Horizon Scanning in Surgery: Application to Surgical Education and Practice

Sentinel lymph node mapping for colorectal cancer

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This report is not a comprehensive systematic review. Rather, it is an assessment of an emerging surgical procedure or technology in which the methodology has been limited in one or more areas to shorten the timeline for its completion.

Therefore, this report is a limited evidence-based assessment that is based on a search of studies published in the peer-reviewed literature. This report is based on information available at the time of research and cannot be expected to cover any developments arising from subsequent improvements in health technologies. This report is based on a limited literature search and is not a definitive statement on the safety, effectiveness or cost-effectiveness of the health technology covered.

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Objective

This horizon scanning assessment provides short, rapidly completed, 'state of play' documents. These provide current information on technologies to alert clinicians, planners and policy makers of the advent and potential impact of a new or emerging procedure or device. This information can then assist clinicians, planners and policy makers to control and monitor the introduction of new health technologies as well as assist in the prioritization and allocation of resources to promote efficient utilization of available resources.

Introduction

Indications

The identification and removal of regional lymph nodes in patients with solid neoplasms is essential for accurate cancer staging, assessment of prognosis, and determination of adjuvant therapies (Saha et al 2004). For more than 100 years, radical lymphadenectomy has been the diagnostic and therapeutic gold standard for the management of metastatic nodal disease, despite the well-known morbidities associated with the procedure, such as lymphadema and nerve damage (Saha et al 2004). In conventional nodal staging, the resected lymph nodes are stained with hematoxylin and eosin (H&E) and examined by a pathologist (Chen et al. 2006).

In patients with cancer, the sentinel lymph node (SLN) is commonly defined as the first lymph node that receives lymphatic drainage from the primary tumor (Chen et al 2006). It is thought that the localization, removal and histopathological analysis of SLNs can provide important information on the spread of the primary tumor through the lymph system. SLN mapping was developed as an alternative method for accurately staging the nodal disease status associated with solid tumors so that radical lymphadenectomy may be performed selectively, thus sparing

many patients from the morbidities associated with the procedure (Saha et al 2004). In addition, advances in cancer screening techniques have increased the proportion of solid tumors detected at earlier stages of disease, thus reducing the need for complete removal of the regional lymph nodes. SLN biopsy has already proven useful in patients with skin melanoma and breast cancer (Sticca 2006).

In colorectal cancer, lymph node status after tumor resection is one of the most important prognostic factors used to determine treatment as the presence and extent of nodal metastases assist in estimating survival and local-regional failure. Nodal metastasis occurs in 65% of colorectal cancer cases irrespective of the size of the primary tumor (Fazio and Kiran 2003). Patients with nodal disease are usually given adjuvant chemotherapy because this has been shown to reduce mortality and recurrence by up to 33% and 40%, respectively, but there is no definitive evidence of benefit in patients who are node-negative (Stage II[1]) (Fricker 2006, de Haas et al 2007). The 5-year survival of node-positive patients is 45% to 50% compared with 80% for node-negative patients (Fazio and Kiran 2003). While it is possible that a considerable number of node-negative patients have occult nodal metastases that are not detected by conventional histopathological analysis, administering adjuvant chemotherapy to all Stage II patients is both unnecessary and costly (de Haas et al 2007).

Burden of disease

Colorectal cancer is the second most common malignancy in developed countries, and is the second leading cause of cancer-related death worldwide (van Scheltinga et al 2006). In the United States, colorectal cancer is the third most common cause of cancer-related mortality (Saha et al 2000). In 2009, 146,970 new cases of colorectal cancer were diagnosed in the United Stated, and approximately 49,920 people died from the disease (National Cancer Institute 2010).

Approximately 20% to 30% of node-negative patients eventually die as a result of local tumor relapse or overwhelming metastatic disease (de Haas et al 2007). Systemic tumor recurrence can be partly explained by hematogenous spread without lymphatic metastases; however, another explanation for this is the failure of conventional histopathologic examination to identity lymph node micrometastases (Deelstra et al 2008). Standard surgical protocols, such as total mesocolon/rectum excision, do not take into account aberrant lymph drainage patterns or lymph nodes anatomically distant from the primary tumor. Therefore, these aberrant lymph nodes are often not resected even though they may harbor metastatic disease (Deelstra et al 2008).

Technology

Sentinel node identification involves injecting a tracer to map the lymphatic drainage pathway from the tumor. The most common mapping techniques use a combination of blue dye and radioisotope as their tracer, or blue dye or radioisotope alone (Chen et al 2006). SLN mapping may be employed as an *in vivo* or *ex vivo* technique. In patients with colorectal cancer, *in vivo* SLN mappinig involves injecting the tracer into the subserosal surface of the bowel immediately adjacent to the base of the tumor. After several minutes, the mesentery is visually inspected to determine the location of sentinel nodes, which are characterized by the uptake of blue dye. If a radioisotope tracer was injected, a gamma counter is also used to pinpoint the nodes. All SLNs are marked with sutures or clips and are later removed and examined for tumor cells by a

[1] **Stages of colorectal cancer:** ***Stage 0/T0*** refers to a very early stage of colorectal cancer where the cancer cells are confined within the lining of the bowel; ***Stage 1/T1*** indicates that the cancer has grown through the inner lining of the bowel but there is no cancer in lymph nodes; ***Stage 2/T2*** indicates that the cancer has grown through the outer covering of the bowel into tissues or organs next to bowel but there is no spread to the lymph nodes or another area of the body; ***Stage 3/T3*** indicates the cancer has spread to the lymph nodes but not to other areas of the body; ***Stage 4/T4*** indicates the cancer has spread to other parts of the body via the lymphatic system or bloodstream.

pathologist (Read et al 2005). In the *ex vivo* technique the tracer is injected into the subserosal surface of the tumor immediately after its removal from the patient. The identified SLNs are then marked and submitted for pathologic examination, as in the *in vivo* technique.

In order to detect nodal metastases, SLN mapping utilizes intensive 'ultrastaging' techniques, which require fewer nodes and are less costly than conventional pathologic examination. Ultrastaging utilizes a combination of three techniques (Chen et al 2006):

1. Serial sectioning, which involves making a number of consecutive cuts in the SLN (identified by the previously mentioned modalities) so that each section can undergo immunohistochemical examination
2. Immunohistochemistry (IHC), which involves the microscopic localization of specific antigen markers (i.e. S-100 proteins) for colorectal micrometastases or isolated tumor cells using specific antibodies labeled with fluorescent or pigmented material
3. Reverse-transcriptase polymerase chain reaction (RT-PCR), where amplification of a sequence of DNA is achieved by first reverse-transcribing a RNA sequence into its DNA complement using the enzyme reverse-transcriptase. This complementary DNA is then amplified using real-time PCR methods and used to detect a single tumor cell among 10 million normal cells (Lindblom 1998).

Stage of development

SLN sampling is routinely used in the United States for skin melanoma and breast cancer. In the 1980s researchers at the University of California developed the technique of lymphatic mapping to identify SLNs in patients with melanoma, and SLN mapping for breast cancer was first reported in 1994 (National Cancer Institute 2005). Since this time techniques of SLN mapping have developed and improved. The use of SLN mapping in patients with colorectal cancer appears to be less routine in the United States, with trials recently being conducted.

International utilization
SLN mapping for colorectal cancer appears to be in use in France, Italy, the Netherlands and Japan.

Current clinical trials
Searches of Current Controlled Trials *meta*Register (which encompasses searches of multiple trial registers including NHS in England and US clinicaltrials.gov) for clinical trials using broad search terms such as 'sentinel node' and 'colorectal cancer' did not reveal any relevant trials. The trials retrieved from these searches applied almost exclusively to breast cancers and skin melanomas.

Current treatment and alternatives

The comparator of SLN mapping for colorectal cancer is conventional nodal staging, which involves resecting all regional lymph nodes and subjecting them to standard histopathological analysis. Accurate cancer staging requires a detailed analysis of all lymph nodes recovered; however, because this is impractical, labor intensive, time consuming and expensive, resected nodes are usually only halved and then stained with H&E before being examined by a pathologist (Chen et al 2006). Examining only one to two sections of the node increases the likelihood of tumor cells being missed. As well as this, micrometastases might not be visible using conventional histological techniques; therefore, sampling fewer (sentinel) nodes more thoroughly may be a more efficient way of detecting and staging cancer.

Literature review

Objective

Compare the diagnostic accuracy of SLN mapping with conventional nodal staging in patients with colorectal cancer. Studies may utilize SLN mapping in place of, or in conjunction with, conventional mapping.

Search criteria

Keyword/MeSH terms utilized:
Keywords: sentinel lymph node, sentinel lymph node mapping, sentinel lymph node biops*, lymph node excision, neoplasm staging, colonic neoplasm*, colorectal cancer, colorectal tumo*

MeSH terms: Sentinel lymph node biopsy, Lymph node excision, Neoplasm staging, Colorectal neoplasms, Sentinel lymph node, Lymph node, Lymphadenectomy, Cancer staging, Colon tumor, Colorectal cancer.

Databases utilized:
PubMed, EMBASE

Inclusion criteria

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Systematic reviews; randomized controlled trials; non-randomized comparative studies[2]
Patient	Patients with colorectal (not anal) cancer undergoing tumor resection
Intervention	Sentinel lymph node mapping using *ex vivo* or *in vivo* identification techniques
Comparator	Conventional lymph node mapping
Outcome	Sentinel lymph node detection rate, true/false-negative rate, true/false-positive rate, sensitivity/specificity, cancer upstaging rate, survival rate
Language	English only

Included studies[3]

A total of 316 studies were identified using the above search strategy. Of these 77 articles were potential inclusions in this report. Closer investigation of the potential studies revealed a total of eight studies eligible for inclusion. These included five systematic reviews, one randomized controlled trial (RCT), and two non-randomized comparative studies. Excluded studies, along with the reason for their exclusion are presented in Appendix A. Table 2 below describes the level of evidence and characteristics of the included studies in greater detail.

[2] Comparative studies reported in detail in an included systematic review were not reported separately.

[3] Study selection and quality appraisal was undertaken by one reviewer and data extraction was undertaken by one reviewer and checked by a second reviewer.

Table 2 Characteristics of included studies

Study/Location	Level of Evidence (Appendix B)	Search end date	Number of studies and/or patients	Identification technique	Aim/Comparison
Cahill et al 2008 *France*	Pseudo level I	July 30 2008	52 studies Level III (n=8)* Level IV (n=44)* 3390 patients	*In vivo* only (n= 40 studies) Supplementary *ex vivo* (n= 12 studies)	Determine the diagnostic accuracy of *in vivo* sentinel lymph node mapping.
de Haas et al 2007 *The Netherlands*	Pseudo level I	December 1 2005	17 studies Level IV (n=17) 914 patients	*In vivo* only (n=15 studies) *Ex vivo* only (n=2 studies)	Determine the diagnostic accuracy of sentinel lymph node mapping with blue dye versus combination blue dye and radioactive tracer.
Des Guetz et al 2007 *France*	Pseudo level I (with meta-analysis)	May 1 2006	33 studies Level III (n=1)* Level IV (n=32)* 1794 patients	*In vivo* only (n=18 studies) *Ex vivo* only (n=11 studies) *In vivo* and *ex vivo* (n=4 studies)	Determine the diagnostic accuracy of sentinel lymph node mapping.
Doekhie et al 2005 *The Netherlands*	Pseudo level I	2004	25 studies Level III (n=2)* Level IV (n=23)* 1163 patients	*In vivo* only (n= 19 studies) *Ex vivo* only (n=3 studies) *In vivo* and *ex vivo* (n=3 studies)	Determine the diagnostic accuracy of sentinel lymph node mapping with blue dye versus radioactive tracer versus combination blue dye and radioactive tracer.
Tuech et al 2004 *France*	Pseudo level I	December 2003	17 studies Level IV (n=17)* 682 patients	*In vivo* only (n=15 studies) *Ex vivo* only (n=2 studies)	Determine the diagnostic accuracy of sentinel lymph node mapping.
Stojadinovic et al 2007 *US, Israel, Serbia*	Level II	NA	175 patients	*Ex vivo*	Compare the diagnostic accuracy of step sectioning and cytokeratin immunohistochemistry of sentinel lymph nodes versus conventional histopathology.
van der Zaag et al 2009 *The Netherlands*	Level III-2	NA	132 patients	*Ex vivo*	Compare the diagnostic accuracy of sentinel node mapping in patients with colon cancer versus rectal cancer.
Nagata et al 2006 *Japan*	Level III-3	NA	48 patients	NR; likely to be *in vivo*	Compare the diagnostic accuracy of sentinel lymph node mapping using infrared ray laparoscopy versus conventional laparoscopy.

*Level of evidence of included studies was not reported Examination of included studies abstracts was used to obtain these values.
Patient overlap was apparent:

	Cahill et al	de Haas et al	Des Guetz et al	Doekhie et al	Tuech et al
Cahill et al	NA	16 studies	18 studies	14 studies	9 studies
de Haas et al	16 studies	NA	10 studies	8 studies	7 studies
Des Guetz et al	18 studies	10 studies	NA	20 studies	10 studies
Doekhie et al	14 studies	8 studies	20 studies	NA	13 studies
Tuech et al	9 studies	7 studies	10 studies	13 studies	NA

	Cahill et al	de Haas et al	Des Guetz et al	Doekhie et al	Tuech et al
Cahill et al	NA	16 studies	18 studies	14 studies	9 studies
de Haas et al	16 studies	NA	10 studies	8 studies	7 studies
Des Guetz et al	18 studies	10 studies	NA	20 studies	10 studies
Doekhie et al	14 studies	8 studies	20 studies	NA	13 studies
Tuech et al	9 studies	7 studies	10 studies	13 studies	NA

Critical appraisal

Systematic review evidence

Five systematic reviews were considered eligible for appraisal and inclusion in this report (Cahill et al 2008; de Haas et al 2007; Des Guetz et al 2007; Doekhie et al 2005; Tuech et al 2004). Evidence tables of included papers are presented in Appendix C in date and alphabetical order.

Cahill et al (2008), the largest and most recent of the included systematic reviews, assessed *in vivo* SLN mapping techniques in regards to its accuracy detecting early stage disease. In this study, a comprehensive search of the Cochrane Library, PubMed and EMBASE databases was conducted to identify studies published from January 1st 1999 to July 30th 2008. The search terms used were broad and included appropriate MeSH terms. This systematic review was the most methodologically sound of those included, with a focused clinical question, and explicit and thorough inclusion and exclusion criteria provided. Date and language (English-language only) limitations were used. The review presented a sufficient description of study selection, data extraction, and appraisal methods. For example, each study identified was analyzed for suitability of inclusion according to an evidenced base tool for the assessment of the quality of diagnostic assessment studies (QUADAS), and two separate researchers were responsible for data extraction (using tables developed *a priori*). Third party mediation was undertaken to resolve disagreements where necessary. Reference lists of all full publications retrieved were cross-checked for additional relevant publications; however, hand-searching of relevant journals was not reported. As well as this, possible patient duplication across the included studies was noted but no exclusions were made.

