NICE advice

OSNA for colon cancer staging

Medtech innovation briefing
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Summary

- The **technology** described in this briefing is the OSNA in vitro diagnostic molecular assay system. It is used for detecting lymph node metastases in people with colon cancer.
- The **innovative aspects** of OSNA are that unlike standard histopathology, OSNA can analyse the whole lymph node as well as partial lymph nodes. This may improve cancer staging accuracy because it reduces tissue allocation bias.
- The intended **place in therapy** would be as an alternative to standard post-operative histopathology for lymph node staging in people after surgical resection for early-stage colon cancer.
- The **key points from the evidence** summarised in this briefing are from 3 prospective observational studies including 253 people. The studies found that the diagnostic performance of OSNA was better than standard histopathology and that the results with OSNA led to upstaging from lymph node negative to lymph node positive in up to one-quarter of the study population.
- **A key uncertainty** around the evidence is that none of the studies investigated OSNA

for analysing the whole lymph node, which is described as a key innovation for the system.

- The average **cost** per patient (including capital, maintenance, and disposable costs) ranges from £568 to £608 (excluding VAT), depending on the cost of disposables (reagents and consumables).

The technology

OSNA (one-step nucleic acid amplification; Sysmex Corporation) is an automated molecular assay system, which is designed to detect metastatic colon cancer cells in the lymph nodes (LNs). It detects the level of expression of the cytokeratin-19 (CK19) gene, a tissue biomarker, the levels of which correlate with the number of metastatic cells.

The system consists of the RD-100i automated real-time nucleic acid analyser unit and the Lynoamp HTS reagent kit, containing all the reagents needed for preparing samples and carrying out the analysis.

During surgery for colon cancer, cancerous parts of the colon and regional lymph nodes are routinely surgically removed, packed on ice, and sent directly to the histopathology laboratory. The OSNA test can be used to analyse LNs weighing 50–600 mg, which must be harvested from fresh tissue within 60 minutes of removal. Each LN is processed according to the manufacturer's instructions, giving a single sample per LN.

Up to 8 samples can be placed in the RD-100i unit for analysis at the same time. The unit adds reagent, with the primers, nucleotides, enzyme and buffer needed for CK19 expression amplification, to the samples, and then does the test and analysis. The time taken to produce results, excluding harvesting the LNs, depends on the number of LN samples being analysed; for example, about 30 to 45 minutes for 8 samples and about 90 minutes for 12 samples.

Results are allocated to one of 3 categories: (++) indicates a macrometastatic tumour burden; (+) indicates a micrometastatic tumour burden; and (–) indicates no metastatic disease. Results correlate directly with the measured copy numbers of CK19 mRNA.

The OSNA technology can also be used to detect lymph node metastases in people with breast or gastric cancer, but these uses are beyond the scope of this briefing.

The innovation

In standard post-operative histopathology, in which partial LNs are analysed, there is a risk that metastatic foci that may be unevenly distributed throughout the LN, are missed. OSNA can analyse whole or partial LNs, with the aim of eliminating or reducing the risk of tissue allocation bias.

Results of OSNA are available in a relatively short time, and so intraoperative analysis of sentinel LNs (those located near the tumour) may in future be possible, although this method of analysis has not been established in routine clinical practice.

Current NHS options

Surgical resection is the main treatment for early stage colon cancer. A pathologist assesses the resected colon tissue to grade and stage the cancer. Resected tissue is processed and cut into sections or levels, stained using haematoxylin and eosin, and examined under a microscope by a consultant histopathologist. The Royal College of Pathologists, in its standards and datasets for reporting cancers, recommends that at least 12 regional LNs from the resected tissue should be investigated. The guidance recommends embedding each whole LN, if it is less than 4 mm, or removing a central block through the longest axis for larger nodes. Typically, a single section is cut and examined from each node.

NICE's guideline on diagnosing and managing colorectal cancer recommends that pathological characteristics of the lesion, imaging results and previous treatments should be considered when deciding further treatment in locally excised, pathologically confirmed stage I cancer.

Population, setting and likely place in therapy

OSNA may be used for LN analysis in people with early stage colon cancer as an alternative to standard post-operative histopathology.

OSNA is intended for use in secondary care by pathologists or biomedical scientists, who have been trained to use the system.

