection alone. The SLNs were ultra-staged when they were negative on routine haematoxylin and eosin examination.”</td>
<td></td>
</tr>
</tbody>
</table>

Levenback et al. 2012†

Levenback et al. 2012†
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study design; location</th>
<th>Patient number (N), Age, Study duration</th>
<th>Patient status</th>
<th>Follow up (months)</th>
<th>Outcomes measured</th>
<th>Technique</th>
<th>Level / Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zekan et al 2012</td>
<td>Case series; Croatia</td>
<td>N=25 , Age=69 (median) , Study duration=3 years</td>
<td>Patients with early stage vulval cancer (28% T1 or 72% T2 SCC)</td>
<td>NR</td>
<td>Sensitivity, specificity and NPV of SLN detection with Technetium-99m albumin (immunohistochemical analysis). “Technetium-99m colloid albumin was injected intradermally around the tumor for lymphoscintigraphic mapping and intraoperative hand-held gamma probe detection of sentinel nodes. For all patients, sentinel node biopsy was</td>
<td>lymphoscintigraphy and intraoperative radio localized were optional. Beginning 2 years after study activation, preoperative lymphoscintigraphy and intraoperative radio localization were required. Intraoperative intradermal injection of blue dye was performed following induction of anaesthesia and sterile preparation and draping. Five minutes after dye injection, an incision was made in the groin, and blue efferent channels and blue lymph nodes were identified. If radiocolloid was used intraoperatively, a handheld gamma counter was passed over the nodal tissue to identify lymph nodes emitting the tracer. &quot;</td>
<td>III-2 / Moderate</td>
</tr>
<tr>
<td>Author, Year</td>
<td>Study design; location</td>
<td>Patient number (N), Age, Study duration</td>
<td>Patient status</td>
<td>Follow up (months)</td>
<td>Outcomes measured</td>
<td>Technique</td>
<td>Level / Quality</td>
</tr>
<tr>
<td>-------------------</td>
<td>------------------------</td>
<td>----------------------------------------</td>
<td>----------------------------------------------------</td>
<td>-------------------</td>
<td>---------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Terada et al 2006</td>
<td>Case series (retrospective); Hawaii, USA</td>
<td>N=21, Age=72 (median), Study duration=7 years</td>
<td>Patients with T1 vulval cancer (at least 1mm invasion)</td>
<td>54</td>
<td>Negative predictive value and recurrence in negative SLN</td>
<td>“Patients underwent pre-operative lymphoscintigraphy and sentinel lymph node dissection using technetium sulfur colloid and isosulfan blue dye. The primary tumor was removed with radical local excision. Patients with negative sentinel nodes did not receive any additional treatment. Survival was calculated using life table analysis.”</td>
<td>III-3 / Low</td>
</tr>
<tr>
<td>Moore et al 2008</td>
<td>Observational (prospective); USA</td>
<td>N=36, Age=63 (median), Study duration=5 years</td>
<td>Patients with vulval cancer (biopsy proven SCC)</td>
<td>29</td>
<td>Groin recurrence; Sensitivity and negative predictive value of SLN</td>
<td>“Peritumoral injection of Tc-99 sulfur colloid and methylene blue dye was used to identify SLNs intraoperatively. Patients with SLNs negative for metastatic disease were followed clinically. Patients with metastasis detected in a SLN subsequently underwent a full groin node dissection followed by standard treatment protocols.”</td>
<td>IV / Moderate</td>
</tr>
</tbody>
</table>

The role of sentinel node biopsy in the treatment of women with early stage vulvar cancer
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study design; location</th>
<th>Patient number (N), Age, Study duration</th>
<th>Patient status</th>
<th>Follow up (months)</th>
<th>Outcomes measured</th>
<th>Technique</th>
<th>Level / Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van der Zee et al 2008</td>
<td>Observational; The Netherlands, Belgium, Italy, Germany, UK and Canada</td>
<td>N=406, Age=NR, Study duration=6 years</td>
<td>Patients with vulval cancer (T1 or T2, less than 4 cm, SCC with a depth of invasion more than 1 mm and clinically no suspicious inguinofemoral lymph nodes)</td>
<td>35 (median follow-up of 276 patients only)</td>
<td>SLN detection using radioactive tracer and blue dye; groin recurrence</td>
<td>“The sentinel node procedure was performed with the combined technique (radioactive tracer and blue dye). When more than one intranodal metastasis and/or extranodal growth was detected, post-operative external-beam radiotherapy (50 Gy) to the groin/pelvis was recommended.”</td>
<td>III-1 / High</td>
</tr>
<tr>
<td>de Hullu et al 2001</td>
<td>Questionnaire; The Netherlands</td>
<td>N=117, Age=63 (median), Study duration=8 years</td>
<td>Patients with vulval cancer</td>
<td>118</td>
<td>False negative rate of the SLN procedure</td>
<td>“Structured questionnaires were sent to both patients and gynaecologists. The patients had been treated for vulvar cancer and were all in complete remission with a median follow-up of 118 months (range: 76-185). Questions to the patients dealt with experienced side-effects of the standard treatment and opinion on the acceptable false-negative rate of the sentinel lymph node procedure.”</td>
<td>IV / Moderate</td>
</tr>
<tr>
<td>Hefler et al 2008</td>
<td>Case series (retrospective);</td>
<td>N=75, Age=67.7 (mean, SLN dissection), 64.1</td>
<td>Patients with vulvar cancer with an invasion depth of no</td>
<td>35.5</td>
<td>Postoperative morbidity in sentinel lymph node vs.</td>
<td>“After preoperative counselling, 29 and 19 patients opted for the sentinel lymph node technique”</td>
<td>III-3 / Low</td>
</tr>
<tr>
<td>Author, Year</td>
<td>Study design; location</td>
<td>Patient number (N), Age, Study duration</td>
<td>Patient status</td>
<td>Follow up (months)</td>
<td>Outcomes measured</td>
<td>Technique</td>
<td>Level / Quality</td>
</tr>
<tr>
<td>--------------</td>
<td>------------------------</td>
<td>----------------------------------------</td>
<td>----------------</td>
<td>-------------------</td>
<td>------------------</td>
<td>-----------</td>
<td>----------------</td>
</tr>
<tr>
<td>Vienna, Austria</td>
<td>(mean, complete IFLN dissection). Study duration= 11 years</td>
<td>more than 1 mm</td>
<td>complete inguinal lymph node dissection and complete inguinal lymph node dissection, respectively. Routine histopathological examination of the sentinel and all other lymph nodes was performed using haematoxylin-eosin staining and serial sections with standard techniques. In the case of negative sentinel nodes, additional immunohistochemical cytokeratin examination was performed.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oonk et al 2009</td>
<td>Questiranne; The Netherlands</td>
<td>N=62, Age=69 (mean), Study duration=5 years</td>
<td>Patients with vulval cancer who participated in GROINSS-V study</td>
<td>Every 2 months for 24 months, and then biannually</td>
<td>QOL of patients treated with a SN procedure compared to with a IFLND procedure</td>
<td>Patients who participated in the GROningen INternational Study on Sentinel nodes in Vulvar cancer (GROINSS-V) were invited to fill out three questionnaires: the EORTC QLQ-C30, a vulvar specific questionnaire and a questionnaire about the opinion of patients on new treatment options. Patients who only underwent SLN procedure were compared to those who subsequently underwent inguinofermoral lymphadenectomy because of a</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>III-2 / High</td>
</tr>
<tr>
<td>Author, Year</td>
<td>Study design; location</td>
<td>Patient number (N), Age, Study duration</td>
<td>Patient status</td>
<td>Follow up (months)</td>
<td>Outcomes measured</td>
<td>Technique</td>
<td>Level / Quality</td>
</tr>
<tr>
<td>--------------</td>
<td>------------------------</td>
<td>----------------------------------------</td>
<td>----------------</td>
<td>-------------------</td>
<td>-------------------</td>
<td>-----------</td>
<td>----------------</td>
</tr>
<tr>
<td>Novackova et al 2012</td>
<td>Case-control cohort; Prague, Czech Republic</td>
<td>N=29, Age=64.1 (mean, Control group), 66.5 (mean, CONS group), 73.8 (mean, RAD group), Study duration=2 years</td>
<td>Patients with vulval cancer</td>
<td>6</td>
<td>Prevalence of secondary lower-limb lymphedema after surgical treatment (circumference measurements and MFBIA technique); compare quality of life (QoL) before and 6 months after vulvar surgery</td>
<td>“Seventeen patients underwent inguinofemoral lymphadenectomy (RAD), and 12 underwent sentinel lymph node biopsy (CONS). Patients were examined before and 6 months after vulvar surgery by measuring the circumference of the lower limbs and with MFBIA. A control group of 27 healthy women was also measured. To evaluate QoL, the European Organisation for Research and Treatment of Cancer (EORTC) QoL questionnaires (QLQ-C30 and QLQ-CX24) were administered to patients before and 6 months after surgery.”</td>
<td>IV / Low</td>
</tr>
</tbody>
</table>