Inclusion criteria stated that only studies reporting outcomes in patients with colon cancer would be included, and it was intended that studies reporting outcomes in patients with rectal cancer would be excluded. As well as this, only studies using *in vivo* SLN mapping techniques were eligible for inclusion. In reality, studies that reported outcomes in patients with colon and rectal cancer (but did not separate them in their results) were included in the review, despite pre-determined exclusion criteria.

de Haas et al (2007) assessed the current status of SLN mapping in patients with colon cancer, in regards to the feasibility and accuracy of the different techniques. This systematic review included seventeen studies, of these 15 described SLN mapping using blue dye and two described SLN mapping using a combination of blue dye and radioisotope tracers.

PubMed was the only database searched to identify studies published from inception to December 1st 2005. The search terms used were provided and were sufficiently broad. Language restrictions were used to limit the evidence base to English-language only. Study selection and appraisal methodology were described and included identifying potentially relevant studies by their title and abstract and determining their level of evidence using a ranking system provided by the authors. It is unclear how many researchers were involved in this process or whether a formal quality appraisal tool was employed. Extensive inclusion and exclusion criteria were also described. Prospective studies assessing SLN mapping, both *in vivo* and *ex vivo*, in patients with colon cancer were eligible for inclusion.

Cross-referencing of the papers initially retrieved from the search took place to identify further articles eligible for inclusion. Hand-searching of relevant journals was not reported.

Des Guetz et al (2007) compared the diagnostic accuracy of SLN mapping with that of the reference standard (conventional histopathologic examination) through a systematic review of the literature and meta-analysis.

The search strategy employed in this study utilized one database (PubMed) and simple search terms (colorectal cancer AND sentinel node). There were no date limitations in place and the language of the included studies was limited to English and French. Brief inclusion and exclusion criteria were described, with studies dealing with either colon or rectal cancer eligible for inclusion. Studies that dealt with cancer at sites other than the colon or rectum, case reports, and animal studies were not eligible for inclusion. Additional studies not retrieved from the PubMed search were obtained from hand-searching of the retrieved studies' (including reviews and editorials) reference lists, and abstracts from the American Society of Clinical Oncology's annual meetings from 1998-2004 were also searched.

Study selection, data extraction and appraisal methodology was clearly provided. Information was independently extracted from all of the included studies by two researchers using standardized data collection forms. Discrepancies in the data extracted were resolved by discussion between the two researchers. The authors state that studies were not assigned a weight by a quality score because no such score had received general agreement for use in meta-analysis, especially for observational studies. Duplication of data was avoided by examining each included publication for repetition in authors' names and the institutions at which the trial took place. Where duplicate studies were identified, the study with the largest number of patients from which data could be extracted and/or the most recently published study was included in the review. The meta-analysis that took place in this systematic review was conducted according to a predefined written protocol.

The systematic review by Doekhie et al (2005) assessed the feasibility and reliability of SLN mapping in patients with colorectal cancer, with particular emphasis on the differences in mapping techniques used.

Again, PubMed was the only database searched; however, cross-referencing of the papers retrieved from the search took place to identify further relevant studies. Articles published between 1953 and 2004 were identified using specific search term combinations that may have not been adequate in retrieving all articles related to SLN mapping as terms such as 'lymph node' were not used (only 'sentinel'). Only English-language studies were eligible for inclusion. The methodological quality of this review was generally poor. Despite its focused research question, inclusion criteria were not provided and only limited exclusion criteria were reported. In addition study selection methods were described (it is unclear how many researchers were involved in this process) but appraisal of the included studies did not appear to take place. All of the articles identified by the PubMed search were individually checked for suitability of inclusion based on if they addressed the subject of the review. Articles with 'anal cancer' in the title were excluded.

Finally, the systematic review by Tuech et al (2004) evaluated SLN mapping as it applies to colon cancers, with focus on its indications, limitations, benefits, implications, and future direction. A comprehensive search of databases including Current Contents, Medline, EMBASE, and the Cochrane Library was undertaken in order to identify studies published from inception to December 2003. The search strategy was comprehensive and likely to have identified most of the relevant studies. Language restrictions were not reported. Inclusion and exclusion criteria were thoroughly described, with prospective series assessing lymphatic mapping using either an *in vivo* procedure performed via laparotomy or laparoscopy, or an *ex vivo* procedure, eligible for inclusion. Studies were also required to have more than 20 patients in order to be included in the

review. Multiple publications of the same study, abstracts, and case reports were not eligible for inclusion. Study selection methods were described, whereas, data extraction and critical appraisal methods were not.

The authors evaluated the references of each article retrieved from the initial search to find any other report not covered by the electronic search. Hand-searching of relevant journals was not reported.

Randomized controlled trial evidence

One RCT was considered eligible for appraisal and inclusion in this report (Stojadinovic et al 2007). An evidence table for this included paper is presented in Appendix C.

The authors randomly assigned patients with colon cancer to undergo standard complete surgical resection of their tumor-bearing colon with en bloc regional lymphadenectomy followed by conventional histopathologic evaluation (n=82) or SLN mapping, biopsy, and ultrastaging (n=93). The method of randomization used was likely to be adequate in achieving random patient selection for each group, and although allocation concealment for patients and those administering the treatment was not achieved it was unlikely to have confounded the results obtained. A single senior study pathologist, who was blinded to the nodal staging results of each patient, conducted a centralized review of all of the SLN sections. The procedural characteristics of each group, in regards to operative approach (open or laparoscopic), was not significantly different, as were the patients' baseline characteristics in each group. Sample size calculations were performed *a priori* to determine the number of patients required to have 80% power to detect a 25% difference in the proportion of patients with node-positive status using a "two-tailed" test – the result of this test found 69 patients per group would be adequate.

Losses to follow-up did occur after randomization; reasons for these were given in each case; however, intention to treat analyses did not appear to take place.

Non-randomized comparative evidence

Two non-randomized comparative studies were considered eligible for appraisal and inclusion in this report (van der Zaag et al 2009; Nagata et al 2006). Evidence tables of the included papers are presented in Appendix C in date order.

van der Zaag et al (2009) compared the efficacy of SLN mapping in patients with colon cancer versus rectal cancer, and Nagata et al (2006) compared SLN detection using infrared ray laparoscopy with conventional laparoscopy in patients with colorectal cancer. Patient numbers were large in each study; however, statistical calculations to determine the number of patients required to detect significant differences between the groups/interventions were not carried out, therefore it is unknown if the sample sizes employed were sufficient to detect significant differences between the groups/interventions to an acceptable level.

Overall, of the included non-randomized comparative studies, van der Zaag et al (2009) provided brief inclusion criteria and detailed exclusion criteria, and Nagata et al (2006) provided detailed inclusion criteria and no exclusion criteria. Allocation concealment was achieved in one of the non-randomized comparative studies (van der Zaag et al 2009) by having the immunohistochemically stained lymph node slides evaluated independently by two pathologists who were blinded to the clinical data. Nagata et al (2006) did not report if allocation concealment took place in their study.

A summary of the methodological characteristics of the included RCT and non-randomized comparative evidence is presented below in Table 3.

Table 3 Methodological characteristics of included comparative studies

Study/Location	Study period	Randomization method	Number of patients	Operator details	Inclusion criteria	Exclusion criteria	Allocation concealment
van der Zaag et al 2009 *The Netherlands*	November 2006-May 2008	NA	Colon cancer n=100 Rectal cancer n=32 Concurrent control: NR	NR	Colorectal cancer, curative surgery	T4 carcinoma, 2 adjacent colorectal carcinoma, locally advanced rectal cancer undergoing neo-adjuvant chemoradiotherapy	Immunohistochemically stained slides evaluated by two independent, blinded pathologists
Stojadinovic et al 2007 *US, Israel, Serbia*	August 2002-April 2006	Stratified permuted block scheme	Control n=82 Intervention n=93	Six surgeons at 5 medical centers performed all of the procedures	Biopsy-proven, primary, non-metastatic colon carcinoma or colon tumors confirmed by pathology	Recurrent or metastatic colon carcinoma, prior radio-/chemotherapy, non-pathologically confirmed adenocarcinoma	Patients and surgeons not blinded. Single senior pathologist blinded to nodal staging results conducted centralized review of all sentinel node sections
Nagata et al 2006 *Japan*	July 2002-Decemeber 2004	NA	n=48 Concurrent control: none	Three surgeons confirmed all green and black-enhanced nodes	Laparoscopy-assisted colectomy for colorectal or tumors in situ, including malignant polyps partially or completely removed during colonoscopy that required segmental colon resection or large malignancy tumors that could not be removed during colonoscopy	NR	NR

NA: not applicable; NR: not reported; T4 carcinoma: indicates the cancer has spread to other parts of the body via the lymphatic system or bloodstream.

Safety and efficacy

Safety

One systematic review and one non-randomized comparative study provided safety data (Doekhie et al 2005; Nagata et al 2006).

The systematic review by Doekhie et al (2005) stated that there were no reports in its patient population that linked radioactive tracers with allergic reaction or interference with patient monitoring.

The study by Nagata et al (2006) reported that there were no complications specifically related to conventional or infrared ray laparoscopy, and that no patients had their procedures converted to open surgery as a result of uncontrollable bleeding or trauma. This study also reported no incidence of tumor puncture during dye injection.

It is not known if the absence of safety data in many of the included studies means complications did not occur or if, quite simply, safety was not the main concern of the included studies thus was not reported. This report does not provide sufficient data to draw conclusions about the safety of the SLN mapping procedure in patients with colorectal cancer.

Efficacy

All of the included studies reported efficacy outcomes for SLN mapping (van der Zaag et al 2009; Cahill et al 2008; de Haas et al 2007; Des Guetz et al 2007; Stojadinovic et al 2007; Nagata et al 2006; Doekhie et al 2005; Tuech et al 2004). The most common reported outcomes included SLN detection rate, false-negative rate and tumor upstaging rate. Detailed reporting of these and other outcomes are presented in Appendix C.

Accuracy of SLN mapping in patients with colon cancer

Two systematic reviews assessed SLN mapping primarily in patients with colon cancer (Cahill et al 2008; Tuech et al 2004). Considerable variation in SLN detection rate and false-negative rate were apparent in both of these reviews (Table 4 and 5). Cahill et al (2008) reported that according to the use of SLN mapping in breast cancer, detection rates consistently > 90% and false-negative rates consistently < 10% were required to deem SLN mapping in colon cancer acceptable for clinical use. Of the included studies, 21% did not meet the threshold for SLN detection rate and 63% did not meet the threshold for false-negative rate. In the same systematic review, critical appraisal of the included studies reporting low performance results revealed several factors that may have been responsible, including inexperienced surgeons, small sample size (n < 60), mixed patient populations (inclusion of patients with rectal cancer), a high proportion of patients with locally advanced disease (T3/T4 compared with T1/T2), and increased body mass index (BMI). Overall, at least 21 of the studies included in the review by Cahill et al (2008) included patients with T4 tumors within their cohort, and 25 studies possessed high T3/T4 to T1/T2 ratios. In addition, five studies specifically considered tumor length/diameter as a factor that may affect mapping performance; four of these studies found false-negative rate to be higher in patients with larger tumors. One study found a significant positive correlation between tumor size and the quantity of dye required for mapping.

Table 4: SLN detection rate in patients with colon cancer

Study	No. of studies reporting outcome	SLN detection rate range	No. of studies with SLN detection rate >90%	No. of studies with SLN detection rate >95%	No. of studies with 100% SLN detection rate
Cahill et al	52 (100%)	58-100%	41 (79%)	29 (56%)	12 (23%)
Tuech et al	17 (100%)	58-100%	9 (53%)	5 (29%)	2 (12%)

Note: the values presented in the above table were taken from tabled data reported in both systematic reviews, which were contradictory to the values reported in the text.

Tuech et al (2004) noted similar possible causes of variation in detection rates reported in its included studies. Inexperience in lymphatic mapping and multi-surgeon studies may have contributed to the low detection rates observed. In particular, this review performed calculations in regards to the learning curve associated with SLN mapping and found almost 100% SLN detection could be achieved after 5 consecutive cases. Other factors that may have contributed to low detection rates include incomplete circumferential injection of dye around the tumor, large tumors that require larger amounts of dye, obstruction of lymphatic channels in nodes replaced by the tumor, and patients with previous colon surgery that may have altered lymphatic flow pathways.

The studies that used *ex vivo* mapping techniques, included in this systematic review, identified SLNs in 88-92% of patients. *Ex vivo* SLN mapping avoids intraoperative manipulation of the specimen to identify SLNs; however, it could not identify an aberrant lymphatic route. In the studies that used laparoscopic techniques SLNs were identified in 100% of patients.

Table 5: False-negative rate in patients with colon cancer

Study	No. of studies reporting outcome	False-negative rate range	No. of studies with false-negative rate <20%	No. of studies with false-negative rate <10%	No. of studies with 0% false-negative rate
Cahill et al	51 (98%)	0-75%	35 (69%)	18 (35%)	6 (12%)
Tuech et al	17 (100%)	0-60%	10 (59%)	6 (35%)	1 (6%)

Note: the values presented in the above table were taken from tabular data reported in both systematic reviews, which were contradictory to the values reported in the text.

In the systematic review by Cahill et al (2008) only 15 studies included analyses of false-negative rates. Twelve studies found increasing tumor stage was inversely related to non-SLN tumors. Five studies found detection rate and diagnostic accuracy was 100% among their T1 and T2 cohorts. One study found the presence of lymphovascular invasion was significantly associated with false-negative events (data not shown) but that lymph node invasion was not a statistically significant predictor. Another study analyzed its results by tumor stage and found no significant difference with either tumor stage or an arbitrarily decided lesion diameter.