Costs

Device costs

Table 1 shows the unit price for each component of the technology.

Table 1 Prices of standard OSNA components (excluding VAT)

Product	Price per unit
RD-100i including image processing unit, monitor and keyboard	£74,031.10
Fastprep-24 complete instrument	£7,098
Lynoamp HTS kit	£2,284.40
Lynorhag	£206.60
Pipette tips	£345.70
Detector cells	£325.10

Note: The Lynoamp HTS kit is for colorectal cancer only. All other components listed are generic and can also be used for other cancer analyses.

The cost of additional consumables and reagents would vary depending on how many samples are tested in each batch. For example, based on analysing 12 LNs per patient, the indicative cost of disposables is £550 to £590 per patient (excluding VAT). The cost could be as low as £33.50 per LN if the consumables are maximised and samples from more than 1 patient are tested in a single batch. The system has a 12-month warranty, and the current price of an annual maintenance contract for the system (which would apply from year 2 after installation) is £6,628.48 (excluding VAT).

The manufacturer states that the lifespan of the OSNA system is at least 6 years. The test takes about 90 minutes for 12 LN samples, so samples from up to 5 patients can be analysed per day (7.5 hours), and 1,200 in 1 year (240 annual working days). Using the standard annuity method with a discount rate of 3.5%, the average cost per patient (including capital, maintenance, and disposable costs) ranges from £568 to £608, depending on the cost of disposables.

The manufacturer offers procurement of the system via a 5-year lease rental or reagent rental option (in which the analyser is provided and reagents are bought on a cost-per-test

basis). For the reagent rental, the cost per patient depends on the number of patients whose samples are analysed in the centre.

Costs of standard care

NHS reference costs 2013 to 2014 list the cost of histopathology and histology (DAPS02) as £10, but there is no stratification of histopathology by sample type (for example, type of specimen or tissue preparation), which may affect the cost.

Resource consequences

Training is included in the purchase price and no additional facilities or devices would be needed alongside the OSNA system. Fresh tissue harvesting is not routine practice in NHS laboratories, therefore additional OSNA training includes discussion of the awareness needed to avoid contamination of molecular tests, which can be associated with fresh tissue harvesting. No other practical difficulties have been identified in using or adopting the technology.

In the absence of published economic evaluations for OSNA and post-operative histopathology for colon cancer, the economic consequences of using OSNA in the NHS are unclear.

OSNA is currently being evaluated for use in colon cancer in 1 NHS hospital in Wales.

Regulatory information

OSNA was CE marked as an in vitro diagnostic medical device in March 2006. The product is regulated under the medical device (98/79/EC) directive and is classed as a general device.

A search of the Medicines and Healthcare Products Regulatory Agency website identified no manufacturer Field Safety Notices or Medical Device Alerts for this technology.

Equality considerations

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering

good relations between people with particular protected characteristics and others. In producing guidance and advice, NICE aims to comply fully with all legal obligations to: promote race and disability equality and equality of opportunity between men and women, eliminate unlawful discrimination on grounds of race, disability, age, sex, gender reassignment, marriage and civil partnership, pregnancy and maternity (including women post-delivery), sexual orientation, and religion or belief (these are protected characteristics under the Equality Act 2010).

Most people with colorectal cancer are over 60 years. Some bowel conditions, such as severe ulcerative colitis or Crohn's disease, increase the risk of developing colorectal cancer. People with these conditions may be considered to be disabled under the Equality Act if the condition has a substantial and long-term adverse effect on their ability to carry out normal day-to-day activities. Age and disability are protected characteristics under the Equality Act 2010. People with cancer are protected under the Act from the point of diagnosis.

Clinical and technical evidence

A literature search was carried out for this briefing in accordance with the published process and methods statement. This briefing includes the most relevant or best available published evidence relating to the clinical effectiveness of the technology. Further information about how the evidence for this briefing was selected is available on request by contacting mibs@nice.org.uk.

Published evidence

Three prospective observational studies were selected for inclusion (n=2,232 lymph node [LN] specimens from 253 people) and reported that the diagnostic performance of OSNA was better than standard histopathology.

Table 2 summarises the clinical evidence as well as its strengths and limitations.