Abbreviations: BCC: basal cell carcinoma; ILND: inguinofemoral lymph node; LN: lymph node; dissection; LNE: lymphadenectomy; NP or NPV: negative predictive values; SCC: squamous cell carcinoma; SLB: sentinel lymph node biopsy; SLN: sentinel lymph node; SLNB: sentinel lymph node biopsy; SN: sentinel node; SNB: sentinel node biopsy.
Table 3 Number of patients with Sentinel Lymph Node (SNL) detected (29 relevant studies) by technique.

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Number of patients (N)</th>
<th>Blue Dye</th>
<th>Radio-Isotope</th>
<th>Blue Dye + Radio-Isotope</th>
<th>False Negatives</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N allocated</td>
<td>N detected</td>
<td>%</td>
<td>N allocated</td>
</tr>
<tr>
<td>Ansink et al 199911</td>
<td>51</td>
<td>51</td>
<td>18</td>
<td>35</td>
<td>NA</td>
</tr>
<tr>
<td>de Hullu et al 2000d</td>
<td>59</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Sideri et al 200023</td>
<td>44</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>de Hullu et al 200133*</td>
<td>117</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Levenback et al 2001#</td>
<td>52</td>
<td>76</td>
<td>57</td>
<td>75</td>
<td>NA</td>
</tr>
<tr>
<td>Slutz et al 200217</td>
<td>26</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Moore et al 20031d</td>
<td>21</td>
<td>31</td>
<td>2</td>
<td>6.5</td>
<td>80</td>
</tr>
<tr>
<td>Merisio et al 20059</td>
<td>20</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Martinez-Paloness et al 200614</td>
<td>55</td>
<td>55</td>
<td>44</td>
<td>80</td>
<td>55</td>
</tr>
<tr>
<td>Terada et al 200626</td>
<td>21</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Hauspy et al 20077</td>
<td>41</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>Rob et al 20073</td>
<td>59</td>
<td>16</td>
<td>11</td>
<td>68.8</td>
<td>43</td>
</tr>
<tr>
<td>Vakseli et al 200712a</td>
<td>35</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Haml et al 20085</td>
<td>127</td>
<td>127</td>
<td>8</td>
<td>6.3</td>
<td>127</td>
</tr>
<tr>
<td>Heffet et al 200826*5</td>
<td>75</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Author, Year</td>
<td>Number of patients (N)</td>
<td>Blue Dye</td>
<td>Radio-isotope</td>
<td>Blue Dye + Radio-isotope</td>
<td>False Negatives</td>
</tr>
<tr>
<td>------------------------------</td>
<td>------------------------</td>
<td>-----------------------------------</td>
<td>-----------------------------------</td>
<td>--------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Johann et al 2008(^4)</td>
<td>63</td>
<td>45/1 2.2</td>
<td>45/9 20</td>
<td>45/33 73.3</td>
<td>1 1.6%</td>
</tr>
<tr>
<td>Moore et al 2008(^27)</td>
<td>36</td>
<td>NA/NA NA</td>
<td>NA/NA NA</td>
<td>36/36 100</td>
<td>2 5.6%</td>
</tr>
<tr>
<td>Van der Zee et al 2008(^5)</td>
<td>403</td>
<td>NA/NA NA</td>
<td>NA/NA NA</td>
<td>NA/NA NA</td>
<td>8 2.0%</td>
</tr>
<tr>
<td>Achimas-Cadariu et al 2009(^15)</td>
<td>56</td>
<td>NR/NR NR</td>
<td>NR/NR NR NR</td>
<td>NR/NR 95-100</td>
<td>7 12.5%</td>
</tr>
<tr>
<td>Oonk et al 2009(^14) *(^2)</td>
<td>62</td>
<td>NA/NA NA</td>
<td>NA/NA NA</td>
<td>NA/NA NA</td>
<td>NA/NA</td>
</tr>
<tr>
<td>Crosbie et al 2010(^10)</td>
<td>32</td>
<td>NR/NR NR</td>
<td>NR/NR NR NR</td>
<td>32/31 97</td>
<td>1 3.1%</td>
</tr>
<tr>
<td>Lindell et al 2010(^20)</td>
<td>77</td>
<td>17/16 94</td>
<td>77/75 97.4</td>
<td>60/59 98</td>
<td>2 2.6%</td>
</tr>
<tr>
<td>Radziszewski et al 2010(^22)</td>
<td>56</td>
<td>NR/NR NR</td>
<td>NR/NR 100</td>
<td>NR/NR NR</td>
<td>8 14.3%</td>
</tr>
<tr>
<td>Akrivos et al 2011(^14)</td>
<td>34</td>
<td>NR/NR NR</td>
<td>NR/NR NR NR</td>
<td>34/34 100</td>
<td>3 8.8%</td>
</tr>
<tr>
<td>Devaja et al 2011(^21)</td>
<td>60</td>
<td>60/56 93.3</td>
<td>NR/NR NR</td>
<td>60/59 98.3</td>
<td>0 0.0%</td>
</tr>
<tr>
<td>Ennik et al 2011(^16)</td>
<td>64</td>
<td>2/1 50</td>
<td>33/30 91</td>
<td>30/30 100</td>
<td>5 7.8%</td>
</tr>
<tr>
<td>Levenback et al 2012(^4)</td>
<td>452</td>
<td>418/100 24</td>
<td>418/64 15</td>
<td>418/254 61</td>
<td>11 2.4%</td>
</tr>
<tr>
<td>Novackova et al 2012(^18)</td>
<td>29</td>
<td>NA/NA NA</td>
<td>NA/NA NA</td>
<td>NA/NA NA</td>
<td>NA/NA</td>
</tr>
<tr>
<td>Zekan et al 2012(^13)</td>
<td>25</td>
<td>NA/NA NA</td>
<td>25/25 100</td>
<td>NA/NA NA</td>
<td>1 4.0%</td>
</tr>
</tbody>
</table>

Notes: NA: not applicable (technique not analysed); NR: not reported (technique data not shown); *Number of patients with SLN identified by technique not reported; #Number of false negatives not reported; ¥Reported only by groin, not by number of patients; Rate % reported by study, not calculated.
Table 4 Identification of the sentinel lymph node (SLN)

<table>
<thead>
<tr>
<th>Number of publications</th>
<th>No. Patients</th>
<th>No. SLN groin dissections</th>
<th>SLN identification/patient with blue dye only</th>
<th>SLN identification/patient with RI +/- blue dye</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ref 3, 4, 5, 11, 16, 20, 21</td>
<td>Ref 3, 5, 6, 7, 8, 9, 10, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25</td>
</tr>
<tr>
<td>23</td>
<td>1957</td>
<td>3084</td>
<td>2.2-94%</td>
<td>35.4-100%</td>
</tr>
</tbody>
</table>

The data in Table 4 suggest that the combined modality of radio-isotope (RI) plus blue dye injection is superior to blue dye alone in the identification of SLN, although this is based largely on low level evidence (III-2 – IV). The interpretation of individual reports is hampered because of inconsistent information about the injection procedure (volume, isotope activity) in many studies. However, in studies which reported SLN detection with blue dye alone and with blue dye plus RI, the combination technique was associated with a superior rate of detection in six out of the eight studies (see Table 5).

