Accuracy of sentinel lymph node biopsy for inguinal lymph node staging of penile squamous cell carcinoma: systematic review and meta-analysis of the literature


CRD summary
This review found that sentinel lymph node mapping in penile squamous cell carcinoma was associated with high sensitivity and detection rates. The lack of information on included studies means the results should be interpreted with caution and the authors’ conclusions may not be reliable.

Authors’ objectives
To evaluate the accuracy of sentinel lymph node biopsy for inguinal lymph node staging of penile squamous cell carcinoma.

Searching
Six databases and other sources including MEDLINE and Google Scholar were searched to December 2010 for relevant studies without language restrictions; search terms were reported. The reference lists of the retrieved articles were checked for additional studies and the authors of the studies were contacted for further information.

Study selection
Studies of at least five patients with penile squamous cell carcinoma that used modern techniques of sentinel lymph node mapping (blue dyes or radiotracers) were eligible for inclusion. For inclusion in the analysis of sensitivity, studies were required to report the number of groins with involved lymph nodes (identified by inguinal lymph node dissection or inguinal recurrence during follow-up) and the numbers of false negative groins. For the analysis of detection rates, the studies were required to report the total number of groins and the number of groins with detected sentinel nodes during surgery.

All of the studies were prospective cohort studies. Some studies included only patients with palpable lymph nodes or patients with intermediate risk; all the others included an appropriate spectrum of patients. The radiotracers 99m Tc-Sulfur colloid or Tc-nanocolloid were used at a range of doses in most studies; one study each used 99m Tc-phytate and 99m Tc-rhenium. The injection sites were intradermal in most studies; other studies used subdermal and subcutaneous sites proximal to the tumour. The methods of mapping were by radiotracer and isosulphane blue dye, by radiotracer alone or by blue dye alone. The time intervals between surgery and injection ranged from 30-60 minutes to the previous day before the injection. The reference standards in the studies were inguinal node dissections, lymphadenectomies and follow-up.

Two reviewers independently performed the study selection; any disagreements were resolved by a third reviewer.

Assessment of study quality
Methodological quality was assessed using the Oxford Centre for Evidence Based Medicine checklist for diagnostic studies in terms of the consecutive inclusion of patients, the spectrum of included patients, the description of the diagnostic tests, the reference standard used, the duration of follow-up and the reporting of patients lost to follow-up.

The authors did not state how many reviewers performed the quality assessment.

Data extraction
Data were extracted to calculate specificity and detection rates and 95% confidence intervals (CI) for the estimates.

Data were extracted by two independent reviewers; any discrepancies were resolved by a third reviewer.

Methods of synthesis
Pooled sensitivity and detection rates were calculated using a DerSimonian and Laird random-effects model. Statistical heterogeneity was evaluated using the Cochran Q-statistic and the I² test. The reviewers assessed the potential for
publication bias using funnel plots, the Egger's regression test and the Duval and Tweedie trim-and-fill method.

**Results of the review**

Seventeen studies of 1,385 groins, plus 20 patients in which number of groins studied were not specified, were included in the review. Three studies had two subgroups of patients which were considered as separate studies. Including the subgroups, 18 studies were used for the detection rate analysis and 19 studies were included in the analysis of sensitivity. Eight studies reported consecutive patient inclusion 15 studies included an appropriate spectrum of patients. Fourteen studies described the tests and only three studies reported numbers of patients lost to follow-up. Where reported, the duration of follow-up ranged from one month to 95 months.

The detection rate was 88.3% (95% CI 81.9 to 92.6) with statistically significant heterogeneity ($I^2$=83.95%, $p<0.0001$). The subgroup analysis of studies that used blue dye and radiotracers for sentinel lymph node mapping using one method had detection rates of 90.1% (95% CI 71.3 to 92.9) versus using one method (85.1, 95% CI 1.3 to 92.9).

The pooled sensitivity was 88% (95% CI 83-92% with significant statistical heterogeneity ($I^2$=42%, $p=0.0285$).

Subgroup analysis of the mapping method showed a pooled sensitivity of 60% (95% CI 15 to 95) for blue dye alone and 84% (95% CI 72 to 92) when radiotracer was used alone. Sensitivity was 90% (95% CI 85 to 95) when both methods were used. In another analysis where two studies of patients with palpable inguinal nodes were excluded, pooled sensitivity was 90% (95% CI 85 to 94). The pooled sensitivity of studies using radiotracer and blue dye for sentinel lymph node mapping and recruiting patients with node-negative disease was 92% (95% CI 86 to 96). The pooled sensitivity of two studies where inguinal ultrasonography was used to detect suspicious inguinal lymph nodes was 93% (95% CI 85 to 97).

There was no evidence of publication bias found for any of the outcomes, although the reviewers acknowledged the limitations of the tests because of low power, particularly for detection rates.

**Authors' conclusions**

Sentinel lymph node mapping in patients with penile squamous cell carcinoma was a diagnostic method with high sensitivity and detection rates. In addition, the use of radiotracer and blue dye for sentinel lymph node mapping and including only patients with clinical node negative cancer ensures high detection rate and sensitivity.

**CRD commentary**

The review addressed a clear question and criteria for the inclusion of studies in the review were stipulated. Appropriate databases were searched for relevant studies without language restriction, and attempts were made to identify unpublished studies. Steps were described to minimise errors and bias for study selection and data extraction. The authors did not state how many reviewers performed the assessment of methodological quality, which was conducted using validated methods for diagnostic tests. Little information was provided in the review on the patient populations included in the review. It was unclear if the authors' decision to pool the results of the studies in a meta-analysis was justified because of the potential clinical heterogeneity in patient populations and administration of the diagnostic and reference tests. Significant statistical heterogeneity was also observed across the results.

The authors' conclusions were based on the evidence presented, but the relatively low quality of the included studies, lack of information on the patients and heterogeneity of the results means that the reliability of the results is not clear.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that a potential learning curve effect with the use of sentinel lymph node mapping may have an effect on the results because of the relative rarity of penile cancer. Future studies should examine the role of such a learning curve on accurate lymph node mapping.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.