A systematic review and economic evaluation of intraoperative tests [RD-100i one-step nucleic acid amplification (OSNA) system and Metasin test] for detecting sentinel lymph node metastases in breast cancer

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Scientific summary

OSNA and Metasin for detecting SLN metastases

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Scientific summary

Background

One of the key steps in the management of breast cancer is determining if there is spread to the axillary lymph nodes (ALNs) from the main (primary) tumour.

Sentinel lymph node biopsy (SLNB) is first carried out at the same time as removal of the main tumour to determine if there are regional metastases in the sentinel lymph nodes (SLNs), the first ALNs into which the breast drains lymph. If there are any more than isolated tumour cells in the SLNs, complete axillary lymph node dissection (ALND) is required because of the possibility that tumour cells have spread beyond the SLNs into the other ALNs.

Whether the SLNB is positive or not is usually determined by histopathology – examining slides under a microscope – after the operation to remove the primary tumour, and so there is a delay before an ALND is performed, if required. If positivity of the SLNB could be established during the operation, intraoperatively, ALND could be performed without delay, with potential benefits for the patient and the health service.

One-step nucleic acid amplification (OSNA) (Sysmex, Norderstedt, Germany) and Metasin (Cellular Pathology, Princess Alexandra Hospital NHS Trust, Harlow, Essex, UK) are two types of test that claim to be able to accurately diagnose regional metastases in the SLNs sufficiently quickly to be used intraoperatively. OSNA is an automated molecular test in which genetic material (messenger ribonucleic acid, mRNA) is amplified and the presence of the cytokeratin-19 (*CK19*) gene is detected. OSNA does not require the mRNA to be extracted from the tissue and purified before being analysed. Minimal details are available for the Metasin test, which detects the presence of *CK19* and mammaglobin. However, for the Metasin test it appears that ribonucleic acid (RNA) must be extracted from tissue, purified and quantified before nucleic acid amplification and analysis.

The OSNA and Metasin tests could be used as a replacement for postoperative histopathology or as an adjunct to it. If used as a replacement all of each SLN would be used in either the OSNA test or the Metasin test intraoperatively; if used as an adjunct, half of each node would be used in either the OSNA test or the Metasin test and half would be used for histopathology if the OSNA or Metasin test result was negative.

Tissue allocation bias (TAB) is a major challenge when evaluating OSNA and Metasin, particularly their accuracy. The SLNs are divided between the test of interest (OSNA or Metasin) and the test with which OSNA or Metasin is being compared (usually histopathology) and therefore tumour cells may be present in only one of the sections. Apparent errors in identifying metastases may therefore not be the fault of the test but rather a problem with sampling.

Objective

To evaluate the clinical effectiveness and cost-effectiveness of OSNA and Metasin, if used in the NHS in England, for the intraoperative analysis of metastases in SLNs of breast cancer patients.

Methods

The assessment comprises a systematic review of clinical effectiveness and cost-effectiveness studies, a review and critique of data supplied by the manufacturer and a de novo economic analysis.

Clinical effectiveness systematic review

A systematic review was conducted to summarise the evidence on the clinical effectiveness of RD-100i (OSNA) and Metasin for the intraoperative analysis of breast cancer metastases in SLNs. The search strategy focused on the interventions specifically applied to lymph node diagnosis.

The following bibliographic databases were searched in this review: MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations and EMBASE (all via Ovid), Web of Science (including conference proceedings, via ISI), The Cochrane Library (all) and the NHS Economic Evaluations Database (EED) (via The Cochrane Collaboration). The searches did not use any form of limit (e.g. date).

The following trials registries were also searched: ClinicalTrials.gov, Current Controlled Trials, the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) and the European Union Clinical Trials Register. The Google search engine (Google Inc., Menlo Park, CA, USA) was also used to identify grey literature and conference publications. Items included after full-text screening were forward citation chased using Web of Science (Thompson Reuters).

Critical appraisal was performed using the Cochrane risk of bias tool and the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool. Results were summarised in tables and text, stratified by level of data (patient or node), node analysed (sentinel or axillary) and correction for TAB.

Cost-effectiveness systematic review

In addition to the electronic sources searched for the clinical effectiveness review, EconLit and the bibliographies of relevant studies were searched for cost, cost-effectiveness and cost–utility studies of intraoperative testing options for metastatic disease in early breast cancer.

Peninsula Technology Assessment Group cost-effectiveness analysis

The Peninsula Technology Assessment Group (PenTAG) model was split into two sections: the diagnostic pathway and the management pathway.

The diagnostic pathway was a decision tree built to represent the diagnosis of regional metastases in the SLNs. Three pathways were examined: current practice histopathology (the 'gold standard'), replacement testing of the full node by intraoperative testing and half-node intraoperative testing followed by histopathology on the other half node.