Tuech et al (2005) stated the majority of false-negatives (skip-metastases) may be explained by surgical disruption of lymphatic drainage (causing the lymph to drain via an alternate route), and to a lesser extent it may be explained by inaccurate injection of dye. Studies reporting the use of SLN mapping in patients with breast cancer and melanoma suggest that SLN mapping failures due to inappropriate technique or inadequate pathological examination may result in under-treatment. However, in patients with colorectal cancer, SLN mapping does not always preclude the excision of all regional lymph nodes. When SLN mapping is used in conjunction with standard mapping, each lymph node is subjected to conventional pathological testing (while SLNs undergo

more rigorous testing), thus, patients with skip metastases will still receive the appropriate adjuvant chemotherapy and will not be undertreated, according to conventional standards (Saha et al. 2006). Nodal metastases may lead to obstruction and drainage through alternate pathways, and increasing tumor stage is inversely related to the probability of finding isolated metastases in the SLNs.

Upstaging rate (proportion of patients whose cancer stage was increased as a result of the findings of SLN mapping) and aberrant lymphatic drainage were also reported in the systematic review by Tuech et al (2005), in 13 and 3 of its included studies, respectively. In these studies, upstaging rate ranged from 0-25%. In the two studies that utilized *ex vivo* SLN mapping techniques, upstaging occurred in 8.7% and 16.7% of patients, and in the study that utilized laparoscopic techniques, upstaging occurred in 14% of patients. Aberrant drainage occurred in 0-29% of patients. The authors stated that when aberrant drainage was identified a more radical resection and lymphadenectomy should be performed to achieve a more complete tumor excision.

Accuracy of SLN mapping in patients with colon cancer versus rectal cancer

The level III study by van der Zaag et al (2009) compared the efficacy of SLN mapping in patients with colon cancer and rectal cancer. The mean total number of lymph nodes and SLNs identified were significantly greater in patients with colon cancer ($P<0.05$). Similarly, overall detection rate, accuracy, and negative predictive value were significantly higher in patients with colon cancer (Table 6).

Table 6: Predictive value of (*ex vivo*) SLN mapping reported by van der Zaag et al (2009)

Rate	Overall (n=132)	Colon cancer (n=100)	Rectal cancer (n=32)	P value
Detection	89%	92%	78%	0.03
Accuracy	91%	95%	76%	0.005
Sensitivity	75%	83%	57%	0.06
Negative predictive value	87%	93%	65%	0.002

Factors that may influence SLN mapping accuracy in patients with colon cancer include the depth of tumor invasion ($P = 0.06$) and the number of positive nodes detected ($P = 0.01$). In addition to these factors, preoperative radiotherapy may influence the accuracy of SLN mapping in patients with rectal cancer ($P=0.05$). Tumor size did not appear to significantly influence the accuracy of SLN mapping in patients with colon or rectal cancer.

The results from this study indicate SLN mapping in patients with rectal cancer may be less reliable than SLN mapping in patients with colon cancer due to the preoperative radiotherapy which usually takes place.

Accuracy of SLN mapping versus conventional lymph node mapping

One RCT compared the diagnostic accuracy of SLN mapping with conventional lymph node mapping (Stojadinovic et al 2007). This RCT found no significant difference in the mean number of lymph nodes and positive non-SLNs detected with conventional mapping or SLN mapping. Also in this study, nodal upstaging rate (defined by individual tumor cells or cell aggregates identified by H&E and/or immunohistochemistry) was found to be significantly greater in patients undergoing SLN mapping compared with conventional mapping ($P=0.019$) and 10.7% (6/56) of nodal upstaging was identified by mapping in patients who were found to be node-negative by

conventional pathological assessment (false-negative). There were eight false-negative cases reported in patients undergoing SLN mapping. The number of SLNs identified demonstrated a statistical correlation with the occurrence of a false-negative event; that is, 75% (6/8) of false-negative cases occurred in patients who had only one SLN identified and no false-negative cases occurred in patients with 4 or more SLNs identified. The mean number of SLNs identified in false-negative cases was significantly smaller (1.4) than the mean number of SLNs identified in true-positive cases (3.2) (P=0.07).

The systematic review by Des Guetz et al (2007) conducted a meta-analysis using diagnostic accuracy odds ratios (combining sensitivity and specificity) to compare the efficacy of detecting nodal metastases using SLN mapping relative to the reference standard of conventional histopathologic examination of non-SLNs. The results of the meta-analysis found the global sensitivity of SLN mapping to be 70% (95% confidence interval 66-73%) and the global specificity to be 81% (95% confidence interval 78-83%). A pooled diagnostic odds ratio was calculated, which combines sensitivity and specificity into a single indicator of test performance. The pooled diagnostic accuracy odds ratio (DAOR) was 10.7 (95% confidence interval 7.0-16.5) using the random effects model, and the median risk of false-negative results was 9%. Therefore, the meta-analysis found that patients with a SLN containing tumor cells would be 10.7 times more likely to have a node positive result than a patient who has a node negative result. The authors of this study removed one study, which contributed the majority of heterogeneity, from their meta-analysis and found the DAOR (12.0) to be similar; therefore, the results may be considered robust. Overall, the authors felt the results of their meta-analysis indicted that future studies on the use of SLN mapping in colorectal patients should use blue dye for reasons of simplicity, be performed by experienced surgeons and pathologists, be prospective, and include more than 40 consecutive patients.

Accuracy of SLN mapping using different detection modalities

Two systematic reviews examined SLN mapping using dye, radioactive tracers, or a combination of both modalities (de Haas et al 2007; Doekhie et al 2005). SLN detection rates and false-negative rates are presented below in Table 9 and Table 10, respectively.

Table 9: SLN detection rate (*in vivo* or *ex vivo*) using different tracer modalities

Study	SLN modality	No. of studies reporting outcome	SLN detection rate range	No. of studies with SLN detection rate >90%	No. of studies with SLN detection rate >95%	No. of studies with 100% SLN detection rate
de Haas et al	Blue dye	15 (100%)	71-100%	9 (60%)	6 (40%)	4 (16%)
	Blue dye and radioactive tracer	2 (100%)	88-98%	1 (50%)	1(50%)	0 (0%)
Doekhie et al	Blue dye	19 (100%)	58-100%	11 (58%)	5 (26%)	1 (5%)
	Radioactive tracers	2 (100%)	91-96%	2 (100%)	1 (50%)	0 (0%)
	Blue dye and radioactive tracer	4 (100%)	75-100%	2 (50%)	2 (50%)	1 (25%)

In the systematic review by de Haas et al (2007), three of the four included studies which had a SLN detection rate of 100% performed SLN mapping via a laparoscopic approach. Doehkie et al

(2005) reported overall SLN detection rate and sited factors that may have contributed to the failed procedures reported; they included incomplete circumferential injection around the tumor, insufficient volumes of tracer for large tumors, the inclusion of advanced tumors, and learning curve. In particular, two studies included in this review demonstrated a learning curve by excluding the first SLN mapping procedures from their analyses; consequently detection rates increased to approximately 100%.

In one study (included in both systematic reviews) that reported outcomes of SLN mapping using blue dye combined with radioactive tracers, 51% of blue nodes were also radioactive, whilst 81% of radioactive nodes were also blue. Another study found SLN mapping with blue dye to be successful in 100% of patients compared with 89% when using a radioactive tracer alone. Significantly more SLNs detected by radioactive tracers and blue dye (19.8%) had nodal metastases compared with those detected by blue dye (10.7%) alone (P=0.028), suggesting the use of both tracer modalities in conjunction is more accurate. Conversely, another two studies using radioactive tracers in conjunction with blue dye found there was no sufficient identification improvement.

Table 10: False-negative rate (*in vivo* or *ex vivo*) using different tracer modalities

Study	SLN modality	No. of studies reporting outcome	False-negative rate range	No. of studies with false-negative rate <20%	No. of studies with false-negative rate <10%	No. of studies with 0% false-negative rate
de Haas et al	Blue dye	14 (93%)	0-54%	10 (71%)	9 (62%)	3 (21%)
	Blue dye and radioactive tracer	2 (100%)	17-45%	1 (50%)	0 (0%)	0 (0%)
Doekhie et al	Blue dye	19 (100%)	0-63%	6 (32%)	3 (16%)	2 (11%)
	Radioactive tracers	2 (100%)	18-56%	1 (50%)	0 (0%)	0 (0%)
	Blue dye and radioactive tracer	4 (100%)	0-50%	2 (50%)	1 (25%)	1 (25%)

Possible reasons for high false-negative rates reported in the systematic review by Doekhie et al (2005) included nodal replacement and large tumors, leading to occluded lymphatic vessels leading to lymph drainage through an alternate route. Also in this review, 36% (9/25) of studies reported a false-negative rate <20%, four of which considered the first four blue nodes identified to be true SLNs. The limitation of considering the first blue nodes to be true SLNs includes the chance of missing blue nodes by inspection alone due to their location near the serosa within the mesocolic fatty tissue. A more reliable method of detection is suggested to be immediate examination of the entire mesocolon by inspection, palpation and incision, and considering the first to fourth blue nodes closest to the tumor to be sentinel.

Upstaging rate was reported by de Haas et al (2007). In the studies that used blue dye alone, possible upstaging percentages were 3-20%, and true upstaging varied from 0-26%. True upstaging rate in the study that used a combination of blue dye and radioactive tracers was similar at 19%. In addition, aberrant lymphatic drainage was detected in 0-36% of patients, with the highest frequency of aberrant drainage registered with laparoscopic procedures.

In the non-randomized comparative study by Nagata et al (2006) infrared ray laparoscopy provided much better visualization of lymph nodes and vessels in the mesenteric adipose tissue compared with white light (conventional laparoscopy) in the same region, at the same time. A significantly greater mean number SLNs were detected per patient using infrared ray laparoscopy compared with conventional laparoscopy, and the range of SLNs detected per patient was also significantly higher ($P<0.001$). In particular, identification of SLNs in a patient with a BMI of 30 was achievable using infrared ray laparoscopy. Identification of lymph node metastases appeared to be feasible using SLN mapping on infrared ray laparoscopy for stage T1 and T2 colorectal cancers.

Cost impact

There was no cost-effectiveness studies retrieved for SLN mapping for colorectal cancer at the time of writing. Theoretically, SLN mapping is more cost-effective than conventional lymph node mapping because fewer nodes are required for accurate staging, and because the occurrence of false-negative events are reduced. This means the costs associated with node-negative patients who would traditionally undergo precautionary adjuvant chemotherapy are reduced.

Cost-effectiveness literature for SLN mapping for melanoma and breast cancer was available. Although this literature cannot be directly translated to colorectal cancer, given the differences in the cancer types (including mortality rates and treatment regimens), it can be used as a loose guide to the cost effectiveness of SLN mapping. One study by Wilson et al (2002) modeled the cost-effectiveness of SLN mapping as a determinant of adjuvant interferon therapy in patients with stage II melanoma. A decision analytical model was used to compare four treatment strategies in patients following surgical excision of their stage II melanoma; the four strategies were:

1. treat all patients with low-dose interferon therapy
2. use SLN mapping to identify positive nodes and treat them with high-dose interferon therapy
3. use SLN mapping to identify positive nodes and treat them with high-dose interferon therapy and treat negative nodes with low-dose interferon therapy
4. surgery only (no SLN mapping, no interferon therapy).

Treatment, toxicity, follow-up and relapse costs were analyzed over a 5-year period with the primary outcome being cost per quality-adjusted relapse-free life year saved. Compared with surgery alone, all three strategies offered incremental benefits. The cost-effectiveness of using SLN mapping and treating some patients with high-dose interferon therapy (strategy 2) compared with surgery alone was $18,700/quality-adjusted life-years (QALY). Using SLN mapping and treating patients appropriately (strategy 3) was also cost-effective compared with strategy 2, at $31,100/QALY. In conclusion, this study found appropriate dosing of adjuvant therapy based on SLN mapping to be cost-effective in patients with stage II melanoma (Wilson et al 2002).

Similar studies are required to determine the cost-effectiveness of SLN mapping in patients with colorectal cancer. As well as studies comparing the costs associated with conventional lymph node mapping directly with SLN mapping.

Clinical practice guidelines and consensus statements

Several clinical practice guidelines regarding colorectal cancer were retrieved. There were no guidelines available that specifically addressed the use of SLN mapping in patients with colorectal cancer at the time of writing. The key recommendations regarding colorectal tumor and lymph node resection, lymph node pathology, and lymph node cancer involvement made included:

- A minimum of 12 lymph nodes should be examined to adequately stage colon and rectal cancer, particularly in the case of T3/4 neoplasm, although an effort should be made to identify all lymph nodes.
    - The 12 lymph node target may not be achievable in patients with T1/2 tumors or in some patients who receive neoadjuvant therapy.
- All lymph nodes present must be examined histologically (not just the first 12 nodes). It is particularly important to find small lymph nodes close to the underlying bowel wall.
- All grossly negative or equivocal lymph nodes must be submitted to pathology in their entirety. However, if a node is grossly positive, partial submission is acceptable.
- The number of lymph nodes involved by micrometastases and isolated tumor cells should be reported separately from typical (macro) metastases.
    - Micrometastases are defined as tumor deposits >0.2mm by <2.0mm
    - Isolated tumor cells are defined as single cells or clusters ≤ 0.2 mm
- Special measures to detect micrometastases or isolated tumor cells, such as, multiple tissue levels of paraffin blocks, immunohistochemistry, and RT-PCR, are not recommended for the routine examination of regional lymph nodes.

Training and education impact

A learning curve for SLN mapping in patients with colorectal cancer was illustrated in several of the studies included in this report. Very few studies demonstrated surgeon competency before undertaking their trials and consequently SLN detection and false-negative rates varied. On several occasions, the exclusion of the first SLN procedures from detection rate analyses resulted in an improvement in these outcomes, supporting the idea that surgeon experience may be responsible for the low performance of SLN mapping evident in some cases.

There was no literature retrieved in regards to the minimum number of procedures required to be undertaken before surgeon competence in SLN mapping is achieved. Evidence in regards to this, along with specific training requirements is needed.

Summary

Overall, discordant results were achieved in regards to SLN detection (58% to 100%) and false-negative rate (0% to 75%). Possible reasons for this include surgeon learning curve and a lack of standardized technique and clear definition of which stained nodes should be considered sentinel. However, given accurate detection of SLNs and focused histopathological examination of these nodes, SLN mapping offers potential for significant upstaging of patients. Tumor stage may also cause variation in false-negative rate; SLN mapping is more feasible in colorectal tumors of stage I and II. Many of the included studies found SLN mapping to be unreliable in patients with lymph nodes containing macrometastases.

Tumor size (length/diameter) and the quantity of tracer required were found to be positively correlated. A protocol for the amount of dye appropriate in regards to the size of the colorectal tumor may be necessary. Several studies found false-negatives were obtained more in patients with large tumors, which also suggests SLN staging may be more appropriate in stage I and II patients compared with those with more advanced disease. Data were equivocal in regards to the most efficacious tracer (dye or radioactive) or combination of tracers used for SLN mapping. Some studies noted dye should be used for reasons of simplicity, and others found a combination of dyes and radioactive tracers was more thorough.

