Sentinel-lymph-node procedure in colon and rectal cancer: a systematic review and meta-analysis

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CRD summary
This review concluded that the sentinel-lymph-node procedure showed a low sensitivity for the assessment of nodal status in patients with colorectal cancer regardless of T stage, localisation or pathological technique. This cautious conclusion reflects the data reported, but the possibility of missing studies and some limitations in review methods should be considered.

Authors' objectives
To assess the diagnostic performance of the sentinel-lymph-node procedure for assessment of nodal status in patients with colorectal cancer.

Searching
PubMed and EMBASE were searched from inception to March 2010; search terms were reported and more details were provided in a web appendix. The bibliographies of included studies, reviews and textbooks were screened for additional articles.

Study selection
Prospective studies that assessed the diagnostic performance of sentinel-lymph-node procedure in patients with colorectal cancer were eligible for inclusion. Studies had to include at least 20 participants and report positivity rates (clearly describe histopathological analysis and specimen handling).

Twenty-six studies used the four quadrant method. Tracers used included isosulfan blue, patent blue, $^{99m}$Tc, methylene blue and indocyanine green; amounts of dye and radioactivity varied. The definition of a sentinel lymph node varied between studies (generally fluorescent, blue, hot or blue and hot). More than half of the included studies used in-vivo sentinel lymph node identification techniques. Most studies used immunohistochemical staining of the sentinel lymph node. Two studies used reverse transcription-polymerase chain reaction when the haematoxylin and eosin staining result was negative. Serial sectioning was not universal.

Fifteen studies were excluded because they were reported in languages for which no translation was available.

The authors did not state how many reviewers selected studies for inclusion.

Assessment of study quality
Methodological quality assessment was based on the QUADAS tool with criteria divided into internal and external validity. Internal validity included: valid reference tests (histology); consecutive recruitment; blinded interpretation of pathology results; and prospective study. External validity included: stage of disease; range of diseases demographic information; specification of inclusion and exclusion criteria; whether the reference standard was described in sufficient detail to permit replication; and whether uninterpretable test results were reported.

Two reviewers independently assessed study quality using a standard form.

Data extraction
Numbers of true positive, true negative and false negative sentinel lymph node procedures were extracted and used to calculate sensitivity with 95% confidence intervals (CIs).

A true positive sentinel lymph node was defined as a positive sentinel lymph node identified with or without additional staging (serial-sectioning, immunohistochemistry or reverse transcription-polymerase chain reaction). Sentinel-lymph-node procedures yielding tumour-negative sentinel node(s) in combination with tumour-positive non-sentinel nodes were classified as false negative.
The percentage of patients who were clinically up-staged (N0 to N1), based on additional staging (other than single-section haematoxylin and eosin staining) was calculated. The detection rate (number of procedures in which at least one sentinel lymph node was identified, divided by the total number of procedures) was also calculated.

Two reviewers extracted data using a standard form.

**Methods of synthesis**

A pooled estimate of sensitivity (with 95% CIs) was calculated using a random-effects model. Between-study heterogeneity was assessed using $\chi^2$. A logistic regression analysis of individual patient data was undertaken, using data from 19 studies; T stage and localisation (colon or rectum) were used as stratifying variables.

A subgroup analysis of high-quality studies was conducted. High-quality studies were defined as those with: at least 20 sentinel lymph node procedures per year in all participating centres; exclusion of patients with clinical signs of lymph-node involvement or metastatic disease; harvest or marking of sentinel lymph nodes directly after injection of the tracer in fresh material; data presented separately for colon and rectal cancer. Studies describing the use of indocyanine green or methylene blue considered experimental and were excluded from the subgroup analysis.

**Results of the review**

Fifty-two studies (total number of participants unclear) were included in the review. The results of quality assessment were reported in an online appendix, but were not fully incorporated into the results.

The overall pooled estimate of sensitivity was 76% (95% CI 72% to 80%), $I^2=82.2\%$. No significant differences in sensitivity were identified between procedures. The pooled detection rate was 94% (95% CI 92% to 95%) and again, no significant difference was identified between tracers. The weighted mean proportion of patients up-staged was 15% (95% CI 12% to 19%), based on data from 45 studies.

A subgroup analysis of eight high-quality studies gave a pooled estimate of sensitivity for colon cancer of 90% (95% CI 86% to 93%) and a corresponding mean detection rate 96% (95% CI 90% to 99%). For rectal cancer, the pooled estimate of sensitivity was 82% (95% CI 60% to 93%) and the mean detection rate 95% (95% CI 75% to 99%). The mean proportion of up-staged patients was 11% (95% CI 6% to 22%).

Individual patient data analysis indicated no significant differences in sensitivity when patients were stratified by cancer stage (T1, T2, T3 and T4), or between patients with colon and rectal cancer.

**Authors' conclusions**

The sentinel-lymph-node procedure shows a low sensitivity, regardless of T stage, localisation or pathological technique.

**CRD commentary**

The review stated a clear objective and defined appropriate inclusion criteria. Several sources were searched for relevant studies, but the exclusion of 15 studies for which no translation could be obtained may have resulted in loss of relevant data and raised the possibility of language bias. It was not clear whether the review process included measures to reduce error and/or bias (the number of reviewers was reported for some stages, but without details of the process).

The results of quality assessment of included studies were reported in an online appendix, but were not fully incorporated in the results of the review. Appropriate meta-analytic methods were used. The authors' conclusions were appropriately cautious, but should be interpreted with consideration to the methodological limitations outlined.

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

**Practice**: The authors stated that the sentinel lymph node procedure should be considered in all patients diagnosed with colon or rectal cancer without clinical evidence of lymph node involvement or metastatic disease, as it may improve staging of patients.

**Research**: The authors stated that future studies should focus on patients with stage I and II cancer, as those with stage III and IV cancer already meet the criteria for adjuvant chemotherapy and their treatment would not be changed by adding sentinel lymph-node procedure to the diagnostic work-up. The authors further stated that large, prospective
studies were needed to establish the prognostic significance of upstaging and its consequences for adjuvant therapy.

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