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Published in:
Critical Reviews in Oncology/Hematology

DOI:
10.1016/j.critrevonc.2020.103149

Publication date:
2021

Critical Reviews in Oncology / Hematology 158 (2021) 103149

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

In vivo sentinel lymph node identification using fluorescent tracer imaging in colon cancer: A systematic review and meta-analysis

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ARTICLE INFO

Keywords:
Fluorescence
Sentinel lymph node
Colon cancer

ABSTRACT

Introduction: The use of fluorescence might improve the performance of the sentinel lymph node procedure in patients with colon cancer. This systematic review was conducted to gain insight in the performance and applicability of the sentinel lymph node procedure using fluorescence.
Method: A systematic literature search was performed. Databases were searched for prospective studies concerning sentinel node identification using fluorescence in colon cancer. Detection rate, accuracy rate and sensitivity of the sentinel lymph node procedure were calculated for early stage (T1-T2) and more invasive (T3-T4) tumours.
Results: Analyses of five included studies showed for respectively T3-T4 and T1-T2 tumours a detection rate of 90 % and 91 %, an accuracy rate of 77 % and 98 %, and a sensitivity of 30 % and 80 %.
Conclusion: The sentinel lymph node procedure using fluorescence in early stage (T1-T2) colon cancer seems to be promising. Larger cohorts are necessary to confirm these results.

1. Introduction

Since the introduction of nationwide population screening programs for colorectal cancer, an initial increase of colon cancer was seen. More importantly, an increase in the incidence of T1-T2 tumours was found, with a subsequent increase in local excisions and polypectomies as treatment (de Neree tot Babberich et al., 2017; De Neree Tot Babberich et al., 2018).

Although the share of local treatment modalities for smaller colon tumours increases, the gold standard for the treatment of colon cancer consists of the en-bloc segmental colonic resection, including the adjacent mesocolon containing the draining lymph nodes (Landelijke werkgroep Gastro Intestinale Tumoren, 2019). However, these resections bear the risk of serious postoperative morbidity and mortality. Consequently, local resections seem a logical alternative for smaller colon tumours. Despite the low risk of lymph node metastases in smaller colon tumours, one of the problems regarding local resection is the inability to assess lymph node status after local resection. The resection of these adjacent draining lymph nodes is not only therapeutic, but also diagnostic, since lymph node status is one of the most important factors determining the use of adjuvant chemotherapy in patients (Landelijke werkgroep Gastro Intestinale Tumoren, 2019; Kapiteijn and van De Velde, 2000).

In addition to this, the tools routinely used for diagnosing lymph node metastases might be insufficient. Patients with stage I-II colon cancer do not have lymph-node metastases. However, around 20 % of these patients will develop recurrent disease (Weixler et al., 2016; Saha et al., 2018; Quasar Collaborative Group et al., 2007). This can possibly be explained by lymph node (micro)metastases that are missed using routine histopathological examination. Studies using 'ultrastaging' techniques report upstaging in 14–18 % of the patients (Bilchik and Trocha, 2003; Protic et al., 2015; Kelder et al., 2007). These upstaged patients are associated with a poor prognosis and could benefit from adjuvant chemotherapy (Liefers et al., 2002; Sirop et al., 2011; Bilchik et al., 2007). However, ultrastaging is time-consuming and expensive and therefore not applicable for current clinical practice.

A possible solution for both problems would be to use ultrastaging techniques for the sentinel lymph node (SLN). This is the first draining lymph node, which has the highest chance of containing metastatic tumour cells. Hereby ultrastaging could be implemented in patients

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https://doi.org/10.1016/j.critrevonc.2020.103149
Received 25 April 2020; Received in revised form 31 October 2020; Accepted 2 November 2020
Available online 11 November 2020

undergoing segmental resection without being time-consuming or expensive. In addition, the SLN procedure could provide clinicians with lymph node status in patients that undergo local resection.

Previous research on the concept of SLN identification in colon cancer showed disappointing results (Currie, 2019; van der Pas et al., 2011; Des Guetz et al., 2007). This is partly explained since many studies used patent blue or radiocolloid as a tracer. However, indocyanine green (ICG) has been advocated to be more useful in SLN identification for colon cancer, since fluorescent tracers such as ICG penetrate relatively deep in the adipose mesocolon compared to patent blue. Furthermore, a relatively high percentage of more invasive (T3-T4) tumours was included, while it has been suggested that large tumours lead to a disrupted lymphatic flow, resulting in higher false-negative rates (Joosten et al., 1999; Patten et al., 2004; Doekhie et al., 2006; Grinnell, 1966; Cahill et al., 2009a).