SLN mapping was able to identify micrometastases in SLNs, missed by conventional techniques, resulting in subsequent upstaging. In particular, SLN mapping in patients with colon cancer is more reliable than in patients with rectal cancer due to preoperative radiation therapy. Preoperative therapy has been associated with a decrease in the number of nodes retrieved and may potentially alter lymphatic flow, yielding false-positive non-SLN staining.

There was no evidence to support the use of either *in vivo* or *ex vivo* mapping techniques over the other. Consequently, standardization of working definitions (such as which nodes can be considered truly sentinel), training, mapping technique, and pathologic processing are critical to the success of SLN mapping for colorectal cancer. Before proper assessment of the efficacy of SLN mapping can be undertaken standardization of the procedure is required. Whilst different centers continue to perform the procedure using a slightly different modality, meaningful comparisons between studies is not possible. This also hinders the refinement of the SLN mapping procedure for colorectal cancer.

Further research is required (particularly controlled trials) where SLN mapping is compared (as a stand alone procedure) with conventional mapping. Future studies should also report clinical outcomes, such as patient survival rates and recurrence rates, so that the prognostic value of SLN mapping can be established.

Recommendation

Based on the available evidence, SLN mapping for colorectal cancer produced varied results in regards to SLN detection rate and false-negative rate. The most significant factors that may have contributed to this variation were learning curve and the lack of a standardized SLN mapping protocol (including how much tracer is required depending on the size of the tumor and which nodes can be considered sentinel). The safety of SLN mapping for colorectal cancer could not be determined by the available evidence.

The literature suggests SLN mapping has improved diagnostic accuracy in patients with stage I and II disease and in patients with colon versus rectal cancer. Further high-quality studies are required to determine: the role of SLN mapping in colorectal cancer (i.e. as a stand alone procedure or adjunct to conventional lymph node mapping), what is adequate training for the procedure and an optimal procedural protocol (i.e. which tracers should be used, ex vivo versus ex vivo), as well as the prognostic value of the procedure by reporting clinical outcomes.

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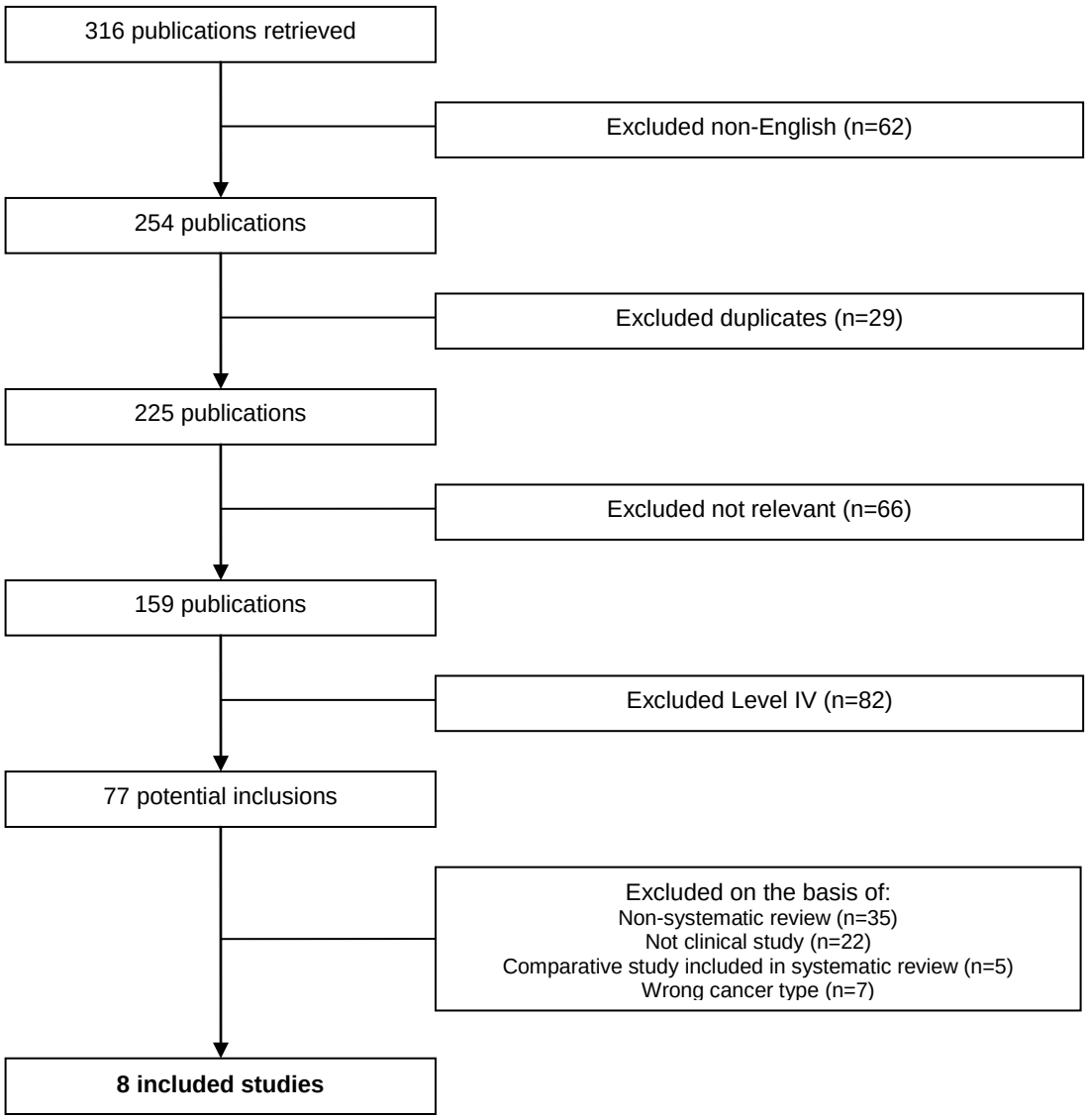
Appendix A

Additional papers not included in this assessment

Article reference	Level of evidence	Number of patients	Conclusions	Reason for exclusion
Saha S, Seghal R, Patel M, Doan K, Dan A, Bilchik A, Beutler T, Wiese D, Bassily N, Yee C. A multicenter trial of sentinel lymph node mapping in colorectal cancer: prognostic implications for nodal staging and recurrence. *The American Journal of Surgery* 2006; 191(3): 305-310.	III-3	868	Sentinel lymph node mapping is highly feasible and accurate for staging colorectal cancer with higher detection of nodal metastasis and lower recurrences than standard nodal staging techniques.	Included in systematic review
Tiffet O, Kaczmarek D, Chambonniere ML, Guillan T, Baccot S, Prevot N, Bageacu S, Bourgeois E, Cassagnau E, Lehur PA, Dubois F. Combining radioisotopic and blue-dye technique does not improve the false-negative rate in sentinel lymph node mapping for colorectal cancer. *Dis Colon Rectum* 2007; 50(7): 962-970.	III-3	64	The addition of a radioisotope method using submucosal injection does not improve the false-negative rate. The sentinel lymph node technique in colorectal cancer is feasible, although the false-negative rate is such that the technique should still be considered experimental.	Included in systematic review
Saha S, Monson KM, Bilchik A, Beutler T, Dan AG, Schochet E, Wiese D, Kaushal S, Ganatra B, Desai D. Comparative analysis of nodal upstaging between colon and rectal cancers by sentinel lymph node mapping: a prospective trial. *Dis Colon Rectum* 2004; 47(11): 1767-1772.	III-2	407	Despite higher success rates in sentinel lymph node identification for colon patients, sentinel lymph node mapping was highly successful in rectal patients, nodal upstaging, skip metastases, and occult metastases were similar.	Included in systematic review
Bilchik AJ, Nora DT, Sobin LH, Turner RR, Trocha S, Krasne D, Morton DL. Effect of lymphatic mapping on the new tumor-node-metastasis classification for colorectal cancer. *J Clin Oncol* 2003; 21(4): 668-672.	III-2	490	Conventional examination of lymph nodes for colorectal cancer is inadequate for the detection of micrometastases and isolated tumor cells as described in the new tumor-node-metastasis classification. Thus, lymphatic mapping and focused sentinel node analysis should be considered to fully stage colorectal cancer.	Included in systematic review
Tuech JJ, Pessaux P, Di Fiore F, Nitu V, Lefebure B, Colson A, Michot F. Sentinel node mapping in colon carcinoma: in-vivo versus ex-vivo approach. *Eur J Surg Oncol* 2006; 32(2): 158-161.	III-3	32	*Ex vivo* sentinel lymph node mapping is as accurate as the *in vivo* technique in defining sentinel lymph node and does have the ability to upstage some patients with colorectal cancer. The *ex vivo* technique could be used either as a primary lymphatic mapping procedure or secondarily for failed *in vivo* attempts at lymphatic mapping.	Included in systematic review

Studies excluded from this assessment



Appendix B

NHMRC Evidence Hierarchy: designations of 'levels of evidence' according to type of research question

Level	Intervention 1	Diagnostic accuracy 2	Prognosis	Aetiology 3	Screening Intervention
I 4	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomized controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard,5 among consecutive persons with a defined clinical presentation6	A prospective cohort study[7]	A prospective cohort study	A randomized controlled trial
III-1	A pseudorandomized controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard,5 among non-consecutive persons with a defined clinical presentation6	All or none8	All or none8	A pseudorandomized controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: ▪ Non-randomized, experimental trial9 ▪ Cohort study ▪ Case-control study ▪ Interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst persons in a single arm of a randomized controlled trial	A retrospective cohort study	A comparative study with concurrent controls: ▪ Non-randomized, experimental trial ▪ Cohort study ▪ Case-control study
III-3	A comparative study without concurrent controls: ▪ Historical control study ▪ Two or more single arm study10 ▪ Interrupted time series without a parallel control group	Diagnostic case-control study6	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: ▪ Historical control study ▪ Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)11	Case series, or cohort study of persons at different stages of disease	A cross-sectional study or case series	Case series

Explanatory notes

1. Definitions of these study designs are provided on pages 7-8 *How to use the evidence: assessment and application of scientific evidence* (NHMRC 2000b*)*.

2. The dimensions of evidence apply only to studies of diagnostic accuracy. To assess the effectiveness of a diagnostic test there also needs to be a consideration of the impact of the test on patient management and health outcomes (Medical Services Advisory Committee 2005, Sackett and Haynes 2002).

3. If it is possible and/or ethical to determine a causal relationship using experimental evidence, then the 'Intervention' hierarchy of evidence should be utilised. If it is only possible and/or ethical to determine a causal relationship using observational evidence (ie. cannot allocate groups to a potential harmful exposure, such as nuclear radiation), then the 'Aetiology' hierarchy of evidence should be utilised.

4. A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence. Systematic reviews of level II evidence provide more data than the individual studies and any meta-analyses will increase the precision of the overall results, reducing the likelihood that the results are affected by chance. Systematic reviews of lower level evidence present results of likely poor internal validity and thus are rated on the likelihood that the results have been affected by bias, rather than whether the systematic review itself is of good quality. Systematic review *quality* should be assessed separately. A systematic review should consist of at least two studies. In systematic reviews that include different study designs, the overall level of evidence should relate to each individual outcome/result, as different studies (and study designs) might contribute to each different outcome.

5. The validity of the reference standard should be determined in the context of the disease under review. Criteria for determining the validity of the reference standard should be pre-specified. This can include the choice of the reference standard(s) and its timing in relation to the index test. The validity of the reference standard can be determined through quality appraisal of the study (Whiting et al 2003).

6. Well-designed population based case-control studies (eg. population based screening studies where test accuracy is assessed on all cases, with a random sample of controls) do capture a population with a representative spectrum of disease and thus fulfil the requirements for a valid assembly of patients. However, in some cases the population assembled is not representative of the use of the test in practice. In diagnostic case-control studies a selected sample of patients already known to have the disease are compared with a separate group of normal/healthy people known to be free of the disease. In this situation patients with borderline or mild expressions of the disease, and conditions mimicking the disease are excluded, which can lead to exaggeration of both sensitivity and specificity. This is called spectrum bias or spectrum effect because the spectrum of study participants will not be representative of patients seen in practice (Mulherin and Miller 2002).

7. At study inception the cohort is either non-diseased or all at the same stage of the disease. A randomized controlled trial with persons either non-diseased or at the same stage of the disease in *both* arms of the trial would also meet the criterion for this level of evidence.

8. All or none of the people with the risk factor(s) experience the outcome; and the data arises from an unselected or representative case series which provides an unbiased representation of the prognostic effect. For example, no smallpox develops in the absence of the specific virus; and clear proof of the causal link has come from the disappearance of small pox after large-scale vaccination.

9. This also includes controlled before-and-after (pre-test/post-test) studies, as well as adjusted indirect comparisons (ie. utilise A vs B and B vs C, to determine A vs C with statistical adjustment for B).

10. Comparing single arm studies ie. case series from two studies. This would also include unadjusted indirect comparisons (ie. utilise A vs B and B vs C, to determine A vs C but where there is no statistical adjustment for B).

11. Studies of diagnostic yield provide the yield of diagnosed patients, as determined by an index test, without confirmation of the accuracy of this diagnosis by a reference standard. These may be the only alternative when there is no reliable reference standard.

Note A: Assessment of comparative harms/safety should occur according to the hierarchy presented for each of the research questions, with the proviso that this assessment occurs within the context of the topic being assessed. Some harms are rare and cannot feasibly be captured within randomized controlled trials; physical harms and psychological harms may need to be addressed by different study designs; harms from diagnostic testing include the likelihood of false positive and false negative results; harms from screening include the likelihood of false alarm and false reassurance results.

Note B: When a level of evidence is attributed in the text of a document, it should also be framed according to its corresponding research question eg. level II intervention evidence; level IV diagnostic evidence; level III-2 prognostic evidence.

Source: Hierarchies adapted and modified from: NHMRC 1999; Bandolier 1999; Lijmer et al. 1999; Phillips et al. 2001.

Appendix C

Extraction tables for included systematic review evidence.

