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Evidence-Based Series 4-17 Version 2

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

Sentinel Lymph Node Biopsy in Vulvar Cancer

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

Report Date: January 26, 2018

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

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

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

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Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 Email: ccopgi@mcmaster.ca

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Guideline Report History

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

Evidence-Based Series #4-17: Section 1

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

Sentinel Lymph Node Biopsy in Vulvar Cancer: Guideline Recommendations

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

Report Date: July 17, 2014

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

GUIDELINE OBJECTIVES

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

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

TARGET POPULATION

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

INTENDED USERS

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

NOTE:

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

RECOMMENDATIONS, KEY EVIDENCE, AND JUSTIFICATION

RECOMMENDATIONS FOR PATIENT SELECTION

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

Summary of Key Evidence for Recommendations for Patient Selection

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

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

Justification for Recommendations for Patient Selection

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

The Working Group chose to recommend SLNB for patients with unifocal disease based on the large GROningen INternational Study on Sentinel nodes in Vulvar cancer (GROINSS-V)

by van der Zee et al. in 2008 (1). Also, since most studies included patients with tumours that were <4 cm, the Working Group recommended SLNB for this subgroup of patients. SLNB was not recommended for patients with clinically suspicious groin nodes because of the potential elevated false-negative rate and because this subgroup of patients were not included in many of the studies.

RECOMMENDATIONS FOR APPROPRIATE TECHNIQUES AND PROCEDURES

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

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

Qualifying Statements for Recommendations for Appropriate Techniques and Procedures

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

Summary of Key Evidence for Recommendations for Appropriate Techniques and Procedures

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

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

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

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

Justification for Recommendations for Appropriate Techniques and Procedures

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

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

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

Ultrastaging examines more sections than usual in addition to immunohistochemical staining and was recommended because the evidence suggested it may increase the detection of metastases in sentinel lymph nodes previously found to be negative and may have a positive effect on survival rate. The Working Group believed the benefit of increased

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

Other Considerations

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

FUTURE RESEARCH

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

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Updating

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

Contact Information

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Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 email: ccopgi@mcmaster.ca

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