Table 5 Studies with Blue Dye and Blue Dye plus Radio Isotope (R-I)

<table>
<thead>
<tr>
<th>Studies</th>
<th>Blue dye (%)</th>
<th>Blue dye + R-I (%)</th>
<th>Incremental difference (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ennik et al 2001</td>
<td>50.0</td>
<td>100.0</td>
<td>50.0</td>
</tr>
<tr>
<td>Moore et al 2003</td>
<td>6.5</td>
<td>35.4</td>
<td>28.9</td>
</tr>
<tr>
<td>Rob et al 2007</td>
<td>68.8</td>
<td>100</td>
<td>31.2</td>
</tr>
<tr>
<td>Hampel et al 2008</td>
<td>6.3</td>
<td>56.6</td>
<td>50.3</td>
</tr>
<tr>
<td>Johann et al 2008</td>
<td>2.2</td>
<td>73.3</td>
<td>71.1</td>
</tr>
<tr>
<td>Lindell et al 2010</td>
<td>94</td>
<td>98</td>
<td>4.0</td>
</tr>
<tr>
<td>Devaja et al 2011</td>
<td>93.3</td>
<td>98.3</td>
<td>5.0</td>
</tr>
<tr>
<td>Levenback et al 2012</td>
<td>24</td>
<td>61</td>
<td>37.0</td>
</tr>
</tbody>
</table>

3.1.1 Site of the lesion on the vulva – midline tumours

Ten studies were identified that reviewed the effect of the site of the lesion on the vulva on detection of the sentinel lymph node. 3-5, 7-9, 19, 23, 25, 27

The assumption in managing vulvar cancer has been that midline tumours are likely to spread to either right and/or left inguino-femoral lymph node groups, and bilateral lymphadenectomy is essential in managing midline tumours. The definition of midline tumour is variable in the studies reviewed; involvement of anterior labium minor and lesions within 1cm or 2cm of the mid-vulvar line are variably used, with some studies not defining the measurement.
Data presented on failure to detect a SLN on one side for midline tumours should be regarded with caution when interpreting many of the studies. In some respects, failure to detect a SLN is likely to have little impact on patient survival outcome, as the default management in the absence of a SLN is complete IFLD. This variable definition makes assessment of the significance of these data problematic. In the ten publications available for analysis, 14 out of 393 patients (3.5%) with midline tumours and a sentinel node identified, had a false negative SLNB. This is very similar to the false negatives seen in the entire SLN cohort and does not suggest that midline tumours have a higher false negative rate when a SLN is identified. (Level IV).

### 3.1.2 Previous excisional vulvar surgery

The potential for excisional surgery on the vulva to affect the lymphatic drainage pattern and the identification of SLN is not adequately addressed in the four studies identified, and so limited conclusions can be made.

In the largest published series of 452 patients, Levenbeck\(^\text{22}\) included patients who had previously had the primary vulvar malignancy excised, but did not undertake a subgroup analysis to look at the impact of this surgery on the identification of SLN.

Three studies were identified that specifically address the impact of excisional biopsy of the primary vulvar lesion on the identification rate of SLN.\(^\text{4, 16, 19}\) The 90 patients reported had a SLN identified in 92% of cases. In the two studies reporting the use of both R-I and blue dye, a SLN was identified in 94% of cases. In the series by Crosbie et al 2010\(^\text{19}\), a comparator group of patients (n=17) having an incisional biopsy prior to SLN, showed similar rates of SLN identification to those patients (n=15) who had an excisional biopsy (93% vs. 100%)\(^\text{19}\) The level of evidence on the effect of excisional biopsy on the rate of SLN identification is very low (Level IV).

### 3.1.3 Accuracy of sentinel lymph node biopsy

The accuracy of SLN procedure can be determined by three methods.

1. Complete IFLN dissection after SLN excision to determine the presence or absence of tumour when the SLN is shown to be negative for tumour
2. Tumour recurrence in a groin where a SLN biopsy alone was performed and the SLN was negative for tumour
3. Tumour recurrence in an undissected groin where the contralateral groin had a negative SLN.

Of the 29 publications reporting on SLN identification, 22 reported the result of IFLD after SLNB where the SLN was negative for tumour. Once again, the interpretation of published results is hampered by the heterogeneous patient population included in the studies.

Only publications that excluded non squamous histology, lesions >4cm and patients with suspicious, enlarged lymph nodes from analysis were included in the final data (See Table 6)
Table 6 Overall outcomes measured and results from the primary evidence (29 relevant) studies.

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Patient number (N), Age, Study duration</th>
<th>Primary and Secondary Outcomes</th>
<th>Results</th>
<th>Conclusion (per Authors)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ansink et al 1999¹</td>
<td>N=51, Age=701 (mean), Study duration=3 years</td>
<td>Negative predictive value of SLN detection with blue dye</td>
<td>One or more blue lymph nodes were detected in only 52 groins (56%). Nine (17%) of these were tumor positive, and 6 blue lymph nodes were the only tumor positive lymph nodes in the specimen in which they were found. There were two false-negative blue lymph nodes. The negative predictive value: 0.953 (41 out of 43 lymph nodes). No adverse effects of the patent blue were observed either during or after surgery.</td>
<td>“It was shown in this multicentre study that sentinel lymph node detection in vulvar carcinoma patients with blue dye only is not feasible because its negative predictive value is too low.”</td>
</tr>
<tr>
<td>de Hullu et al 2000²</td>
<td>N=59, Age=69 (median), Study duration=3 years</td>
<td>Negative predictive value of SLN and detection of false negative SLN</td>
<td>Unilateral-positive LN=13 patients; bilateral-positive SLN=27 patients; SLN=negative in 68 groins.</td>
<td>“Sentinel lymph node procedure with the combined technique is highly accurate in predicting the inguinofemoral lymph node status in patients with early-stage vulvar cancer.”</td>
</tr>
<tr>
<td>Author, Year</td>
<td>Patient number (N), Age, Study duration</td>
<td>Primary and Secondary Outcomes</td>
<td>Results</td>
<td>Conclusion (per Authors)</td>
</tr>
<tr>
<td>---------------------</td>
<td>----------------------------------------</td>
<td>------------------------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Sideri et al 2000</td>
<td>N=44, Age=NR , Study duration=3 years</td>
<td>Detection of SN using lymphoscintigraphy and gamma detecting probe.</td>
<td>A mean of 1.5 SN per groin was surgically detected with gamma detecting probe; 13 cases had positive nodes, in 10 cases the SN was the only positive node; 31 patients showed negative SN.</td>
<td>“The pathological status of SN was predictive of groin status in a 100% of cases; there were no skip metastases and 31 patients with tumor-negative SN had no lymph node metastases.”</td>
</tr>
<tr>
<td>Levenback et al 2001</td>
<td>N=52, Age=58(median), Study duration=2 years</td>
<td>Effectiveness of intraoperative lymphatic with blue dye alone to identify sentinel nodes</td>
<td>SLN total=57/76 (75%) dissected groins; SLN lateral=22/25, 88%.</td>
<td>“Experience and careful patient selection can permit sentinel node identification with blue dye injection alone in more than 95% of patients with vulval cancer.”</td>
</tr>
<tr>
<td>Slutz et al 2002</td>
<td>N=26, Age=40-89, Study duration=2 years</td>
<td>SNL detection (technetium99m) with gamma probe</td>
<td>“Scintigraphy showed focal uptake in all 26 patients. All sentinel nodes were detected intraoperatively by hand held gamma probe. Histologically positive SLN were found in 9 patients.”</td>
<td>“Identification of sentinel nodes in vulvar cancer is feasible with preoperatively administered technetium99m-labeled microcolloid.”</td>
</tr>
<tr>
<td>Moore et al 2003</td>
<td>N=21, Age=79 (median), Study duration=NR</td>
<td>SLN detection with blue dye and Technetium-99m sulfur colloid radio-isotope.</td>
<td>Metastatic status: 22 groins with SLN negative and Non-SLN negative; 4 groins with SLN positive and Non-SLN negative; 5 groins with SLN positive and Non-SLN positive; SLN detected=82.</td>
<td>“Tc-99m sulfur colloid is superior to isosulfan blue dye in the detection of sentinel nodes in inguinal dissections of patients with vulval cancer. A sentinel”</td>
</tr>
</tbody>
</table>