Review details	Aim and search methods	Study design and inclusion/exclusion criteria	Results and author(s) conclusions	Comments
Cahill RA, Leroy J & Marescaux J, 2008 *BMC Surgery*	Aim: to systematically review the literature pertaining to *in vivo* sentinel lymph node mapping techniques in regards to its accuracy detecting early stage disease. Review question: could lymphatic mapping and sentinel node biopsy provide oncological providence for local resectional techniques for colon cancer? Search period: January 1st 1999 to July 30th 2008. Databases searched: PubMed, Cochrane Library, and EMBASE. Search terms: expanded MeSH terms included 'sentinel node', 'lymphatic mapping', 'colon cancer', 'colon tumo(u)rs', 'colorectal	Inclusion criteria: studies reporting outcomes in human patients with colon (not rectal) cancer where *in vivo* mapping and node identification took place. (Intraoperative marking of sentinel lymph nodes rather than actual excisional biopsy also allowed inclusion). Exclusion criteria: studies utilizing *ex vivo* sentinel node mapping techniques and data presented in meeting abstracts. Study selection and appraisal methods: each study identified was analyzed for suitability of inclusion according to QUADAS criteria (an evidenced base tool for the assessment of the quality of diagnostic assessment studies). The study needed to be of sufficient quality to be included in the review. Subsequently, data was extracted by two authors and cross-checked to ensure validation (disagreement in regards to data extraction was resolved with third party	*Fifty-two studies* reporting outcomes in *3390 patients* were included. Patient demographics: • 3 studies had predominately male populations and two studies had predominately female populations – reasons for this were unclear. • Only 4 studies reported body mass index data – which is an important predictive factor for error in node detection and false-positive rate due to obscurement of colored nodes in the mesentery. • Only 50% of studies looked at patients with colon cancer alone, the majority of other studies included rectal cancer also. Results were generally not reported separately per tumor type. Sentinel node detection rate and false-negative scores: • Considerable variation in detection (58-100%) and false-negative rates (0-75%). • Detection rates greater than the 90% threshold were apparent in 41 included studies (29 had rates >95% and 12 had 100% detection). • 5/9 studies with detection rates <90% also had false-negative rates >20%. Only 9/41 studies with detection rates >90% had false-negative rates >20%. • False-negative rates below 10% occurred in 18 studies, 8 of which reported rates ≤5%. • Therefore, 21% (n=11) and 63% (n=33) of all included studies did not meet these thresholds. • Critical appraisal of studies with low performance results revealed several factors that may have been responsible for this, including: unproven surgeon experience, small (n<60 patients) sample size, mixed patient populations (inclusion of patients with rectal cancers), high proportion of patients with locally advanced disease (T3/T4 compared with T1/T2), and increased body mass index. NOTE: according to the use of sentinel node mapping in breast cancer, detection rates consistently >90% and false-negative rates consistently <10% are required to deem the technique acceptable for clinical use. Tumor profile: • 19 studies included patients with distant metastases or mesenteric deposits or grossly involved lymph nodes. • 7 studies excluded patients with distant metastases. • 9 studies included only patients with 'clinically localized' or 'resectable' disease.	• Extensive search strategy • Specific inclusion criteria • Minimal exclusion criteria provided • Date restrictions • Language restriction • Handsearching of reference lists of all included studies and other relevant sources • No hand searches of relevant journals • No consultation of relevant online health services • Data extraction and appraisal methodology described • Two reviewers responsible for data extraction (third party mediation where necessary) • Flow chart of study selection provided • Data extraction tables created *a priori* • Extensive description of included studies • Explanation for

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	cancer/tumo(u)rs', 'large intestine', and 'gastrointestinal'. Language restrictions: English language publications only. Additional information: reference lists of all full publications (including consensus papers, review articles, editorials, and relevant book chapters) were cross-checked for additional relevant publications.	mediation where necessary). Excel extraction tables created *a priori* were used. Where quantitative results were not presented and were not extractable only data useful to analysis were extracted, otherwise the paper was excluded.	• Overall, at least 21 studies included T4 tumors within their cohort, and 25 studies possessed high T3 and T4 to T1 and T2 ratios. • 5 studies specifically considered tumor length/diameter as a factor that may affect mapping performance: 4 of these found false-negatives to be more likely in patients with larger tumors – one study considered how tumor size and the quantity of dye required for mapping may be related and found a significant positive correlation. • 21 studies included patients with considerably less nodes than what is considered adequate and 25 studies did not state the mean number/range of non-sentinel nodes harvested, raising concerns regarding the quality control mechanisms in place for the procedure. Technical methodology: • 5 studies ensured surgeon experience before commencing the trial. • 45 protocols used intraoperative subserosal injection of the mapping agent and 3 used submucosal injection. • 39 studies used a colorimetric mapping agent, 1 study used a radioisotope mapping agent alone, and 11 studies used both. One study used dye alone and dye along with a radioisotope in subsets of their patient population. • 6 studies specifically included laparoscopic operations, 3 of which employed the approach exclusively. All commenting authors agreed the technique was easily performed regardless of the operative approach and that the use of laparoscopy had a minimal effect on overall operative time. • Mean number of sentinel nodes found was consistently approximately 2. • Considerable variation among how identified nodes were histologically analyzed was found: 4 studies examined only a single section of the node while 9 other studies used neither immunohistochemistry nor reverse transcriptase-polymerase chain reaction to look for micrometastases or isolated tumor cells. • Only 15 studies included analyses of false-negatives: 12 studies found increasing tumor stage was inversely related to non-sentinel node tumors, 5 studies found detection rate and diagnostic accuracy was 100% among their T1 and T2 cohorts, 1 study found the presence of lymphovascular invasion was significantly associated with false-negatives but that lymph node invasion did not reach significance as a predictor, 1 study analyzed its results by tumor stage but found no significant difference with either tumor stage or an arbitrarily decided lesion diameter. Safety: No safely outcomes were reported. Authors conclusions: • Heterogeneity in patient and tumor characteristics, along with differences in surgeon	excluded studies • Search terms clearly provided • Extensive tabular data, including result summaries and profiles of included studies • Possible duplications of results in numerous cases (although noted at time of data extraction) • Studies reporting outcomes in patients with rectal cancer were included despite exclusion criteria.

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			experience and the protocols utilized may explain the discordant results achieved in regards to sentinel node detection and false-positive rate. • A lack of clarity and consistency in the literature (to date) means it is not possible to definitively judge if lymphatic mapping may be sufficient in providing oncological proprietary for curative surgery for early stage cancers without en bloc mesenteric resection (despite it appearing biologically plausible).	
de Haas RJ, Wicherts DA, Hobbelink MGG, Borel Rinkes IHM, Schipper MEI, van der Zee JA & van Hillegersberg R, 2007 *Annals of Surgical Oncology*	Aim: to systematically review the literature to assess the current status regarding the feasibility and accuracy of different sentinel lymph node mapping techniques (blue dye and/or radiocolloid tracers) in patients with colon cancer. Review question: what is the most optimal procedure for identifying sentinel lymph nodes in patients with colon cancer? Search period: unlimited; anything published before the day of search (December 1st 2005) Databases searched: PubMed Search terms: 'sentinel node', 'colon cancer', 'colorectal cancer',	Inclusion criteria: prospective studies assessing sentinel lymph node mapping in patients with colon cancer. Studies reporting the use of blue dye and/or radiocolloid tracers during *in vivo* or *ex vivo* procedures were eligible for inclusion. Exclusion criteria: studies reporting outcomes in patients with rectal cancer (due to the different pattern of spread and recurrence, its more difficult anatomical access, and its different operative treatment compared with colon cancer.) As well as this, preoperative radiotherapy is frequently applied to rectal cancer patients and may disrupt lymphatic architecture making sentinel lymph node mapping less accurate. Study selection and appraisal methods: potentially relevant articles were identified by their title and abstract. These articles were retrieved and their level of evidence determined.	*Seventeen case series studies* (reporting outcomes in *914 patients*) were identified for inclusion: 15 studies described sentinel lymph node mapping using blue dye (in 832 patients) and 2 studies described sentinel lymph node mapping using a combination of blue dye and radiocolloid (in 82 patients). *one study used both blue dye and radiocolloid in the first few cases and found the same sentinel lymph nodes identified by both tracers, subsequently this study used only blue dye thus its results were attributed to blue dye only. Procedure: • After identification of the sentinel lymph nodes, microscopic examination using conventional hematoxylin and eosin staining was performed first in several of the included studies. • Multisectioning hematoxylin and eosin staining and/or immunohistochemical staining were performed on the sentinel lymph nodes in most of the studies. • Immunohistochemical staining was carried out using antibodies against cytokeratin and in one study against carcinoembryonic antigen. • The use of reverse transcriptase-polymerase chain reaction was only described in one study. • The non-sentinel lymph nodes usually only underwent conventional hematoxylin and eosin examination. In 4 studies they were examined in the same way as sentinel nodes. • In all of the included studies the remainder of the surgical specimen was processed in the standard manner for colon cancer specimens. Blue dye: • Most studies used an open, *in vivo* technique. One study used the *ex vivo* technique and 3 studies used a laparoscopic procedure. • The time between injection of the dye and identification of the sentinel node varied between the included studies, in general the period lasted several minutes. • In most studies the first 4 stained nodes were considered sentinel. • 10 studies reported an identification rate between 90-100%. (In the 3 studies using a laparoscopic technique identification rate was 100%) • The other 5 studies reported identification rates of 71, 79, 82, 85, and 87%, respectively. • An intraoperative identification rate of 50% found in 1 study was likely to be due to fat in the mesocolon (associated with increased body mass index). During subsequent pathological analysis identification rate increased to 90%.	• Limited databases searched • Adequate search terms used • Extensive inclusion criteria • Extensive exclusion criteria • No date restrictions • Language restriction • Handsearching of reference lists of all included studies • No hand searches of relevant journals • No consultation of relevant online health services • Data extraction and appraisal methodology not described • Critical appraisal of included studies not performed • Explanation for excluded studies • Search terms clearly provided • Extensive tabular data, including result summaries

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	'colloid'. Language restrictions: English language publications only. Additional information: further articles were selected by cross-referencing from the initially retrieved papers.		• 0-36% abnormal lymphatic drainage was reported (the highest percentages were reported in association with laparoscopic techniques). When this was identified, lyphadenectomy was extended to include all sentinel lymph nodes. • Reported accuracy ranged from 78-100%. 4 studies did not provide enough data to calculate accuracy. • False-negative rates varied from 0-10% in 9 studies and 5 other studies reported false-negative rates of 17, 24, 38, 50, and 54%, respectively. Several studies did not provide enough data to calculate false-negative rates and one study did not mention false-negative rates at all. • Possible upstaging percentages were 3-20%. True upstaging varied from 0-26% and several studies did not provide the appropriate data to calculate this. Combination blue dye and radiocolloid: • One study used an open *ex vivo* technique and the other an open *in vivo* technique. • Identification rate in the *ex vivo* study was 88%. • Sensitivity rate in the *ex vivo* study was 55%. • False-negative rate in the *ex vivo* study was 45%. • Also in this study, only 51% of blue nodes proved to be radioactive, whilst 81% of radioactive nodes were found to be blue. • In the *in vivo* study, identification rate was 98%. • Sensitivity rate in the *in vivo* study was 83%. • False-negative rate in the *in vivo* study was 17%. • Also in this study, a true upstaging rate of 19% was found after performing analysis of the sentinel nodes. • 10 additional sentinel nodes were identified by the use of radiocolloid; however, only one additional positive sentinel node was revealed that would not have been found by blue dye alone. Safety: No safely outcomes were reported. Authors conclusions: • Sentinel lymph node mapping remains experimental. Varying results reflect the lack of standardized technique and univocal definition of which stained nodes should be considered sentinel. • Identification rates are hard to interpret because it is unknown if all of the sentinel lymph nodes can truly be considered sentinel. • Given accurate identification of sentinel lymph nodes and focused histopathological	

Review details	Aim and search methods	Study design and inclusion/exclusion criteria	Results and author(s) conclusions	Comments
			examination of these nodes the technique offers potential for significant upstaging of patients.	
Des Guetz G, Uzzan B, Nicolas P, Cucherat M, de Mestier P, Morere J-F, Breau J-L & Perret G, 2007 *World Journal of Surgery*	Aim: to perform a meta-analysis to compare the diagnostic accuracy of the sentinel lymph node technique with that of conventional histopathologic examination. Review question: what are the risks of down staging (false-negative) and the benefits of sentinel lymph node mapping (upstaging)? Search period: unlimited; anything published before the day of search (May 1st 2006). Databases searched: PubMed Search terms: colorectal cancer AND sentinel node Language restrictions: English and French language studies only. Additional information: references were also	Inclusion criteria: studies that dealt with colon or rectal cancer, written in English or French. Exclusion criteria: studies that dealt with other cancer sites, as well as case reports and animal data or reviews. Study selection and appraisal methods: initial selection of studies relied on careful reading of their abstracts. Information was independently extracted from all full-length publications in duplicate by two readers using a standardized data collection form. Disagreements were resolved by discussion between the two readers. There was no predefined minimum number of patients per study required to be included in the meta-analysis. Studies were not assigned a weight by a quality score because no such score had received general agreement for use in meta-analysis, especially of observational studies. Duplication of data was avoided by examining the	182 studies identified by PubMed search → 47 references selected based on abstract examination + 7 references identified by other reviews + 1 reference from recent literature = 54 potential articles → 22 duplicate and non exploitable studies removed → *33 studies* analyzed (reporting outcomes in *1794 patients*) Cancer type: • 13 studies included patients with colon cancer alone. • 2 studies included patients with rectal cancer alone. • 15 studies included patients with colon and rectal cancer. • 3 studies did not report the proportion of its patients with colon/rectal cancer. Procedure type: • 18 studies utilized an *in vivo* procedure only. • 11 studies utilized an *ex vivo* procedure only. • 4 studies utilized both *in vivo* and *ex vivo* procedures. Tracer: • Blue dye (patent blue or isosulfan blue) was used in 19 studies. • Radioactive technetium labeling was used in 2 studies. • 1 study compared lymphazurin 1% and ^{99m}Tc sulphur colloid for sentinel node mapping in colorectal cancer. *there was no statistically significant difference seen in the feasibility or accuracy of the two methods, but metastatic yield was significantly higher when sentinel node mapping was performed using the two techniques simultaneously. • Median number of sentinel lymph nodes sampled: 2.5 (1.8-6.0) • Median number of lymph nodes sampled: 15.6 (5.5-29.9) • Mean failure rate of sentinel lymph node mapping: 10% (0-37%) *in 6 studies sentinel node identification rate was 100% Global sensitivity and specificity/DAOR: • Global sensitivity of sentinel node mapping was 70% (95% confidence interval 66-73%) with a specificity of 81% (95% confidence interval 78-83%) • Pooled DAOR was 10.7 (95% confidence interval 7.0-16.5) using the random effects model – (there was heterogeneity among the included studies). o False-negative rate was significantly different between one of the included studies and the rest of the included studies, when sub-group analyses were	• Adequate search strategy • Only one database searched • Minimal inclusion criteria provided • Specific exclusion criteria • No date restrictions • Language restriction (2 languages) • Handsearching of reference lists of all included studies and other relevant sources (including conference proceedings) • No consultation of relevant online health services • Data extraction and appraisal methodology described • Two reviewers responsible for data extraction (third party mediation where necessary) • Flow chart of study selection provided • Data extraction tables created *a priori* • Extensive description of included studies • Explanation for excluded studies