In the diagnostic pathway, patients who were diagnosed with SLN metastases received ALND. For those diagnosed intraoperatively this occurred during the same surgery as their SLNB; for those diagnosed by histopathology this occurred during follow-up surgery.

Diagnostic accuracy was taken from the clinical effectiveness systematic review. For OSNA, studies were split into those that included adjustment for TAB and those that did not include adjustment for TAB.

Patients incurred costs depending on their diagnostic strategy, their surgery, any additional hospital stay and the occurrence of adverse events. The intraoperative test costs (OSNA and Metasin) were derived from information provided by the technology sponsors. Costs for histopathology were taken from a previous study based on data from the Queen Alexandra Hospital in Portsmouth. The costs of surgery were obtained from NHS reference costs and from a previous microcosting study (York Health Economics Consortium costs).

Short-term disutility for patients waiting for results or undergoing a second operation was investigated.

The management pathway was concerned with lifetime results and used an updated version of a previously published discrete event simulation model that followed individual patients through a series of health states, calculating their accrued costs and quality-adjusted life-years (QALYs) according to their

different outcomes in the diagnostic pathway and, consequently, management pathway. The sum of the short- and long-term costs and QALYs gave the overall lifetime costs and QALYs.

Most parameters for the management model were taken from the original report of the model published in 2011, with costs updated when new reports were found, and reflating all costs to 2010 prices.

Sensitivity analysis adopted the range of sensitivity and specificity values identified by the clinical effectiveness systematic review. In addition, the prevalence of SLN metastases was varied from 20% (from the clinical effectiveness systematic review) to 10% and 40%. Costs of tests and surgeries and management costs were varied by plus or minus 10%.

Results

Clinical effectiveness systematic review

Seventeen studies were included that investigated the performance, particularly test accuracy, of either OSNA or Metasin for detecting metastases in the SLNs or ALNs of breast cancer patients. Two of the studies reported on Metasin; however, both were unpublished and reported in draft form. The remaining 15 studies reported on OSNA, with one study reported in two papers.

The majority of studies were considered to be at low risk of bias, although many were considered to have an unclear risk of bias with regard to their method of patient recruitment and patient characteristics.

No data were found for clinical outcomes such as patient anxiety and number of repeat operations. Only one study provided evidence on time spent in the operating theatre.

In accuracy studies the reference standard (i.e. histopathology), although plausible, may be performed with varying levels of analysis and, as such, it may not be a true indicator of the target condition.

The main issue within the included studies has been TAB. Some studies have dealt with this by reanalysing both the histopathology and the molecular samples or by choosing to reanalyse just one technology.

It should also be noted that more than one SLN may be removed from a patient, which means that results for a study may be presented by patient or by individual node or by both. There is also a potential conflict of interest as one of the two unpublished Metasin studies was performed at the institution in which the technology was developed and the majority of the OSNA studies were financially supported by Sysmex, the company that manufactures OSNA.

All accuracy studies implicitly assumed that the reference standard, histopathology, is a true measure of the target disorder.

The pooled OSNA patient node status sensitivity was 84.5% [95% confidence interval (CI) 74.7% to 91.0%] and its specificity was 91.8% (95% CI 87.8% to 94.6%), based on five available studies including a total of 991 subjects. As only two studies reported on Metasin, a meta-analysis was not performed. As these data were taken from draft papers, before peer review, the results, which indicate an increased sensitivity and specificity relative to OSNA results, must be used with caution.

Some studies adjusted for TAB, generally taking a conservative approach by excluding affected samples. This does improve the test accuracy, increasing sensitivity from 84.5% to 91.3% (95% CI 83.6% to 95.6%, with the SLN as the unit of analysis) and increasing specificity from 91.8% to 94.2% (95% CI 91.2% to 96.2%), based on three reports and 453 subjects.

With regard to the time taken to perform OSNA, there was a lack of detail in the studies explaining which aspects of the procedure were monitored. However, the time reported ranged from < 30 minutes to 39.6 minutes for one node. This increases by approximately 5–10 minutes per additional node analysed.

Cost-effectiveness systematic review

Two studies of the diagnostic phase were identified by the searches. One was a study of OSNA conducted in one centre in Spain, which did not measure benefits to patients. The other study evaluated a diagnostic testing option in the UK that has been withdrawn from the market (GeneSearch BLN assay; Veridex, Warren, NJ, USA) and is therefore no longer relevant for the present evaluation. Therefore, a de novo analysis was justified.

Independent Evidence Review Group assessment

In the base case, short-term results show that, in general, half-node OSNA was not cost-effective in terms of cost per patient correctly diagnosed, cost per node-positive case detected or cost per node-negative case detected. In all cases in which half-node OSNA was dominated or extendedly dominated, the cost per additional diagnostic yield of histopathology compared with full-node OSNA was < £17,000. These results were insensitive to setting the sensitivity and specificity of OSNA equal to TAB-adjusted values.