Therefore, this systematic review aims to create an overview of the existing literature regarding in vivo SLN identification with the use of fluorescent tracers in colon cancer. More specifically this study aims to compare early stage tumours (T1-T2) with more invasive (T3-T4) tumours.

2. Materials and methods

A systematic review was conducted according to the PRISMA (Liberati et al., 2009) and MOOSE guidelines (Stroup et al., 2000). The search strategy, as well as the inclusion and exclusion criteria, critical appraisal tool, and selected outcomes of interest were pre-specified. A review protocol was not registered in advance.

2.1. Eligibility criteria and literature search

Pubmed, Embase and Cochrane were used to perform a systematic search by two independent researchers (TAB and ALZ) at October 22nd, 2020, using the following search terms: (sentinel OR (lymph AND node)) AND ((colorectal OR colon) AND (cancer OR carcinoma OR neoplasm)) AND (fluorescence OR indocyanine green OR ICG). Studies were included if: 1) they described in vivo studies using a fluorescent tracer for SLN identification 2) had a prospective study design, 3) contained data on T1-T4 colon cancer. Studies were excluded when they were published in other languages than English, or when they did not resemble an original study.

Screening of title and abstract, and full-text assessment using the pre-specified inclusion and exclusion criteria was performed by the two researchers independently. Additionally, the reference lists of the eligible studies were blindly screened for possible eligible studies. Disagreements were resolved through discussion until consensus was reached. Quantitative analyses were performed in studies in which results of early stage (T1-T2) and more invasive (T3-T4) tumours could be distinguished. Authors of studies that provided insufficient data to distinguish between early stage and large tumours were requested by email to provide additional information.

2.2. Outcomes

Outcomes of interest were a successful SLN procedure, detection rate, accuracy rate, sensitivity and false negative rates of the SLN procedure. A successful SLN procedure was defined as a SLN procedure with detected SLN using a fluorescent tracer. Detection rate was defined as the number of procedures with a detected SLN divided by the total number of procedures. Accuracy rate was defined as the number of correct predictions of the nodal status in the SLN mapping procedure divided by the number of procedures with a detected SLN. Sensitivity was defined as the number of procedures with a tumour positive SLN divided by the number of procedures with a positive lymph node. False negatives were defined as patients with a tumour-negative SLN but with another lymph node being tumour positive. Furthermore safety and feasibility of the SLN procedure was assessed. Safety was defined as reported adverse events. Feasibility was defined as reported practical complications.

2.3. Qualitative analysis

Data was captured using a pre-specified form for all studies, containing data of the total group of patients. This pre-specified form contained author, year, study design, number of patients, location of the tumour, tumour staging, definition of SLN, in or ex vivo, used tracer, injection method, histopathological analysis, adverse events and practical complications. The QUADAS-2 tool was used to assess the quality of the studies. Both researchers (TAB and ALZ) reviewed the articles for the above-mentioned variables independently. Disagreement was resolved through discussion until consensus was reached.

2.4. Quantitative analysis

Data was captured using a pre-specified form for all studies that could present data separately for both T1-T2 and T3-T4 tumours. This pre-specified form contained the number of patients, number of successful SLN mappings, detection rate, accuracy rate, false negatives, and sensitivity. Both researchers (TAB and ALZ) reviewed the articles for the above-mentioned variables independently. Disagreement was resolved through discussion until consensus was reached.

2.5. Statistical analysis

Pooled estimates for detection rate, accuracy rate and sensitivity were calculated using Freeman-Tukey double arcsine transformation. Differences between T1-T2 tumours and T3-T4 tumours regarding detection rate, accuracy rate and sensitivity was calculated and plotted in a forest plot, with fixed or random effect models, based on the heterogeneity. Heterogeneity was assessed by I^2 and its connected Chi-square test. Sensitivity analyses were performed for the following variables: (1) Moderate-high study quality, defined as more high risk ratings than low risk ratings in the QUADAS-2 tool, (2) using ICG-HSA instead of ICG alone (3) using submucosal injection instead of subserosal injection and (4) studies in which a distinction could be made between colon and rectal cancer patients. If less than three studies would be included in the sensitivity analyses, these analyses were not performed. Statistical analysis was performed using R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria) with the package “meta” and “metabin”.