Review details	Aim and search methods	Study design and inclusion/exclusion criteria	Results and author(s) conclusions	Comments
	screened from relevant literature, including all identified studies as well as reviews and editorials. Abstracts from the American Society of Clinical Oncology proceedings of the annual meetings from 1998-2004 were also reviewed. Definitions: True-positive = sentinel node positive/node positive True-negative = sentinel node negative/node negative False-positive = sentinel node positive/node negative False-negative = sentinel node negative/node positive	names of all authors and medical centers involved for each publication. When duplicate studies were retrieved the study with the largest number of patients from which data could be extracted, and usually the most recently published, was included. Meta-analysis characteristics: diagnostic accuracy odds ratio (DAOR) was selected as the single indicator of test performance. In case of heterogeneity between the studies the random effect model was used. Where heterogeneity could be suppressed (in sub-group analysis) the fixed effect model was used. For each study a 2x2 contingency table included true-positives, true-negative, false-negative, and false-positive, or upstaged patients. In each study the status of the sentinel lymph node was compared with that of lymph node invasion seen by conventional histology. *DAOR combines sensitivity and specificity	performed excluding this study heterogeneity was no longer significant, allowing the use of the fixed effects model. o Exclusion of all studies with a "failure to identify the sentinel lymph node" rate higher than 10% showed a significantly lower false-negative rate and led to a DAOR (12.0) slightly superior to the global DAOR (10.7). • Exclusion of studies including < 40 patients provided a DAOR of 9.6. • Rate of upstaged patients ranged from 0-38% (median 9%). • Multiple sections of sentinel node and immunohistochemistry allowed detection of occult tumor cells and micrometastases in sentinel nodes. • Sentinel node mapping could help detect micrometastases and occult tumor cells in lymph nodes. • In 26/33 studies micrometastases were detected using immunohistochemistry: o Cytokeratin was generally used to detect cancer; sometimes antibodies against carcinoembryonic antigen were also used. o Therefore, immunohistochemistry was included in almost all cases to calculate false-positive rate, meaning upstaged patients. • According to the definition of occult tumor cells in one study, the false-negative rate was 12%, but using this definition 70% of patients without lymph node involvement were upstaged. Safety: No safely outcomes were reported. Authors conclusions: • Sentinel node mapping could help detect micrometastases and occult tumor cells in lymph nodes (compared with conventional histopathologic examination) • Based in their meta-analysis results, the authors felt future studies on the use of sentinel node mapping in colorectal patients should use blue dye for reasons of simplicity, be performed by experienced surgeons and pathologists, be prospective, and include more than 40 consecutive patients.	• Search terms clearly provided • Extensive tabular data, including result summaries and profiles of included studies • Possible duplications of results counteracted by extensive checking of study details, and subsequent exclusion where necessary • Meta-analysis performed according to a predefined written protocol
Doekhie FS, Peeters KCMJ, Kuppen PJK, Mesker WE, Tanke HJ,	Aim: to systematically review the literature to assess the feasibility and reliability of sentinel lymph node	Inclusion criteria: NR Exclusion criteria: papers with anal cancer in the title were excluded.	*Twenty-five studies* were included, reporting outcomes in *1163 patients*. Procedural details: • 19 studies used *in vivo* procedure alone, 3 studies used *ex vivo* procedure alone, and 3 studies used both *in vivo* and *ex vivo* procedures.	• Limited databases searched • Adequate search terms used • No inclusion criteria

Review details	Aim and search methods	Study design and inclusion/exclusion criteria	Results and author(s) conclusions	Comments
Morreau H, van de Velde CJH & Tollenaar RAEM, 2005 *European Journal of Surgical Oncology*	mapping in patients with colorectal cancer. Differences in the sentinel node mapping technique were emphasized. Review question: is sentinel lymph node mapping feasible and reliable for use in colorectal cancer? Search period: 1953 to date of search (2004). Databases searched: PubMed Search terms: colonic or rectal or colorectal neoplasm, adenocarcinoma or cancer, and sentinel. Language restrictions: English language publications only. Additional information: additional articles were identified by cross-referencing from papers retrieved in the initial literature search.	Study selection and appraisal methods: all hits from the PubMed search were individually checked, and included only if they addressed the subject of the review.	• Tracers included blue dye (n=19 studies), radioactive tracers (n=2), or both (n=4). Tracers: *Blue dye* • Volume of blue dye used ranged from 0.5-2ml, except in 3 studies where up to 5ml was used. • In all but one study identification time (from injection to labeling of blue node) ranged from 1-60 minutes. The exempt study fixed resected specimens in formalin for 48 hours before blue node identification. *Radioactive tracers* • Identification time was 26 minutes to 20 hours. *Blue dye and radioactive tracers* • In one study 81% of hot nodes were identified by blue dye (those that were not also blue may be due to dye passing through the node within leaving a stain, or that these nodes were more immunologically active resulting in a greater uptake of the radioactive tracer) and 51% of blue nodes were identified by the radioactive tracer (low number may be due to rapid passage of dye through nodes). • Another study found sentinel node mapping with blue dye to be successful in 100% of 57 patients compared with 89% when using the radioactive tracer. Blue dye detected 152 sentinel nodes, radioactive tracers detected 100 sentinel nodes, and both modalities detected 96 sentinel nodes. Significantly more sentinel nodes detected by radioactive tracers and blue dye (19.8%) had nodal metastases compared with those detected by blue dye (10.7%) alone (P=0.028). – suggesting that using both types of the tracers is more accurate. • The 2 other studies using both modalities found the use of radioactive tracers with dye did not lead to sufficient identification improvement. Overall identification rate: • 25 studies reported identification rate; mean rate: 89%; range: 58-100%. • Factors that may have contributed to failed procedures included incomplete circumferential injection around tumor, insufficient volumes of tracer used for large tumors, the inclusion of advanced tumors, and learning curve. • 2 studies demonstrated this learning curve by reporting an identification rate of almost 100% when the first sentinel mapping procedures were not included in the analysis. Overall false-negative rate: • 25 studies reported false-negative rate; mean rate: 33%; range: 0-63%. • False-negative rates in studies using blue dye and radioactive tracers: mean 28%; range: 0-50%.	provided • Limited exclusion criteria • No date restrictions (data from before 1954 would not be relevant to the review) • Language restriction • Handsearching of reference lists of all included studies • No hand searches of relevant journals • No consultation of relevant online health services • Study selection protocol described briefly • Critical analysis of included studies not performed • Data extraction protocol was not reported • Extensive description of included studies • Extensive background • Search terms clearly provided • Adequate tabular data, including result summaries and profiles of included studies

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			• False-negative rates in 2 studies using only radioactive tracers: 18% and 56%. • Reasons for high rate may include nodal replacement and large tumors (leading to occluded lymphatic vessels leading to lymph drainage through an alternate route). • 40% (10/25) of studies reported a false-negative rate ≤20%, 4 of these were the only studies that considered the first 4 blue nodes (usually marked *in vivo*) to be true sentinel nodes. *limitation of considering first blue nodes to be sentinel nodes include the chance of missing blue nodes by inspection alone due to their location near the serosa within the mesocolic fatty tissue. A more reliable method of detection is suggested to be immediate examination of the entire mesocolon by inspection, palpation and incision and considering the first to fourth blue nodes closest to the tumor to be sentinel. • The majority of the 15 studies reporting a false-negative rate >20% considered all blue or radioactive nodes to be sentinel. Overall sensitivity: 25 studies reported sensitivity; mean rate: 67%; range: 38-100%. Overall negative predictive value: 25 studies reported negative predictive value; mean rate 84%; range: 56-100%. Number of hematoxylin and eosin-negative patients: 23 studies reported the number of hematoxylin and eosin-negative patients; mean: 28 patients; range: 4-144 patients. Upstaging percentage: 16 studies reported upstaging percentage in their patient population; mean rate: 15%; range: 0-50%. Sentinel node mapping in rectal cancer • 2 studies included patients with sigmoid colon or rectal cancer and rectal cancer alone, respectively. • First study's identification rate 91% and false-negative rate 18%. • Second study's identification rate 96% and false-negative rate 56%. • Increased false-negative rate in second study may be due to higher proportion of patients (90%) with locally advanced disease, and a high proportion of patients receiving neo-adjuvant radiochemotherapy. Safety: • No reports linked radioactive tracers with allergic reaction or interference with patient monitoring. Authors conclusions: • Sentinel lymph node mapping in colorectal cancer is feasible. • Large variation in false-negative rates usually ascribed to the differences in sentinel node	

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			mapping techniques employed and tumor stage. Most of the included studies found sentinel node mapping in colorectal cancer to be unreliable in patients with lymph nodes containing macrometastases detected with hematoxylin and eosin staining. All of the studies identifying the first 4 blue nodes as sentinel showed low false-negative rates. • No consensus on the best tracer or combination of tracers to be used.	
Tuech JJ, Pessaux P, Regenet N, Bergamaschi R & Colson A, 2004 *Surgical Endoscopy*	Aim: to evaluate sentinel lymph node mapping as it applies to colon cancers, including its indications, limitations, benefits, implications, and future directions. Search period: (presumably from inception) until December 2003. Databases searched: Current Contents, Medline, EMBASE and the Cochrane Library. Search terms: multiple terms were used, as either single terms or matched terms: sentinel, lymph node, lymphatic mapping, staging, ultrastaging, blue dye, patent blue dye, sentinel node, nodal metastasis, metastasis, navigation surgery, molecular staging, micrometastasis, occult metastasis,	Inclusion criteria: prospective series that assessed lymphatic mapping of human patients with colon cancer either using *in vivo* procedure at laparotomy and laparoscopic surgery or using *ex vivo* procedures. Studies with at least 20 patients were considered. Exclusion criteria: multiple publications of the same study, abstracts alone, and case reports were excluded. Study selection and appraisal methods: in the case of multiple publications of the same study, to avoid potential double-counting of patients, the most recently published paper that maximized the overall sample number was used in the calculations conducted by the authors. No critical appraisal was performed.	*Seventeen non-duplicate studies* reported outcomes in a total of *682 patients* who underwent lymphatic mapping for colon cancer. Patient demographics: • No details on patient age or gender were presented. • No details on body mass index were presented. • 2 studies reported upon *ex vivo* lymphatic mapping • 1 study reported upon laparoscopic mapping. Sentinel node detection rate • Overall there was considerable variation in sentinel node identification (58-100%) (Note: text states 58-98%). 8 studies reported an overall detection rate ≥ 90%. *One study reported some technical errors (injection in the colon lumen) that could explain low rate of sentinel node identification (70%) in that study. • Calculated overall learning curve shows almost 100% sentinel node detection rate achievable after 5 cases. Inexperience in lymphatic mapping and multi-surgeon studies may contribute to low identification rate. • Some factors that may have attributed to inadequate sentinel node identification rate include: incomplete circumferential injection of blue dye around the tumor, large tumors that require larger amounts of blue dye, obstruction of lymphatic channels in nodes replaced by the tumor, and patients with previous colon surgery that may alter lymphatic flow patterns. • In the studies that used *ex vivo* techniques sentinel nodes were identified in 88-92% of patients. *this approach avoids intraoperative manipulation of the specimen to identify sentinel nodes; however, it could not identify an aberrant lymphatic route. • In the study that used laparoscopic techniques sentinel nodes were identified in 100% of patients. False-negative scores: • Overall there was considerable variation in false-negative rates (0 to 60%). • Rates below 10% occurred in 6 studies. • In the studies using *ex vivo* techniques false negative rate was 6% and 8.7%. • In the study using laparoscopic techniques false negative rate was 6.6%. • The majority of false-negatives (skip metastases) may be explained by surgical disruption of	• Extensive search strategy • Multiple databases searched • Extensive search terms used • Specific inclusion and exclusion criteria provided • No search date restrictions • Language restriction not reported • Handsearching of reference lists of all included studies • No hand searches of relevant journals • No consultation of relevant online health services • Data extraction and appraisal methodology not described • No description of data extraction tables provided • Extensive background • No profiles of included studies provided • Study duplication was avoided

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	lymphoscintigraphy, immunohistochemistry, step sectioning, RT-PCR, *ex vivo*, *in vivo*, molecular diagnosis, cytokeratin 20, keratin, isolated tumor cells, lymphadenectomy, gastrointestinal neoplasms, cancer, colorectal, colon, rectal, pericolic. Language restrictions: NR Additional information: the authors evaluated the references of each report included in the database as a result of the first search to find any other report not covered by the electronic search.		lymphatic drainage (causing lymph to drain via an alternate route), and to a lesser extent by inaccurate injection of the dye. • Nodal metastases may lead to obstruction and drainage through alternate pathways, and increasing tumor stage is inversely related to the probability of finding isolated metastases in the sentinel lymph nodes. Upstaging: • Overall, 13 studies reported upstaging. In these studies upstaging ranged from 0 to 25%. • In the studies that used *ex vivo* techniques upstaging occurred in 8.7% and 16.7% of patients. • In the study using laparoscopic techniques upstaging occurred in 14% of patients. Aberrant drainage: • This outcome was reported in 3 studies only, and varied from 0% to 29%. *when aberrant lymphatic drainage is identified a more radical resection and lymphadenectomy should be performed to achieve complete tumor excision. • In the studies that used *ex vivo* techniques aberrant drainage was reported in 0 patients. • In the study that used laparoscopic techniques aberrant drainage occurred in 8 (29%) patients – consequently their planned resection was altered. Safety: No safely outcomes were reported. Authors conclusions: • Focused examination of sentinel nodes has demonstrated micrometastases missed by conventional techniques, upstaging 10-15% of colorectal cancers. • The extent of colorectal surgery is defined primarily by the location of the tumor; therefore, the identification of sentinel nodes did not initially influence the extent of surgery. However, the identification of aberrant drainage through lymphatic mapping may result in wider mesenteric resection, thus, influence the extent of surgery. • Further follow-up evaluation to assess the prognostic significance of micrometastases for colon cancers is required before the staging benefits of sentinel node mapping can have therapeutic implications.	