Long-term results revealed that histopathology resulted in more QALYs at a lower cost per QALY than half-node OSNA when both were compared with full-node OSNA. The incremental cost-effectiveness ratio (ICER) of histopathology relative to full-node OSNA was < £5000 per QALY gained, for both costing strategies. When diagnostic test accuracy parameter values in the model were adjusted for TAB, half-node OSNA remained extendedly dominated, except for TAB-adjusted diagnostic test accuracy values reported by Snook *et al.* using NHS reference costs, which resulted in an incremental cost of £8063 per QALY gained for half-node OSNA relative to full-node OSNA (Snook KL, Layer GT, Jackson PA, de Vries CS, Shousha S, Sinnett HD, *et al.* Multicentre evaluation of intraoperative molecular analysis of sentinel lymph nodes in breast carcinoma. *Br J Surg* 2011;**98**:527–35). Using TAB-adjusted values reported by Snook *et al.*, histopathology compared with full-node OSNA had ICERs of < £10,000 per QALY gained using NHS reference costs or York Health Economics Consortium costs (Snook *et al.* 2011). However, when values from the study by Khaddage *et al.* were used, full-node OSNA dominated both half-node OSNA and histopathology under both costing scenarios (Khaddage A, Berremila SA, Forest F, Clemenson A, Bouteille C, Seffert P, *et al.* Implementation of molecular intra-operative assessment of sentinel lymph node in breast cancer. *Anticancer Res* 2011;**31**:585–90).

The long-term ICERs for histopathology compared with full-node OSNA remained at < £20,000 per QALY gained for all values of sensitivity up to 95% and the ICER was £8430 per QALY gained when OSNA had 100% specificity.

Sensitivity analysis was also conducted on the effect of the prevalence of SLN metastases in the patient population. This showed that the lower the prevalence the more attractive histopathology is.

Probabilistic analysis showed that, when comparing full-node OSNA with histopathology, the former has less than a one in three probability of being cost-effective. This result was obtained by combining all of the available accuracy estimates from the three studies that adjusted for TAB. This finding was driven by the studies of Le Frère-Belda *et al.* and Snook *et al.*, which contributed 88% of all patients with available data (Le Frère-Belda MA, Bats AS, Gillaizeau F, Poulet B, Clough KB, Nos C, *et al.* Diagnostic performance of one-step nucleic acid amplification for intraoperative sentinel node metastasis detection in breast cancer patients. *Int J Cancer* 2012;**130**:2377–86; Snook *et al.* 2011).

Altering individual costs and utility parameter values in both sections of the model had very little impact on overall cost-effectiveness results.

Results for Metasin were provided on a purely illustrative basis as the only values available for the sensitivity and specificity of Metasin are unpublished and have not been peer reviewed.

Conclusions

The evidence base for OSNA and Metasin is restricted to studies on their test accuracy (sensitivity and specificity) relative to a reference standard of histopathology. All other conclusions are based on the predictions of a health economic model in a linked-evidence approach.

One-step nucleic acid amplification and Metasin appear to be effective in reducing the number of separate second ALND operations, which leads to cost-savings and benefits to patients. However, this is at the expense of diagnostic errors, both false negatives and false positives.

Overall, the cost-effectiveness evidence on OSNA is inconclusive. The evidence on Metasin is incipient and may only be suggestive. In general, the potential long-term benefits of increased accuracy with histopathology more than compensate for its disadvantage in terms of expediency of test results, but such balance is sensitive to how different studies address the issue of TAB.

The available evidence suggests that full-node OSNA is not cost-effective relative to histopathology. The only study that contradicts this assertion (that by Khaddage *et al.* 2011) represents only 11% of the total study subjects for whom robust evidence exists.

Exploratory analyses clearly suggest that the cost-effectiveness of intraoperative testing is inversely related to the node-positive prevalence rate. Therefore, improvements in the detection of node-positive cases before the first operation for newly diagnosed breast cancer will make the cost-effectiveness of intraoperative testing less likely.

Suggested research priorities

Devoting resources to generating peer-reviewed published research evidence on the test accuracy of Metasin, the costs of alternative tests and the variation in resource utilisation across individual patients is warranted by current limitations in our knowledge on the value of diagnostic approaches in early breast cancer. Observational studies may seek to test and quantify empirically the claimed reductions in the numbers of operations, the anxiety experienced by patients who await test results, the quality of life lost as a result of a second operation and the costs to hospitals that are associated with the introduction of intraoperative testing in SLNB.

A key assumption in the report is that ALND is the usual best treatment if micro- and macrometastases are identified in a SLNB. Evidence on this is evolving and needs to be followed closely as it could impact on decisions about intraoperative testing in SLNB in the future.

Study registration

This study is registered as PROSPERO CRD42012002889.

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