Table 2 Summary of selected studies

Study	Intervention and comparators	Outcomes	Strengths and limitations
Guller et al. 2012 313 LNs from 22 patients (stages I, II and III), prospective observational study. Single centre (Switzerland).	OSNA Standard single-level H&E staining histopathology. Intensive histopathology (5 levels of H&E staining and immuno-histochemistry analyses).	OSNA had a diagnostic performance similar to intensive histopathology and was better than standard H&E staining analysis. Cancer staged as LN negative by standard H&E staining histopathology in 2 of 13 patients was upstaged as LN positive by OSNA. Compared with intensive histopathology, OSNA had 94.5% sensitivity, 97.6% specificity, and a concordance rate of 97.1%.	The study received manufacturer funding. The study did not analyse whole LNs. A key innovation of the OSNA system is that whole LNs can be analysed, reducing the risk of tissue allocation bias. To prevent selection bias, each LN was divided, with 1 portion being analysed using OSNA and the remaining portion being analysed using standard histopathology or intensive histopathology. The sample included a mix of patients with early and advanced stage colon cancer. OSNA is designed for use in people with early stage colon cancer.

Study	Intervention and comparators	Outcomes	Strengths and limitations
Croner et al. (2014) 1,594 LNs from 103 patients (stages I and II), prospective observational study. Multicentre (Germany, Switzerland, Spain).	OSNA Standard single level H&E staining histopathology.	Cancer staged as LN negative by standard H&E staining histopathology in 26 of 103 patients was upstaged as LN positive by OSNA.	The manufacturer sponsored the study. The study did not analyse whole LNs.
Vogelaar et al. (2014) 325 sentinel LNs from 128 patients (stages I and II), prospective observational study. Multicentre (The Netherlands).	OSNA Standard single level H&E staining histopathology. Intensive histopathology (4 levels of H&E staining and immunohisto-chemistry analyses).	Cancer staged as LN negative by standard H&E staining histopathology in 20 of 99 patients was upstaged as LN positive by OSNA. Cancer staged as LN negative by standard H&E staining histopathology in 36 of 99 patients was upstaged as LN positive by intensive histopathology.	The study did not analyse whole LNs. OSNA is designed to detect levels of a tumour biomarker rather than isolated tumour cells, which may account for the difference in results between OSNA and intensive histopathology. Sampling bias may also have affected the results, because the authors noted that tumour cells were only present in specimens analysed by intensive histopathology. The manufacturer provided technical support and study material.

Abbreviations: H&E, haematoxylin and eosin; LN, lymph node.

Strengths and limitations of the evidence

None of the studies were done in the UK, which may affect their generalisability to the NHS. Although all the studies were prospective in design, none were randomised controlled trials which would have helped to systematically control for biases. All 3 studies were observational rather than randomised controlled studies.

Two studies investigated OSNA in LNs, and 1 study assessed OSNA in sentinel LNs. LNs have a differing potential to sentinel LNs to harbour metastases, so the study results may not be directly comparable.

Two studies assessed at least 12 LNs for each patient. Croner et al. (2014) examined a median of 14 LNs (range 5 to 46), and Guller et al. (2012) a median of 13 LNs (range 6 to 24) using OSNA. A third study examined a maximum of 3 sentinel LNs for each patient (Vogelaar et al. 2014). The standard in the NHS is to analyse 12 or more LNs.

Overall, the population complied with the indication for using the test. Two studies only included people with early-stage colon cancer, but the third study also included people with advanced colon cancer. OSNA is designed to be used in people with early-stage colon cancer. People with advanced colon cancer (defined as TNM stage III or IV) will by definition already have been diagnosed with metastatic disease in the LNs.

Post-operative histopathology is the usual approach in the NHS to stage and grade colon cancer. The number of levels examined using histopathology can affect accuracy; more levels can reduce the risk of tissue allocation bias. Typically, a single section is cut from each LN, however the current practice for handling LNs is not uniform and so may vary locally. All studies used single level histopathology as the standard comparator. The number of levels used in intensive histopathology varied in Vogelaar et al. (2014) and Guller et al. (2012) so study results may not be directly comparable. The intensive histopathology approach (including immunohistochemistry) in Guller et al. (2012) may have been more accurate because more levels were examined.