Extraction table for included randomized controlled trial.

<table>
<tr><th>Study details</th><th>Intervention and definitions</th><th>Study design and inclusion/exclusion criteria</th><th>Study population</th><th>Results</th><th>Author(s) conclusions</th></tr>
<tr>
<td>Stojadinovic A, Nissan A, Protic M, Adair CF, Prus D, Usaj S, Howard RS, Radovanovic D, Breberina M, Shriver CD, Grinbaum R, Nelson JM, Brown TA, Freund HR, Potter JF, Peretz T & Peoples GE, 2007

Annals of Surgery

Aim: to determine whether step sectioning and cytokeratin immunohistochemistry of the sentinel lymph node(s) more accurately stages lymph nodes and identifies nodal micrometastasis undetected by conventional histopathology in patients with colon cancer.

Conflicts of interest: research supported by grants from the United States Military Cancer Institute.

NOTE: included in systematic review (Cahill et al 2008) but extracted separately because it is a high-quality study.</td>
<td>Procedure
Patients were randomly assigned to undergo standard complete surgical resection of the tumor-bearing colon, with en bloc regional lymphadenectomy followed by either: conventional histopathologic evaluation (conventional group) or sentinel lymph node mapping, biopsy, and ultrastaging (mapping group).

Mapping modality: ex vivo

Tracer: isosulfan blue dye

Volume of tracer: 0.5mL per cm of tumor diameter.

Injection modality: subserosally at the proximal and distal margin of the tumor along the longitudinal axis of the specimen and at 90 degrees from these injection sites. The injection site was then massaged for 5 minutes.

Operative approach: conventional group: open n=56 (68.3%), laparoscopic n=26 (31.7%). Mapping group: open n=70 (75.3%), laparoscopic n=23 (24.7%). P=0.31

Adjuvant treatment:</td>
<td>Level of evidence: II

Method of randomization: patients were randomized to one of two arms. Randomization was balanced between the two treatment arms stratified by clinical stage and extent of resection. Randomization utilized a stratified permuted block scheme and a separate randomization table for each participating study site with the aim of avoiding inequalities in treatment group assignment. The randomization sequence was concealed until the treatment group was assigned.

Allocation concealment: neither study participants nor those administering the treatment were blinded to group assignment.
A single senior study pathologist blinded to the nodal staging results conducted a centralized pathological review of all sentinel node sections.

Duration of follow-up: ‘no follow-up was required for this clinical trial’.

Losses to follow-up: 13 patients were excluded after randomization due to absence of invasive adenocarcinoma (n=5), gastrointestinal stromal tumor (n=1), distant metastatic disease (n=2), surgical specimen fixation failure (n=3), or failure to identify</td>
<td>Sample size: total 175 patients; conventional group 82 patients; mapping group 93 patients.

Statistical calculations of sample size were performed.

*see table 1 in results column for patient characteristics</td>
<td>Table 1: Baseline characteristics in 175 patients.
<table>
<tr><th>Characteristic</th><th>CG</th><th>MG</th><th>P value</th></tr>
<tr><td>Age</td><td></td><td></td><td></td></tr>
<tr><td>Mean ± SD</td><td>65.7±1.6</td><td>65±1.5</td><td></td></tr>
<tr><td>95% CI</td><td>62.5-68.9</td><td>62.1-68</td><td>0.76</td></tr>
<tr><td>Gender (M/F)</td><td>40/42</td><td>43/50</td><td>0.74</td></tr>
<tr><td>Location of tumor:</td><td></td><td></td><td></td></tr>
<tr><td>Right colon</td><td>29</td><td>43</td><td></td></tr>
<tr><td>Transverse colon</td><td>2</td><td>5</td><td></td></tr>
<tr><td>Left colon</td><td>15</td><td>9</td><td></td></tr>
<tr><td>Sigmoid colon</td><td>30</td><td>28</td><td></td></tr>
<tr><td>Multiple polyps/tumors</td><td>6</td><td>8</td><td>0.26</td></tr>
<tr><td>Extent of colon resection</td><td></td><td></td><td></td></tr>
<tr><td>Segment</td><td>62</td><td>67</td><td></td></tr>
<tr><td>> Segment</td><td>20</td><td>26</td><td>0.59</td></tr>
<tr><td>ASA Category*</td><td></td><td></td><td></td></tr>
<tr><td>I or II</td><td>50</td><td>43</td><td></td></tr>
<tr><td>III</td><td>29</td><td>47</td><td></td></tr>
<tr><td>IV</td><td>3</td><td>3</td><td>0.13</td></tr>
<tr><td>AJCC T and N</td><td></td><td></td><td></td></tr>
<tr><td>T0N0</td><td>3</td><td>6</td><td></td></tr>
<tr><td>TisN0</td><td>2</td><td>1</td><td></td></tr>
<tr><td>T1N0</td><td>6</td><td>6</td><td></td></tr>
<tr><td>T2N0</td><td>12</td><td>9</td><td></td></tr>
<tr><td>T3N0</td><td>26</td><td>37</td><td></td></tr>
<tr><td>T4N0</td><td>1</td><td>1</td><td></td></tr>
<tr><td>T2N1</td><td>4</td><td>7</td><td></td></tr>
<tr><td>T3N1</td><td>21</td><td>16</td><td></td></tr>
<tr><td>T4N1</td><td>0</td><td>1</td><td></td></tr>
<tr><td>T2N2</td><td>0</td><td>2</td><td></td></tr>
<tr><td>T3N2</td><td>6</td><td>7</td><td></td></tr>
<tr><td>T4N2</td><td>1</td><td>0</td><td>0.52</td></tr>
</table>
CG: conventional group; MG: mapping group; SD: standard deviation; CI: confidence interval.
*ASA category definitions not provided; T1: tumor limited to the (sub)mucosa; T2: tumor infiltrates muscularis propria, but not adventitia; T3: tumor infiltrates adventitia; N0: lymph nodes not involved, N1: 1-3 lymph nodes involved, N2: >4 lymph nodes involved.</td>
<td>Sentinel lymph node mapping, step sectioning, and immunohistochemistry identifies small volume nodal disease and improves staging in patients with resectable colon cancer.

False-negatives are attributable to a number of factors including extent of disease, mapping technique, timing and method of pathologic processing, the number of sentinel nodes evaluated, and the method of ultrastaging. The authors state their results suggest that false-negative where 1 or 2 blue nodes are identified are likely to represent technical failures (technical false-negatives) whereas when >2 blue nodes are discovered in false-negative cases they are likely to represent pathologic failure or skip metastases.

Standardization of working definitions, training, mapping technique, and pathologic processing and review are critical to the success of sentinel</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Intervention and definitions</th><th>Study design and inclusion/exclusion criteria</th><th>Study population</th><th>Results</th><th>Author(s) conclusions</th></tr>
<tr>
<td></td>
<td>unclear, 'clinical decisions regarding adjuvant chemotherapy were based on conventional pathologic nodal assessment and not influenced by findings of isolated cells or all clusters in sentinel lymph nodes, as the prognostic importance of micrometastatic disease remained undefined.'

Sentinel lymph node observation: sentinel nodes were defined as the first blue staining nodes to appear within 5-10 minutes of dye injection. All blue nodes (within that time) were dissected from the mesentery.

Pathological examination: conventional histopathologic evaluation (using paraffin embedding, single section hematoxylin and eosin staining, and microscopy), or sentinel lymph node mapping, biopsy, and ultrastaging (using step section with pancytokeratin immunohistochemistry in conjunction with standard histopathologic evaluation).

Tumor definitions
NR

Statistical analysis definitions
Identification rate: proportion of patients</td>
<td>sentinel lymph nodes (n=2; included in assessment of sentinel lymph node mapping and biopsy technique).
A total of 80 and 82 patients completed the study in the control and intervention groups, respectively.

Study period: August 2002 to April 2006

Procedural team details: surgeons participating in the trial were experienced surgical oncologists and colorectal surgeons. Six surgeons at 5 medical centers performed all of the procedures. Specimen procurement, handling, transport, processing, and analysis oversight were provided by senior regional study pathologists experienced with gastrointestinal pathology and cytochemistry.

Inclusion criteria: patients with biopsy-proven, primary, non-metastatic colon carcinoma or colon tumors clinically consistent with cancer and subsequently confirmed by pathology, who were older than 18 years were eligible for inclusion.

Exclusion criteria: patients with recurrent or metastatic colon carcinoma, those who received prior chemotherapy or radiotherapy, and those without pathologically confirmed adenocarcinoma were excluded.</td>
<td></td>
<td>Table 2: Identification rate.
<table>
<tr><th></th><th>CG</th><th>MG</th><th>P value</th></tr>
<tr><td>Total lymph nodes identified
Mean
95% CI</td><td>
16.9±1.2
14.6-19.2</td><td>
18.9±1.1
16.7-21.1</td><td>

0.23</td></tr>
<tr><td>Total positive non-sentinel nodes
Mean
95% CI</td><td>
1.4±0.4
0.6-2.1</td><td>
1.3±0.4
0.6-2.0</td><td>

0.92</td></tr>
</table>
CG: conventional group; MG: mapping group; CI: confidence interval.

Nodal upstaging
Table 3: Nodal upstaging.
<table>
<tr><th></th><th>CG</th><th>MG</th><th>P value</th></tr>
<tr><td>Nodal upstaging*</td><td>38.7%</td><td>57.3</td><td>0.019</td></tr>
<tr><td>Node-positive rate when cell aggregates ≤0.2mm were excluded</td><td>38.7</td><td>39</td><td>0.97</td></tr>
<tr><td>Node-positive patients identified by conventional staging</td><td>38.7</td><td>31.7</td><td>0.35</td></tr>
</table>
*using predetermined definition of node-positive disease defined as individual tumor cells or cell aggregates identified by hematoxylin and eosin and/or immunohistochemistry.
CG: conventional group; MG: mapping group.
• 10.7% (6/56) nodal upstaging was identified by mapping in patients who were found to be node-negative by conventional pathological assessment (false-negative).

Sentinel node ultrastaging
• Sentinel nodes successfully identified in 82/84 (97.6%) of patients.
• Median 2 sentinel nodes/patients. Range: 1-15 nodes/patient:
o 1 sentinel node was identified in 27 patients (32.9%)
o 2 sentinel nodes were identified in 23 patients (28%)
o 3 sentinel nodes were identified in 11 patients (13.4%)
o 4 sentinel nodes were identified in 6 patients (7.3%)
o 5 or more sentinel nodes were identified in 15 patients (18.3%)
• Node positive by conventional staging 26 patients (31.7%).
• Node positive by mapping 47 patients (57.3%).
• Accuracy of sentinel lymph node mapping and biopsy 90.2% (74/82 patients).
• Sensitivity of sentinel lymph node mapping and biopsy 69.2% (18/26 patients).
• No single clinical/pathologic/surgical factor emerged as an independent predictor of a positive sentinel node.
• False negative occurred in 8 cases (9.8%).</td>
<td>lymph node mapping for colon cancer.</td>
</tr>
</table>

Study details	Intervention and definitions	Study design and inclusion/exclusion criteria	Study population	Results	Author(s) conclusions
	having sentinel nodes identified with *ex vivo* dye injection. Accuracy of sentinel lymph node mapping and biopsy: proportion of patients with successful lymphatic mapping having sentinel node examination correctly reflect the tumor status of the nodal basin. Sensitivity of sentinel lymph node mapping: proportion of patients with positive nodes found by routine hematoxylin and eosin staining to have positive sentinel lymph nodes. Upstaging: proportion of patients with negative nodes found by conventional histopathology found to have micrometastatic disease upon focused examination of the sentinel lymph nodes. False-negative rate: proportion of patients with successful lymphatic mapping having tumor-positive non-sentinel nodes but sentinel nodes without apparent tumor cells (false-negatives/[false-negatives + true-positive])			• One variable was significantly correlated with the finding of false-negative sentinel nodes, it was the number of sentinel nodes identified: o For 1 sentinel node, true-positive (30.8%) versus false positive (75%) o For 2 sentinel nodes, 25.6% versus 12.5% o For 3 sentinel nodes, 12.8% versus 12.5% o For 4+ sentinel nodes, 30.8% versus 0% (P=0.049) • Mean number of sentinel nodes identified in false-negative cases was 1.4 and mean number of sentinel nodes identified in true-positive cases was 3.2 (P=0.07). • Exclusive site of metastasis in sentinel nodes found in 6 cases (10.7% of 56 non-sentinel node negative cases) by step section and hematoxylin and eosin staining alone, and in 15 cases by more meticulous ultrastaging of the sentinel node incorporating cytokeratin immunohistochemistry (26.8% of 56 non-sentinel node negative cases). Safety No data reported.	

Extraction tables for included non-randomized comparative evidence.

<table>
<tr><th>Study details</th><th>Intervention and definitions</th><th>Study design and inclusion/exclusion criteria</th><th>Study population</th><th>Results</th><th>Author(s) conclusions</th></tr>
<tr>
<td>van der Zaag ES, Buskens CJ, Kooij N, Akol H, Peters HM, Bouma WH & Bemelman WA, 2009

European Journal of Surgical Oncology

Aim: to compare the predictive value of sentinel node mapping between patients with colon and rectal cancer.

Conflicts of interest: authors declared no conflicts of interest or involvement with funding sources.</td>
<td>Procedure
Mapping modality: ex vivo

Tracer: patent blue V

Volume of tracer: 0.5-2mL

Injection modality: around tumor with colonic specimen intact (followed by gentle massage of the injection site)

Operative approach: colon cancer 64 open, 36 laparoscopic; rectal cancer 17 open, 15 laparoscopic (P=0.3)

Adjuvant treatment: 23 patients with rectal cancer underwent preoperative radiotherapy (some patients did not receive radiotherapy due to imminent occlusion or the preoperative diagnosis of villous adenoma with high grade dysplasia). Operation generally occurred within 5 days of final radiotherapy fraction (maximum 10 days).

Sentinel lymph node observation: for colon carcinoma the mesocolon was inspected and the first 1-4 blue nodes were identified as sentinel lymph nodes and dissected or marked with a suture. For</td>
<td>Level of evidence: III-2

Method of randomization: NA

Allocation concealment: the immunohistochemically stained slides were evaluated blind and independently by two experienced pathologists, who were unaware of the clinical data.

Duration of follow-up: NR

Losses to follow-up: NR

Study period: November 2006 to May 2008.

Procedural team details: NR

Inclusion criteria: patients with colorectal cancer operated on with a curative intent.