The role of sentinel node biopsy in the treatment of women with early stage vulvar cancer
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Patient number (N), Age, Study duration</th>
<th>Primary and Secondary Outcomes</th>
<th>Results</th>
<th>Conclusion (per Authors)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Merišio et al 2005&lt;sup&gt;9&lt;/sup&gt;</td>
<td>N=20, Age=75 (mean), Study duration=4 years</td>
<td>SLN detection by preoperative lymphoscintigraphy with technetium-99 m–labeled nanocolloid and radio guided intraoperative detection</td>
<td>Rate of SLN detection: Tc-99m sulfur colloid 80/82 (97.6%); Isosulfan blue dye 31/82 (37.8%); Groins with a SLN detected: Tc-99m sulfur colloid 31/31 (100%); Isosulfan blue dye 19/31 (61%).</td>
<td>“The sentinel node procedure is feasible and reliable in vulval cancer; however, the value of sentinel node dissection in the treatment of early stage vulval cancer still needs to be confirmed.”</td>
</tr>
<tr>
<td>Martinez-Palones et al 2006&lt;sup&gt;14&lt;/sup&gt;</td>
<td>N=55, Age=70 (mean), Study duration=10 years</td>
<td>SLN identification; recurrence after surgical treatment with or without SN identification</td>
<td>SLN group: 9 tumors were T1 and 19 were T2, with a total of 40 groins dissected and 9 positive nodes in 7 patients. Sixty-two SLN were detected with a mean of 2.2 SN per patient (range 0–4). The false negative rate of SLN dissection: 1 out of 7 (14.3%), and the sensitivity was 6/7 (85.7%). Non-SLN group: 7 tumors were T1 and 20 were T2, with a total of 49 groins dissected and 9 positive nodes in 6 patients. Recurrence: 8 patients (28.6%) in the SLN group and 6 (26.9%) in the non-SLN group (p= 0.8). None of the melanoma patients recurred.</td>
<td>“Sentinel lymph node identification in early stage vulvar cancer is a feasible. Analysis of recurrence may allow considering this procedure as a possible alternative to inguino-femoral lymphadenectomy.”</td>
</tr>
<tr>
<td>Author, Year</td>
<td>Patient number (N), Age, Study duration</td>
<td>Primary and Secondary Outcomes</td>
<td>Results</td>
<td>Conclusion (per Authors)</td>
</tr>
<tr>
<td>-------------------</td>
<td>----------------------------------------</td>
<td>---------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Hauspy et al 2007</td>
<td>N=41, Age=65 (mean), Study duration=2 years</td>
<td>SLN detection with technetium sulfur colloid and/or lymphazurin blue</td>
<td>Improved detection of SLNs and proximity of the cancer to the midline (r=5 0.996; p=0.057). SLN blue=0 (0%); SLN blue + Tc=30 (73%); SLN Tc=11 (27%). There were no false-negative SLN results.</td>
<td>“SLN dissection is feasible and safe to perform in vulval cancer. The ability to identify bilateral sentinel inguinal lymph nodes appears to be related to the proximity of the vulval cancer to the midline.”</td>
</tr>
<tr>
<td>Robert et al 2007</td>
<td>N=59, Age=NR, Study duration=4 years</td>
<td>SLNs in vulval cancer using blue dye and 99mTc radiocolloid</td>
<td>Distribution of SLN=118 in 82 groins; Positive lymph nodes=20/59 (33.9%) of patients. Blue dye group: N=16, SLN bilateral=1, SLN unilateral=10, Detection rate per patient=68.8%, Side specific detection rate=22/12 (54.5%), False negative per patient=1 (6.25%)</td>
<td>“The combined use of 99mTc radiocolloid and blue dye was significantly superior at SLN detection than blue dye alone. 99mTc SLN detection using the intraoperative handheld probes was not enhanced by preoperative scintigraphy scans.”</td>
</tr>
<tr>
<td>Vakselj et al 2007</td>
<td>N=35, Age=65.8 (mean), Study duration=3 years</td>
<td>SLN detection; Negative predictive value of negative SLN</td>
<td>SNB positive (metastatic disease) =10 out of 35 patients (28.6%); bilateral SLN in 4 patients; 2 patients nodes were metastatic on both sides; 1 patient presented a cluster of metastatic nodes; SNB negative (nodes without metastatic disease) =25 out of 35 patients (71.4%). 3 out of 35 patients had recurrence in the inguinal region.</td>
<td>“Sentinel node biopsy is a promising diagnostic tool in the evaluation of vulval carcinoma and of node status as well as of disease stage.”</td>
</tr>
<tr>
<td>Hampl et al 2008</td>
<td>N=127, Age=61.4</td>
<td>Detection of SLN after</td>
<td>Negative groin lymph node status (pNo)=88 patients;</td>
<td>“Identification of SLN in</td>
</tr>
<tr>
<td>Author, Year</td>
<td>Patient number (N), Age, Study duration</td>
<td>Primary and Secondary Outcomes</td>
<td>Results</td>
<td>Conclusion (per Authors)</td>
</tr>
<tr>
<td>--------------</td>
<td>----------------------------------------</td>
<td>--------------------------------</td>
<td>---------</td>
<td>--------------------------</td>
</tr>
</tbody>
</table>
| Johann et al 2008¹ | (mean), Study duration= 3 years | application of 99mTechnetium labeled nanocolloid and/or blue dye. | Positive groin lymph status (≥ pN1)=39 patients  
SLN blue dye=8 (6.3%); SLN Tc=47 (37%); SLN Tc and blue dye=72 (56.6%).  
Lymphonodectomy unilateral=21; Lymphonodectomy bilateral=103, Lymphonodectomy no data=3; Sensitivity 36/39 = 92.3%; False negative rate 3/39 = 7.7%  
Squamous cell cancer of the vulval is feasible, however not highly accurate depending on tumor localization and size.” | |
| Achimas-Cadariu et al 2009¹⁵ | N=59, Age=66 (median), Study duration= 8 years | SNL detection with blue dye and Technetium-99m; recurrence, morbidity and wound break down | Positive lymph nodes in 20.9% of groins with subsequent inguinal LNE.  
Sensitivity of clinical/ultrasound examination = 61.1%; corresponding specificity (92.6%) and accuracy (86.1%).  
Groin surgery (%): LNE only=31 (36.1); SLB and LNE=27  
“Statistically significant benefit with respect to side effects for sentinel lymph node biopsy compared to full LNE either alone or after SLB.” | |
### Summary of Studies