Recent and ongoing studies

No ongoing or in-development trials were identified.

Specialist commentator comments

The specialist commentators noted that the OSNA system can be used to analyse the whole LN, which may be an advantage compared with conventional histopathology. OSNA has the potential to be highly promising for colon cancer staging as either a replacement or adjunctive technique. OSNA may increase the sensitivity of detecting LN metastases compared with conventional analysis and could increase the number of people who would benefit from chemotherapy. People with metastases that are not detected with conventional analyses are currently undertreated. One commentator noted that being able to assess whole LNs may be a useful adjunct in detecting occult tumour cells (that are defined by the presence of LN metastases with an unknown primary tumour). The presence of occult tumour cells is an important prognostic variable, but can be overlooked by conventional histopathology.

The specialist commentators raised several concerns about the potential benefits of OSNA. The benefit for people whose cancer has been upstaged by OSNA cannot be assumed to be the same as for people whose cancer was conventionally staged as LN positive and needs prospective assessment. Extracapsular LN involvement is becoming a significant prognostic factor, but this would not be detected by OSNA. In this context, 1 commentator suggested that although useful, particularly for assessing sentinel LNs, OSNA should not replace detailed histological analysis.

The specialists noted that the evidence base for OSNA in colon cancer is limited. One commentator suggested that the upstaging of colon cancer based on OSNA results could be related to detecting micrometastasis rather than macrometastasis, and questioned the benefit of detecting micrometastasis. The clinical role of micrometastasis seems unclear and so the effect on patient care has yet to be shown. If OSNA is mainly detecting micrometastasis and performs similarly to intensive histopathology with immunohistochemistry as shown in 1 of the studies, then this may be the more appropriate comparator (as opposed to conventional histopathology). One specialist noted a growing number of studies showing that marker genes (such as cytokeratin-19) for metastatic cells in LNs in colorectal cancer are better than conventional histology using haematoxylin and eosin staining, suggesting that using cytokeratin-19 mRNA is a valid method of cancer staging.

One specialist commentator noted that OSNA did not seem to be overly expensive and carried no risk for patients. However, another commentator suggested that the cost of offering the OSNA test to all patients with early colon cancer would be unjustifiable

without stronger evidence showing that the test would have an effect on outcome for patients. If OSNA only detects a small proportion of people with LN macrometastases, then the cost–benefits of investment also need consideration.

Long-term trials would be needed to look at overall survival in patients tested using OSNA compared with current standard techniques. The primary measureable benefit of OSNA would be in the improved survival of patients whose cancer had been upstaged. More subtle aspects, such as toxicity and quality of life, would also be ideally assessed.

Patient organisation comments

Beating Bowel Cancer stated that, based on contact with people affected by bowel cancer, it was supportive of a technology (such as OSNA) which aims to improves staging, leads to earlier diagnoses and treatment, and improves outcomes. It speculated whether OSNA could support more personalised treatment plans and pathways, possibly improving outcomes. It supports technology that could help provide care that is more suited to the needs of specific patients. It noted that any financial assessment should show the full benefits of earlier diagnosis and intervention, such as savings on typically more costly later stage treatment. It highlighted the benefits of earlier diagnosis, citing part 2 of a report by Incisive Health for Cancer Research UK on delivering world-leading cancer service (2015), which suggested that if all clinical commissioning groups could achieve the same level of early cancer diagnosis as the best ones in England then 'savings of over £24 million could be realised (benefitting over 4,500 patients)'.

Specialist commentators

Comments on this technology were invited from clinical experts working in the field and relevant patient organisations. The comments received are individual opinions and do not represent NICE's view.

The following clinicians contributed to this briefing:

- Mr Alec Engledow, Consultant Colorectal Surgeon, University College London Hospitals, no conflicts of interest declared.
- Professor John Bridgewater, Consultant Medical Oncologist, University College London Hospitals, no conflicts of interest declared.

- Mr Pasquale Giordano, Consultant Colorectal Surgeon, Whipps Cross University Hospital, no conflicts of interest declared.
- Professor Sir Nick Wright, Professor of Histopathology, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, no conflicts of interest declared.

Representatives from the following patient organisations contributed to this briefing:

- Beating Bowel Cancer

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