Exclusion criteria: patients with T4 carcinoma, or two adjacent colorectal carcinoma. Patients with locally advanced rectal cancer undergoing neo-adjuvant chemoradiotherapy were also excluded.</td>
<td>Sample size: 100 patients with colon cancer; 32 patients with rectal cancer
*control group consisting of 6 patients who underwent colon resection for benign disease.

Age (mean ± standard deviation): colon cancer 70.4 ± 15 years; rectal cancer 66.4 ± 12 years (P=0.2)

Gender (M/F): colon cancer 42/58; rectal cancer 17/15 (P=0.3)

Colon cancer stage*: Stage 1: 22 patients, Stage 2: 45 patients, Stage 3: 33 patients; rectal cancer Stage 1: 7 patients, Stage 2: 8 patients, Stage 3: 17 patients (P=0.08)
*Stage 1 indicates that the cancer has grown through the inner lining of the bowel but there is no cancer in lymph nodes; Stage 2 indicates that the cancer has grown through the outer covering of the bowel/into tissues or organs next to bowel but there is no spread to the lymph nodes or another area of the body; Stage 3 indicates the cancer has spread to the lymph nodes but not to other areas of the body.</td>
<td>Effectiveness
Table 1: Nodal identification.
<table>
<tr><th></th><th colspan="3">Total number identified (mean ± SD)</th></tr>
<tr><th></th><th>Colon cancer</th><th>Rectal cancer</th><th>P value</th></tr>
<tr><td>Lymph nodes</td><td>16.3 ± 8</td><td>12.4 ± 7</td><td>0.01</td></tr>
<tr><td>Sentinel lymph nodes</td><td>2.3 ± 3</td><td>1.1 ± 1</td><td>0.04</td></tr>
</table>
SD: standard deviation

Table 2: The predictive value of sentinel mapping.
<table>
<tr><th></th><th>Colon cancer</th><th>Rectal cancer</th><th>P value</th></tr>
<tr><td>Detection rate</td><td>92%</td><td>78%</td><td>0.03</td></tr>
<tr><td>Accuracy</td><td>95%</td><td>76%</td><td>0.005</td></tr>
<tr><td>Sensitivity</td><td>83%</td><td>57%</td><td>0.06</td></tr>
<tr><td>Negative predictive value</td><td>93%</td><td>65%</td><td>0.002</td></tr>
</table>
• 62% (62/100) of colon cancer patients considered nodal negative by routine pathology.
• 34% (11/32) of rectal cancer patients considered nodal negative by routine pathology.
• Overall upstaging incidence was not significantly different between patients with colon cancer (29%) or rectal cancer (27%).

Table 3: Factors influencing sentinel node accuracy in colon cancer.
<table>
<tr><th></th><th>Sentinel node correct (n=87)</th><th>Sentinel node not identified/incorrect (n=13)</th><th>P value</th></tr>
<tr><td colspan="4">Depth of tumor invasion</td></tr>
<tr><td>T1</td><td>21</td><td>1</td><td rowspan="3">0.06</td></tr>
<tr><td>T2</td><td>41</td><td>4</td></tr>
<tr><td>T3</td><td>25</td><td>8</td></tr>
<tr><td colspan="4">Number of positive nodes</td></tr>
<tr><td>N0</td><td>62</td><td>5</td><td rowspan="3">0.01</td></tr>
<tr><td>N1</td><td>16</td><td>3</td></tr>
<tr><td>N2</td><td>9</td><td>5</td></tr>
<tr><td>Tumor size</td><td>Mean 5.1 cm</td><td>Mean 4.8 cm</td><td>0.7</td></tr>
</table>
[a] T1: tumor limited to the (sub)mucosa; T2: tumor infiltrates muscularis propria, but not adventitia; T3: tumor infiltrates adventitia.
[b] N0: lymph nodes not involved, N1: 1-3 lymph nodes involved, N2: >4 lymph nodes involved.</td>
<td>Sentinel node mapping can accurately predict nodal status in patients with colon cancer.

Immunohistochemical analysis of sentinel nodes detected micrometastases in 11% of patients who did not display lymph node involvement – these types of patients may benefit from adjuvant therapy.

Sentinel node mapping in patients with rectal cancer is less reliable, this may be due to preoperative radiotherapy.</td>
</tr>
</table>

Study details	Intervention and definitions	Study design and inclusion/exclusion criteria	Study population	Results	Author(s) conclusions
	rectal carcinoma the identification of blue nodes took place in the pathology department (immediately after resection) to keep the circumferential resection margin intact. Pathological examination: tumors were staged according to the American Joint Committee on Cancer (AJCC) Tumor Node Metastasis classification 2002. All lymph nodes were collected and separated according to the location they were found. They were then cut in two with both sides stained with hematoxylin and eosin and evaluated for tumor involvement. If the sentinel node was negative for cancer, serial sectioning was performed at three levels of 500μm intervals. These three sections were stained with three monoclonal antibodies. Positive and negative controls were used to confirm the sensitivity and specificity of the antibodies. Tumor definitions Micrometastases: tumor cell deposits between 0.2-2.0mm Isolated tumor cells: tumor cell deposits smaller than 0.2mm			Table 4: Factors influencing sentinel node accuracy in rectal cancer. Sentinel node correct (n=19) / Sentinel node not identified/incorrect (n=13) / P value Depth of tumor invasion T1: 3 / 4 T2: 8 / 0 T3: 8 / 9 — 0.03 Number of positive nodes N0: 11 / 4 N1: 6 / 4 N2: 2 / 5 — 0.01 Tumor size: Mean 3.3 cm / Mean 3.7 cm — 0.4 Preoperative radiotherapy No: 7 / 2 Yes: 12 / 11 — 0.05 [a] T1: tumor limited to the (sub)mucosa; T2: tumor infiltrates muscularis propria, but not adventitia; T3: tumor infiltrates adventitia. [b] N0: lymph nodes not involved, N1: 1-3 lymph nodes involved, N2: >4 lymph nodes involved. Table 5: Correlation of sentinel node micrometastases and clinicopathological findings in 73 conventional N0 patients with colorectal cancer. No micrometastases (n=65) / Micrometastases (n=8) / P value Depth of tumor invasion T1: 6 / 0 — 0.7 T2: 17 / 2 T3: 42 / 6 Differentiation grade Well: 7 / 0 — 0.6 Moderate: 48 / 6 Poor: 10 / 2 Lymphangio invasion No: 63 / 3 — 0.0001 Yes: 2 / 5 [a] T1: tumor limited to the (sub)mucosa; T2: tumor infiltrates muscularis propria, but not adventitia; T3: tumor infiltrates adventitia. Safety No data reported.	

<table>
<tr><th>Study details</th><th>Intervention and definitions</th><th>Study design and inclusion/exclusion criteria</th><th>Study population</th><th>Results</th><th>Author(s) conclusions</th></tr>
<tr><td></td><td>Statistical analysis definitions
Identification rate (%): number of patients with successfully retrieved sentinel nodes x 100/ number of patients enrolled

Accuracy (%): number of patients with correct prediction of nodal status x 100/ number of patients with successfully retrieved sentinel nodes

Sensitivity (%): number of patients with tumor involved sentinel node x 100/ number of patients with successfully retrieved sentinel node and macrometastases in any lymph node

Negative predictive value (%): number of nodal negative patients with successfully retrieved sentinel nodes x 100/ (number of nodal negative patients + number of false negative patients)</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Nagata K, Endo S, Hidaka E, Tanaka JI, Kudo SE & Shiokawa A, 2006

Anticancer Research

Aim: to determine if infrared ray laparoscopy detects sentinel nodes with greater efficacy than</td><td>Procedure
Mapping modality: NR

Tracer: indocyanine green dye (ICG)

Volume of tracer: 5mL

Injection modality: 25mg of ICG diluted with 5ml distilled water was injected into the colon wall from the</td><td>Level of evidence: III-3

Method of randomization: NA

Allocation concealment: NR

Duration of follow-up: NR

Losses to follow-up: NR

Study period: July 2002 to December 2004</td><td>Sample size: 48 patients

Age (mean ± standard deviation): 63.9 ± 12.6 years, range: 40-88 years

Gender (M/F): 20/28

Body mass index (mean ± standard deviation): 22.5 ± 2.9 kg/m^2, range:</td><td>Effectiveness
Table 1: Identification of sentinel nodes on conventional laparoscopy and on infrared ray laparoscopy in patients with colorectal cancer.
<table>
<tr><th></th><th>Conventional laparoscopy</th><th>Infrared ray laparoscopy</th><th>P value</th></tr>
<tr><td>Number with sentinel nodes</td><td>32</td><td>169</td><td></td></tr>
<tr><td>Mean sentinel nodes/patient</td><td>0.68±0.86</td><td>3.5±1.7</td><td><0.001</td></tr>
<tr><td>Range of sentinel nodes/patient</td><td>0-3</td><td>0-7</td><td><0.001</td></tr>
</table></td><td>Three major findings:

1. Observation of sentinel nodes with ICG stain was far superior by infrared ray laparoscopy compared with conventional laparoscopy.

2. Technique of saline injection before dye injection facilitates easy and precise sentinel node mapping for colorectal cancer during laparoscopy-assisted colectomy.</td></tr>
</table>

<table>
<tr><th>Study details</th><th>Intervention and definitions</th><th>Study design and inclusion/exclusion criteria</th><th>Study population</th><th>Results</th><th>Author(s) conclusions</th></tr>
<tr>
<td>conventional laparoscopy.

Conflicts of interest: NR</td>
<td>serosal side via a percutaneously inserted 25-gauge long needle to ensure correct placement, then the ICG solution was carefully injected just proximal and distal to the tumor.

Operative approach: laparoscopic; conventional or infrared ray.

Adjuvant treatment: NR

Sentinel lymph node observation: 5 minutes after injected green-enhanced sentinel nodes were observed on conventional laparoscopy and black-enhanced sentinel nodes were observed on infrared ray laparoscopy.

Pathological examination: specimens were processed in a standard fashion and stained with hematoxylin and eosin. The primary neoplasm and all lymph nodes underwent routine microscopic analysis.

Tumor definitions
NR

Statistical analysis definitions
NR</td>
<td>Procedural team details: green- and black-enhanced sentinel nodes were confirmed by three surgeons.

Inclusion criteria: patients who underwent laparoscopy-assisted colectomy for colorectal or tumors in situ, including patients with malignant polyps that were partially or completely removed during colonoscopy but required segmental colon resection, or patients with large malignancy tumors that could not be removed during colonoscopy.

Exclusion criteria: NR</td>
<td>17-30 kg/m^2

Tumor site: cecum n=3, ascending colon n=5, transverse colon n=4, descending colon n=1, sigmoid colon n=24, upper rectum n=11

Tumor differentiation: well n=22, moderate n=22, mucinous n= 4

Depth of invasion*: pT1 n=25, pT2 n=4, pT3 n=19
P<0.0001 (pT1-2 versus pT3)
* T1: tumor limited to the (sub)mucosa; T2: tumor infiltrates muscularis propria, but not adventitia; T3: tumor infiltrates adventitia

Tumor node metastases status: I n=25, II n=12, III n=11, IV n=0
P<0.0001 (I/II versus III/IV)</td>
<td>

Infrared ray laparoscopy provided much better visualization of lymph nodes and vessels in mesenteric adipose tissue compared with white light (conventional laparoscopy) in the same region and at the same time.
Identification of sentinel nodes was approximately 5 times better using infrared ray compared with conventional laparoscopy.
In all 48 patients dye injection and tumor localization was performed precisely and successfully.

Table 2: Identification of lymph node metastasis on conventional laparoscopy and infrared ray laparoscopy (T1-T2).
<table>
<tr><th></th><th></th><th colspan="4">Proportion of nodes with metastasis</th></tr>
<tr><th></th><th></th><th colspan="2">Conventional laparoscopy</th><th colspan="2">Infrared ray laparoscopy</th></tr>
<tr><th>Patient</th><th>Num[a]</th><th>Positive [b]</th><th>Negative[c]</th><th>Positive[b]</th><th>Negative[c]</th></tr>
<tr><td>1</td><td>15</td><td>0/1</td><td>1/14</td><td>1/5</td><td>0/10</td></tr>
<tr><td>2</td><td>13</td><td>0/0</td><td>1/13</td><td>1/2</td><td>0/11</td></tr>
<tr><td>3</td><td>16</td><td>0/2</td><td>1/14</td><td>1/6</td><td>0/10</td></tr>
<tr><td>4</td><td>26</td><td>0/1</td><td>1/25</td><td>1/4</td><td>0/22</td></tr>
<tr><td>Total</td><td>70</td><td>0/4</td><td>4/66</td><td>4/17</td><td>0/53</td></tr>
</table>
[a] number of resected lymph nodes
[b] number of histologically confirmed lymph nodes as a proportion of number of resected lymph nodes stained on either laparoscopic technique.
[c] number of histologically confirmed lymph nodes as a proportion of number of resected lymph nodes not stained on either laparoscopic technique.

Black-enhanced nodes identified in 47/48 patients (97.9%) – in one failed case the tumor was pT3 stage.
Metastases were found in non-sentinel lymph nodes in 5 patients, all of these patients had pT3 tumors.
Successful sentinel node mapping, without false-negatives, were achieved in 42 patients.
Tumor site and differentiation were unrelated to the feasibility of sentinel node mapping.
Overall false-negative cases rate with infrared ray was 46.2% (66.7% in T3 disease) – there were no false-negative cases in T1 and T2 disease.
Additional sentinel nodes not detected by conventional laparoscopy but detected with infrared ray occurred in 44/47 patients (93.6%)
From the resected specimens the average number of lymph nodes was 21 ± 11.4 (standard deviation) per patient (range: 6-58)
Infrared ray laparoscopy detected 7 sentinel nodes in a patient with a body mass index of 30 compared with 0 sentinel nodes detected using conventional laparoscopy.
4/29 patients with T1 and T2 colorectal cancer were found to have lymph node metastasis on histopathological examination.

</td>
<td>3. Sentinel mapping on infrared ray laparoscopy might be feasible for stage T1 and T2 colorectal cancer.

The authors concluded their procedure was easy to perform and had a high success rate; however, more experience is necessary before sentinel node mapping could be routinely used during laparoscopic-assisted colectomy in patients with colorectal cancer.</td>
</tr>
</table>

Study details	Intervention and definitions	Study design and inclusion/exclusion criteria	Study population	Results	Author(s) conclusions
				Safety • There were no complications specifically related to conventional or infrared ray laparoscopy. • No patients had their procedure reverted to open surgery due to uncontrollable bleeding or trauma. • No tumors were punctured during dye injection.	