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Patient number (N), Age, Study duration</th>
<th>Primary and Secondary Outcomes</th>
<th>Results</th>
<th>Conclusion (per Authors)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crosbie et al 2010&lt;sup&gt;19&lt;/sup&gt;</td>
<td>N=32, Age=67 (median), Study duration=4 years</td>
<td>SLN detection with 99mTc and blue dye (15 patient’s excisional biopsy and 17 patient’s diagnostic biopsy)</td>
<td>Seventeen patients (53%) had midline vulval tumours; six (19%) had right vulval tumours and nine (28%) had left vulval tumours.</td>
<td>“The SLN procedure may be used to identify malignant groins in selected patients with vulval cancer. The extent to which previous vulval surgery might influence the accuracy of the SLN procedure deserves further investigation.”</td>
</tr>
<tr>
<td>Lindell et al 2010&lt;sup&gt;20&lt;/sup&gt;</td>
<td>N=77, Age=71.2 (mean)</td>
<td>SN detection rate with radioactive tracer and blue</td>
<td>The detection rate of SN: radioisotope plus blue dye=</td>
<td>“Preoperative scintigram is a valuable help to identify and...”</td>
</tr>
</tbody>
</table>

### Additional Details

- **Recurrences** of vulvar cancer diagnosed in 8 out of 46 patients (17.3%). SLB only, observed 1 out of 28 (3.6%) patients with wound breakdown compared to 12 out of 58 (20.7%) patients with conventional LNE.

- **SLN vs LNE:** vulva hematoma (3.6 vs. 6.8%) vulva wound breakdown (14.2 vs. 17.2%) and vulvar lymphedema (0 vs. 1.7%). One (2.2%) patient had groin disease as solely recurrence localization.

- The median number of lymph nodes removed per groin was 11 (range 7-17). Seven patients (23%) and 10 groins (22%) had inguinofermal lymph node metastases.
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Patient number (N), Age, Study duration</th>
<th>Primary and Secondary Outcomes</th>
<th>Results</th>
<th>Conclusion (per Authors)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radziszewski et al 2010^22</td>
<td>N=62 {excluded 6, N=56}, Age=68.9 median, Study duration=4 years</td>
<td>SLN detection (Tc-99m and blue dye); false negative; negative predictive value</td>
<td>A total of 109 inguinal LN were dissected in 56 patients. <strong>SLNs were identified:</strong> patent blue V= 76% groins, Tc-99m= 99% groins. <strong>H-E combined with IHC:</strong> The accuracy differed significantly (p&lt;0.0001) = 7 false-negative SLNs. <strong>The RT-PCR assay:</strong> false-negative SLNs= 8. The sensitivity of the RT-PCR-based assay was 83% (95% CI, 75% to 90%) and the negative predictive value for a negative SLN was 88% (95% CI, 82% to 94%).</td>
<td>&quot;In SLN mapping, the Tc-99m colloid lymphoscintigraphy is superior to the blue dye staining. Our data do not support the concept of the SLN identification as a highly accurate procedure in predicting the inguinofemoral LN status in patients with early stage vulvar cancer. The two diagnostic methods (H-E/IHC and RT-PCR) were found not to differ significantly.&quot;</td>
</tr>
<tr>
<td>Akrivos et al 2011^14</td>
<td>N=34, Age=69.1 (mean) , Study duration=4 years</td>
<td>SLN detection with Tc99m-nanocolloid and methylene blue</td>
<td>Detection rate 34/34–100% per patient, 52/64–81.2% per groin. <strong>Detection rate per groin:</strong> Combined versus blue dye only technique (42/50 vs.</td>
<td>&quot;No significant differences were observed in the detection rate between the two tracers. Tc-99m does not seem to be superior to methylene blue in the detection of SLN in vulvar cancer. Midline location of the tumor did not</td>
</tr>
<tr>
<td>Author, Year</td>
<td>Patient number (N), Age, Study duration</td>
<td>Primary and Secondary Outcomes</td>
<td>Results</td>
<td>Conclusion (per Authors)</td>
</tr>
<tr>
<td>-------------</td>
<td>----------------------------------------</td>
<td>-------------------------------</td>
<td>---------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>Devaja et al 2011&lt;sup&gt;21&lt;/sup&gt;</td>
<td>N=60, Age=63 (median), Study duration=6 years</td>
<td>SLN detection (with Tc-99m and methylene-blue dye)</td>
<td>10/14, (p = 0.43). 99m-Tc vs blue dye in detecting SLN (42/50 vs. 50/64, (p = 0.65)). Four false negatives were observed in three patients with tumors &gt;4 cm. Negative predictive value of SLN was 100% for grade I tumors ≤4 cm in patients ≤71 years.</td>
<td>“Sentinel lymph node detection is safe and accurate in assessing lymph node status in women with vulval cancer undergoing staging. The combined method using Tc-99m and methylene blue dye injection for SLN detection has the best detection rate. Routine ultra-staging of negative SLN improves the detection of nodal metastases.”</td>
</tr>
<tr>
<td>Ennik et al 2011&lt;sup&gt;14&lt;/sup&gt;</td>
<td>N=64, Age=&lt;50, 50-70, &gt;70, Study duration=10 years</td>
<td>SNL detection (blue dye and Technetium-99m), with prior excisional biopsy or not.</td>
<td>Detection rate per groin was 80%. The highest SN detection rate: combined technique (100% of patients and 88% of groins). Detection rate per groin was lower in patients with bilateral/midline tumors (74%) compared with patients with unilateral tumors (94%) ((p=0.029)) and was higher in</td>
<td>“Results indicate that previous excision of a primary vulvar malignancy does not decrease SN detection rates or increase SN false-negative rate. Detection rate per groin in patients who underwent previous total excision</td>
</tr>
</tbody>
</table>

The role of sentinel node biopsy in the treatment of women with early stage vulvar cancer
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Patient number (N), Age, Study duration</th>
<th>Primary and Secondary Outcomes</th>
<th>Results</th>
<th>Conclusion (per Authors)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levenback et al 2012</td>
<td>N=452, Age=&lt;40, 40-81, &gt;81, Study duration=10 years</td>
<td>Negative predictive value of SLN, SLNB sensitivity analysis</td>
<td>There were 132 node-positive women, including 11 (8.3%) with false-negative nodes (90% CI, 4.7% to 13.4%). Twenty-three percent of the true-positive patients were detected by immunohistochemical analysis of the sentinel lymph node. <strong>The sensitivity:</strong> 91.7% (90% lower confidence bound, 86.7%) <strong>The false-negative predictive value</strong> (1-negative predictive value): 3.7% (90% upper confidence bound, 6.1%). In women with tumor less than 4 cm, the false-negative predictive value was 2.0% (90% upper confidence bound, 4.5%).</td>
<td>&quot;Sentinel lymph node biopsy is a reasonable alternative to inguinal femoral lymphadenectomy in selected women with squamous cell carcinoma of the vulva.&quot;</td>
</tr>
</tbody>
</table>
| Zekan et al 2012 | N=25 , Age=69 (median), Study duration=3 years | Sensitivity, specificity and NPV of SLN detection with Technetium-99m (immunohistochemical analysis) | **The sensitivity for patients**=89% (95% CI, 52% to 100%), specificity for patients=100% (95% CI, 79% to 100%). **Negative predictive value for patients**=94% (95% CI, 71% to 100%). The sensitivity for groins=91% (95% CI, 59% to 100%). | "Lymphoscintigraphy and SLNB under gamma-detecting probe guidance proved to be an easy and reliable method for the detection of sentinel node in early vulval cancer. Immunohistochemical
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Patient number (N), Age, Study duration</th>
<th>Primary and Secondary Outcomes</th>
<th>Results</th>
<th>Conclusion (per Authors)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terada et al 2006&lt;sup&gt;26&lt;/sup&gt;</td>
<td>N=21, Age=72 (median) , Study duration=7 years</td>
<td>Negative predictive value and recurrence in negative SLN</td>
<td>The predictive value of a negative sentinel node was 100% (95% confidence interval of 81.5–100%). Positive sentinel nodes= 3 patients. At a median follow-up of 4.6 years: Morbidity: 2 (cancer), and 3 (intercurrent illness). None of the patients with negative sentinel nodes died of cancer. <strong>There was no groin or distant recurrences</strong> in patients with negative sentinel nodes. Three-year disease-free survival for all patients and for patients with negative sentinel nodes was 90% and 100% respectively.</td>
<td>“The survival for patients with early vulvar cancer treated with sentinel node dissection and radical local excision appears excellent.”</td>
</tr>
<tr>
<td>Moore et al 2008&lt;sup&gt;27&lt;/sup&gt;</td>
<td>N=36, Age=63 (median) , Study duration=5 years</td>
<td>Groin recurrence: Sensitivity and negative predictive value of SLN</td>
<td>All SLN dissections were successful with a mean of 2 SLN obtained per groin. <strong>Number of groins with a SLN detected by</strong>: Tc-99m sulfur colloid 48 (88.9%), Methylene blue dye 46 985.2%. There were 24 patients with stage I disease, 8 stages II, 3 stages III and 1 stage IV. A total of 56 SLN dissections</td>
<td>“The recurrence rate for patients undergoing inguinal sentinel node dissection alone is low. These patients did not experience any complications as seen with complete groin node dissections. Sentinel lymph node biopsy improves the sensitivity for the detection of regional micro metastases. The sentinel node assay is highly accurate in predicting the status of the remaining inguinofemoral lymph nodes.”</td>
</tr>
<tr>
<td>Author, Year</td>
<td>Patient number (N), Age, Study duration</td>
<td>Primary and Secondary Outcomes</td>
<td>Results</td>
<td>Conclusion (per Authors)</td>
</tr>
<tr>
<td>-------------</td>
<td>----------------------------------------</td>
<td>--------------------------------</td>
<td>---------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>Van der Zee et al 2008</td>
<td>N=406, Age=NR, Study duration=6 years</td>
<td>SLN detection using radioactive tracer and blue dye; groin recurrence</td>
<td>were performed with 4 patients found to have inguinal metastasis by SLN dissection. There were 31 patients with a total of 46 SLN dissections found to be negative for metastatic disease. The median follow-up: 29 months (range 8 to 51) with 2 groin recurrences for a groin recurrence rate of 4.3% and a recurrence rate per patient of 6.4%. No reports of groin breakdown, extremity cellulitis or lymphedema.</td>
<td>dissection should be considered as an option for evaluation of inguinal nodes for metastatic disease.</td>
</tr>
</tbody>
</table>

**Quality of life (QOL)**
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Patient number (N), Age, Study duration</th>
<th>Primary and Secondary Outcomes</th>
<th>Results</th>
<th>Conclusion (per Authors)</th>
</tr>
</thead>
</table>
| De Hullu et al 2001<sup>13</sup> | N=117, Age=63 (median), Study duration=8 years | False negative rate of the SLN procedure | **The response rate among patients:** 91% (106/117).  
One or more infections in the legs (cellulitis)= 40%  
Either severe pain and/or severe lymphedema in the legs= 49% patients.  
Sixty-six per cent of the patients preferred complete inguinofemoral lymphadenectomy in preference to a 5% false-negative rate of the sentinel lymph node procedure of 5%.  
Their preference was not related to age or the side-effects they had experienced.  
**The response rate among gynaecologists:** 80% (80/700), of whom 60% were willing to accept a 5-20% false-negative rate of the sentinel lymph node procedure. | “While gynaecologists may consider the sentinel lymph node procedure to be a promising diagnostic tool, the majority of vulvar cancer patients, who have undergone complete inguinofemoral lymphadenectomy in the past and have frequently experienced complications, would not advise introduction of this technique because they do not want to take any risk of missing a lymph node metastasis.” |
| Hefler et al 2008<sup>28</sup> | N=75, Age=67.7 (mean, SLN dissection), 64.1 (mean, complete IFLN dissection), Study duration= 11 years | Postoperative morbidity in sentinel lymph node vs. complete inguinal lymph node dissection | **SLN dissected= 46 vs IFLN dissected= 85.**  
**Number of inguinal postoperative morbidity:** SLN=4/46 (8.7%) vs IFLN=27/85 (31.8%), p=0.0006.  
**Days of inguinal drainage:** SLN 3.3 (1.5) vs IFLN 6.9 (4.6) p=0.001  
**Lymphatic secretion (mL):** SLN 131.1 (159.7) vs IFLN 480.7 (664.8), p=0.001.  
SLN was associated with a shorter operation time, a reduced rate of inguinal seromas, wound breakdown and wound infection, fewer days of inguinal drainage, and reduced postoperative lymphatic secretion. | “Evidence of reduced peri- and postoperative morbidity with the sentinel lymph node technique for inguinal lymph node dissection in patients with vulvar cancer was demonstrated.” |
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Patient number (N), Age, Study duration</th>
<th>Primary and Secondary Outcomes</th>
<th>Results</th>
<th>Conclusion (per Authors)</th>
</tr>
</thead>
</table>
| Oonk et al 2009   | N=62, Age=69 (mean), Study duration=5 years | QOL of patients treated with a SN procedure compared to with a IFLN procedure | **No difference in overall quality of life was observed between the two groups:** Mean (SD) SLN vs IFLND = 80 (18) vs 80 (23), p=0.62.  
The major difference was the increase in complaints of lymphedema of the legs after inguinofemoral lymphadenectomy.  
Patients after the **SLN procedure** only were more content with the treatment they had undergone (p=0.04).  
Other functional and symptom scales did not show statistically significant differences.
**SLN procedure false negative rate:** 10%  
**IFLN procedure false negative rate:** 48%  
84% that underwent SLN procedure only would recommend it to relatives. These differences were also observed with a suggested **false negative rate of 1%** and **0.1%**. | “Patients who underwent the SLN-procedure report less treatment related morbidity compared to those who underwent inguinofemoral lymphadenectomy. However, this did not influence overall quality of life. Patients after inguinofemoral lymphadenectomy were more reserved concerning the acceptable false negative rate of a new diagnostic procedure.” |
| Novackova et al 2012 | N=29, Age=64.1 (mean, Control group), 66.5 (mean, CONS group), 73.8 (mean, RAD group). Study duration=2 years | Prevalence of secondary lower-limb lymphedema after surgical treatment (circumference measurements and MFBIA technique); compare quality of life (QoL) before and 6 | **Circumference measurement:** 9 lymphedemas (31%) were diagnosed:  
3 (25%) in the sentinel lymph node biopsy (CONS)  
6 (37.5%) in the inguinofemoral lymphadenectomy (RAD) group (p=0.69). | “Lower radicality in inguinofemoral lymphadenectomy shows a trend toward lower morbidity and significantly improves QoL. Multifrequency Bioelectrical Impedance Analysis was tested” |
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Patient number (N), Age, Study duration</th>
<th>Primary and Secondary Outcomes</th>
<th>Results</th>
<th>Conclusion (per Authors)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>months after vulvar surgery</td>
<td>After vulvar surgery, patients in the RAD group reported more fatigue and worsening of physical and role functioning. When comparing both groups, the RAD group had significantly worse parameters in social functioning, fatigue, and dyspnea.</td>
<td>in these patients as a non-invasive, objective method for lymphedema detection. Detection of lymphedema based on subjective evaluations proved to have an unsatisfactory sensitivity. Less radical surgery showed objectively better results in QoL.”</td>
</tr>
</tbody>
</table>

**Abbreviations**
- QoL: quality of life
- IFLD: inguino-femoral lymphadenectomy node dissection
- IFLN: inguino-femoral lymphadenectomy
- ILND: inguino-femoral lymph node dissection
- LNE: lymphadenectomy
- NP or NPV: negative predictive values
- SLB: sentinel lymph node biopsy
- SLN: sentinel lymph node
- SNB: sentinel lymph node biopsy
The group of 731 patients who underwent SLN followed by complete IFLN dissection had 216 positive sentinel lymph nodes and 11 false negative SLN. The false negative rate (FNR) of SLN in this group of patients with early stage vulvar cancer was 4.84% (FNR = False Neg SLN/ true positive LN + False Neg SLN).3, 5, 7, 9, 10, 13, 17, 18, 22, 23 (Level III-2)

The false negative predictive value of a negative SLN in this same group of patients is 2.13% (Level III-2). The table below represents the percentage of false negative sentinel lymph nodes found in all included studies.

Table 7 False negative sentinel lymph node (%)

<table>
<thead>
<tr>
<th></th>
<th>R-I &amp; Blue Dye</th>
<th>R-I only</th>
<th>Blue Dye</th>
</tr>
</thead>
<tbody>
<tr>
<td>False negative rate</td>
<td>0 - 5%</td>
<td>0 – 7%</td>
<td>2-18%</td>
</tr>
<tr>
<td></td>
<td>Ref 3, 5, 8, 12, 14, 15, 18, 19, 20, 21, 22, 23, 24, 25</td>
<td>Ref 9, 16, 7, 10, 17, 6, 13</td>
<td>Ref 3, 4, 5, 11, 16, 20, 21</td>
</tr>
</tbody>
</table>

3.1.4 Histological assessment of sentinel lymph nodes

The sensitivity to detect tumour in excised SLN will influence the observed false negative rate of the procedure, and ultimately the patient outcome, when complete IFLD is not part of the treatment paradigm. The use of serial sectioning for ultrastaging and immuno-histochemistry in the assessment of SLN has been shown in both the treatment of breast cancer and melanoma to increase the detection rate of tumour in excised SLN.12, 32, 40

Fifteen publications specifically looked at the impact of ultrastaging (US) and immuno-histochemistry (IHC) examination of SLN in the detection of metastatic tumour. Initially routine sectioning and staining with haematoxylin eosin (H&E) of the SLN was performed in seven studies and all negative nodes subjected to US and IHC examination. The other 8 describe US and routine H&E of the excised SLN and IHC examination of negative SLN.3, 5, 7-10, 13-16, 18, 19, 21, 22, 24

Table 8 shows the cumulative data of the effect of IHC examination of negative SLN on initial examination, either by routine sectioning and H&E examination or US and H&E examination.

Table 8 Effect of immunohistochemistry on detection of positive sentinel lymph node

<table>
<thead>
<tr>
<th></th>
<th>Negative SLN on routine pathology</th>
<th>Positive SLN after IHC</th>
<th>% Increased positive SLN detection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routine sections</td>
<td>726</td>
<td>82</td>
<td>11.2%</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>549</td>
<td>47</td>
<td>8.6%</td>
</tr>
</tbody>
</table>

The data support the addition of US and IHC examination for negative SLN on routine H&E as a means of increasing the accuracy of identification of tumour in SLNB. The range of increased detection according to individual publications is 0–41% (Level III-2 or III-3).
3.2 Outcome measures of SLNB

3.2.1 Recurrence

Ultimately, the most critical outcome measure of SLNB is related to the risk of recurrence and death from vulvar cancer following the procedure, where complete IFLN dissection is not performed after identification of a negative SLN. The assessment of risk of groin recurrence after a negative SLNB should be compared to the historical data on risk of groin recurrence after complete IFLN dissection with negative nodes.

Interpreting the significance of groin recurrence after a negative SLNB where a complete IFLD was not performed should be done in conjunction with the known groin recurrence rate after a complete IFLD with negative nodes. The recurrence rate in a groin where a complete IFLN dissection has been performed is reported to be 1.3%, with a range of 0-4.3%.32

A recent review by Reade et al of sentinel lymph node biopsy in vulvar cancer included 11 studies (patients evaluated n =591).32 Across all the studies, the recurrence rate in the groin after a negative SLNB was 3.6% (range 0–22%).32 The quality of the studies was generally poor. Follow up was variable but in most it was at least two years, the expected time for groin recurrence to occur. Many of these studies include mixed histology, advanced stage and had limited information about tumour site or size, and therefore were not included in this review.

The review by Reade et al reported on six studies (n=532) that evaluated the complication rates where the inguinal lymph nodes were treated by SLNB only, if they were found to be negative for tumour. Most studies reported complications per patient, but some reported complications per groin, make comparative analysis difficult. In only three of these studies was the study group clearly defined as early stage vulvar cancer (SCC, size <4cm) (Level III-2 – IV). The reported groin recurrence rate in these studies was 6/293 patients (2.04%, range 0-2.3%).32

3.2.2 Adverse events

The main reason to consider SLN in early stage vulvar cancer is to minimize the potential complications such as wound disruption, acute infection, lymphoedema and cellulitis inherent in complete IFLN dissection.

Eight studies were identified that had some assessment of post-operative complications related to SLNB, however the patient numbers were small, and the information provided was often limited and of poor quality (Level IV).6, 15, 25, 27, 28, 33-35

Acute complications usually infection or wound collection, were more common in patients undergoing IFLN dissection (52/221 patients, 23.5%) than those having SLNB (59/405 patients, 14.5%).

Achimas-Cadariu et al found a statistically significant benefit with respect to side effect for SLNB compared with full node dissection, either alone or after SLNB. Only 1/28 (3.6%) of patients with SLNB had wound breakdown; 12/58(20.7%) in the conventional IFLN dissection group (p=0.0030). The rate of post-operative lymphedema or lymphocele in the groin was
significantly lower after SLNB only, with none in the SLNB group and 13 (22.4%) in the IFLN dissection group (p=0.004).\textsuperscript{15}

Hefler et al reported on post-operative morbidity in 75 patients with vulvar cancer treated with SLNB (n= 29) or ILND (n=46). Twenty-three were early stage in the SLNB group and 25 in the ILND group. \textsuperscript{(Check)} Sentinel lymph node dissection was associated with a shorter operation time (85.5 minutes vs. 120.7 minutes; p=0.002); shorter length of stay (12.6 days vs. 22.9 days; p<0.001); and reduced post-operative lymphatic secretion (131.1 ml vs. 480.7 ml; p=0.006).\textsuperscript{28}

Van der Zee, in the largest prospective series, with SLNB performed in 623 groins of 403 assessable patients with early stage cancer of the vulva, reported short-term morbidity was decreased in patients after sentinel node dissection only when compared with patients with a positive sentinel node who underwent inguinofemoral lymphadenectomy (wound breakdown in groin: 11.7\% v 34.0\%, respectively; P<.0001; and cellulitis: 4.5\% v 21.3\%, respectively; P < .0001). The acute complication rates were similar to the cumulative data seen in the other reports. \textsuperscript{25}

Long term complications were prospectively reported in only two.\textsuperscript{25, 35} The Van der Zee et al 2007 study quantify the assessment of lymphoedema and had sufficient size to provide Level II-2 evidence of benefit of SLNB compared to complete IFLD, with respect to the frequency of both recurrent cellulitis and lymphoedema. Long-term morbidity was less frequently observed after removal of only the sentinel node compared with sentinel node removal and inguinofemoral lymphadenectomy (recurrent erysipelas: 0.4\% v 16.2\%, respectively; P < .0001; and lymphedema of the legs: 1.9\% v 25.2\%, respectively; P< .0001).\textsuperscript{27}

### 3.2.3 Quality of Life

Two studies focused on quality of life (QoL) assessments of women undergoing SLN procedures for vulvar cancer.\textsuperscript{34, 35} The prospective, non-randomised study by Novackova assessed lower limb size using a measurement of leg circumference and Multifrequency Bioelectrical Impedance Analysis (MBIA) before, and six months after, vulvar cancer surgery and found a trend towards improved QoL in those patients having less radical SLN surgery (n=12) compared to those having IFLN (n=17). However, the small number of patients, and the use of post-operative radiotherapy in 12 patients, makes interpretation of the results problematic. \textsuperscript{(Level IV)}.\textsuperscript{35}

Oonk et al 2009\textsuperscript{34} reported on QoL outcomes for 35 patients after SLNB and 27 patients after complete IFLN dissection, who participated in the GROningen International Study on sentinel nodes in vulval cancer (GROINSS-V) between 2000 and 2005. Patients completed three questionnaires, The EORTC QLQ-C30, a vulvar specific questionnaire (VSQ) and a questionnaire about the opinion of patients on new treatment options (median follow up between surgery and questionnaire as 33 months; interquartile range 20-48 months). While patients having SLN had less treatment-related morbidity, there was no difference in QoL outcomes for the two groups. Patients who underwent SLNB alone were more content with the procedure they underwent and were more likely to advise new treatment options to relatives. No information about the timing of the questionnaires was provided \textsuperscript{(Level IV)}.\textsuperscript{34}
de Hullu et al 2001\textsuperscript{33} used a structured questionnaire to ascertain the opinions about the acceptable false-negative rate of SLNB amongst gynaecologists and patients who had previously had a complete IFLN dissection and were in complete remission (median follow up 118 months; range 76-185 months). Gynaecologists were more willing to accept SLN as a treatment option than the patients. Despite 40\% of patients have experienced cellulitis and still experiencing leg pain and/or severe lymphoedema in the legs, 66\% preferred complete inguinofemoral lymphadenectomy in preference to a 5\% false-negative rate with SLNB.\textsuperscript{33}

These small studies all identify the need for better evidence on the QOL outcomes associated with SLNB.

\subsection*{3.2.4 Cost-effectiveness}

While evidence about the cost-effectiveness of SLNB for early stage cancer of the vulva was not specifically searched for, the paper by Reade et al 2012\textsuperscript{32} also sought to address the question of whether sentinel lymph node procedure for early-stage vulvar cancer is cost-effective and feasible in the Canadian health system, compared with the current standard of complete inguinofemoral lymphadenectomy, as many Canadian centres are in the process of switching their practice to include SLNB rather than IFLD.

The paper concluded that SLNB is likely to be more costly to perform that IFLD because of the need for nuclear medicine staff, gamma-probe equipment and ultrastaging of sentinel nodes. Management of a positive SLNB may also incur increased costs if intraoperative frozen section diagnosis is not used and a second operation is required. It was noted however, that there would likely be some cost savings from shorter operating times and shorter length of stay, fewer visits for drain care, wound complications, and lymphedema.
4 Conclusions

While sentinel node biopsy is recommended within the Australian setting in the management of breast cancer\textsuperscript{41} and melanoma\textsuperscript{37, 42} based on limited evidence (Level II-2 – IV), the role of SLN identification and biopsy in the management of early stage squamous cell cancer of the vulvar is still unclear.

The evidence supporting SLNB is of low quality and is particularly hampered by the inclusion in studies of tumours with variable stage, size and non-squamous histology. Apart from the statement by the Royal College of Obstetricians and Gynaecologists, which also notes the absence of good quality evidence, there were no other statements identified regarding the place of SLNB in the management of early vulvar cancer by any national gynaecology or cancer organisations.

The rationale currently driving a modified surgical procedure is based on:

- long-term rate of complications, and
- the impact on groin recurrence, following SLNB.

There are paucity of data about the long-term complications and those studies that examined QoL for women undergoing nodal procedures noted the need for further research.

Despite the limitations identified in the review, the data that are currently available, and were examined in this review, suggest that SLNB has similar clinical outcomes for groin recurrence to that achieved by complete IFLD. Reade et al in a health technology assessment for the Canadian Health care context came to a similar conclusion, although the assessment criteria in their publication, was much broader.

This systematic review of the available evidence indicates that:

- Sentinel node biopsy has similar rates of groin recurrence compared to complete inguinal-femoral lymph node dissection for women with early stage vulvar cancer (2.04% SNB vs. 1.3% IFLN dissection).
- Sentinel node biopsy is associated with less frequent adverse events, including lymphoedema, compared to complete lymph node dissection.
- Sentinel node biopsy does not have an adverse effect on quality of life for women with early stage vulvar cancer compared to those who have complete lymph node dissection. Sentinel node biopsy may be associated with improvements in quality of life, however the data are limited and further studies are required.
- Sentinel lymph node (SLN) identification is enhanced by combined radio-isotope (R-I) and blue dye injection, when compared to the use of blue dye alone. However, the impact of the experience of the injector cannot be evaluated on available evidence.
• The addition of ultrasectioning and immuno-histochemistry evaluation of SLN, found to be negative on routine sections, increases the rate of positive SLN identification in squamous cell cancer of the vulva.
Appendix A  Contributors

The role of sentinel node biopsy in the treatment of women with early vulval cancer: a systematic review was developed by Dr Peter Grant, Gynaecological Oncology, Dr Adam Pendlebury and Dr Julie Lamont.
### Appendix B  FIGO staging Carcinoma of the Vulva

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>Tumor confined to the vulva or perineum, ≤2cm in size with stromal invasion ≤1mm, negative nodes</td>
</tr>
<tr>
<td>IB</td>
<td>Tumor confined to the vulva or perineum, &gt;2cm in size or with stromal invasion &gt;1mm, negative nodes</td>
</tr>
<tr>
<td>II</td>
<td>Tumor of any size with adjacent spread (1/3 lower urethra, 1/3 lower vagina, anus), negative nodes</td>
</tr>
</tbody>
</table>
| IIIA  | Tumor of any size with positive inguino-femoral lymph nodes  
(i) 1 lymph node metastasis greater than or equal to 5 mm;  
(ii) 1-2 lymph node metastasis(es) of less than 5 mm |
| IIIB  | (i) 2 or more lymph nodes metastases greater than or equal to 5 mm;  
(ii) 3 or more lymph nodes less than 5 mm |
| IIIC  | Positive node(s) with extracapsular spread |
| IVA   | (i) Tumor invades other regional structures (2/3 upper urethra, 2/3 upper vagina), bladder mucosa, rectal mucosa, or fixed to pelvic bone  
(ii) Fixed or ulcerated inguino-femoral lymph nodes |
| IVB   | Any distant metastasis including pelvic lymph nodes |

Abbreviations

FIGO  International Federation of Gynaecology and Obstetrics
H & E  haematoxylin eosin
IFLN  Inguino-femoral lymph node
IFLD  inguino femoral lymphadenectomy node dissection
IHC  Immunohistochemistry
LN  lymph node
NHMRC  National Health and Medical Research Council
QOL  quality of life
R-I  radio-Isotope
SLN  sentinel lymph node
SLNB  sentinel lymph node biopsy
US  ultrastaging
Glossary

Sentinel node biopsy  Sentinel node biopsy is a surgical procedure used to determine if cancer has spread beyond a primary tumour into the lymphatic system. The sentinel nodes are the first few lymph nodes into which a tumour drains.
References


The role of sentinel node biopsy in the treatment of women with early stage vulvar cancer


The role of sentinel node biopsy in the treatment of women with early stage vulvar cancer