3. Results

The search was performed on October 22th, 2020 and yielded 505 articles, of which 389 articles remained after removing duplicates. After screening for title and abstract 309 articles were excluded: 204 articles did not regard a sentinel lymph node procedure, 36 papers were reviews and 33 papers were not original articles. This resulted in a total of 80 articles that were screened for full text. 70 articles were excluded: 45 articles did not concern sentinel lymph node identification, nine papers performed ex vivo SLN identification, four articles did not use a fluorescent tracer, 11 articles did not involve colorectal cancer, finally one paper was excluded due to overlap in included patients. This resulted in ten articles included in the qualitative analysis.

Six authors were requested to deliver additional data, only two authors responded and provided additional data of T1-T2 colon cancer patients. No additional papers were found following a manual-cross check. Finally, six articles were eligible for quantitative assessment (Fig. 1).

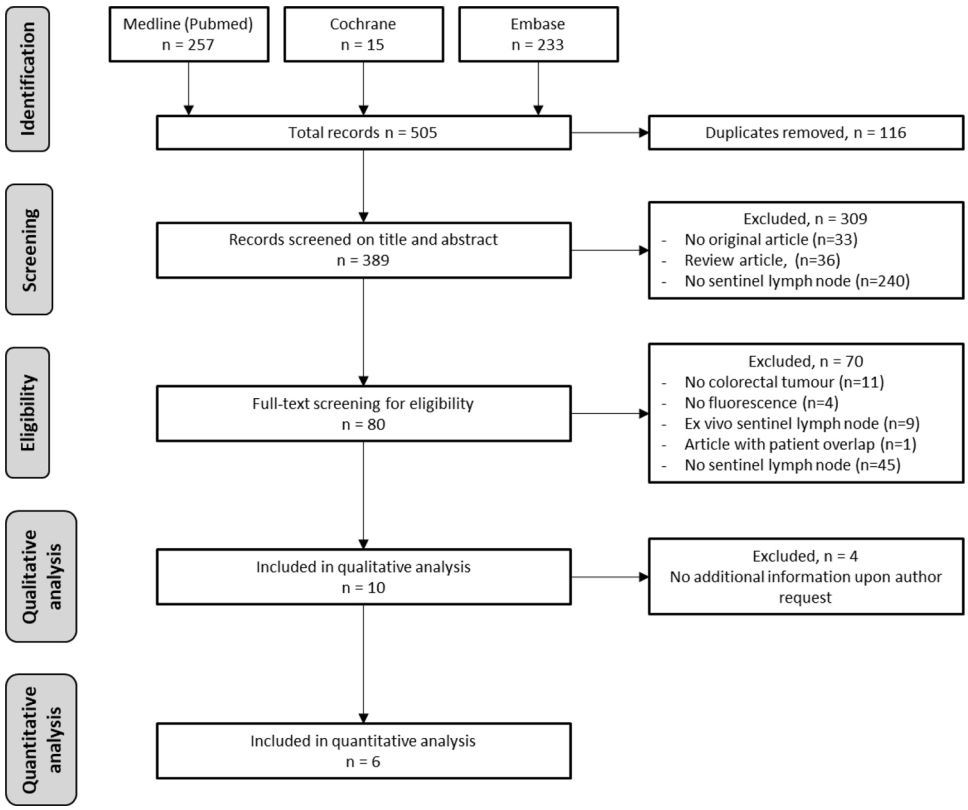

Fig. 1. Flow diagram of study selection procedures.

3.1. Qualitative analysis

The characteristics of the ten eligible studies are presented in Table 1 (Andersen et al., 2017; Currie et al., 2017; Cahill et al., 2012; Chand et al., 2018; Dan et al., 2014; Hirche et al., 2012; Kusano et al., 2008; Nagata et al., 2006; Ankersmit et al., 2019; Carrara et al., 2020). Studies were published between 2004 and 2019, with a total of 418 patients. Except for two studies (Dan et al., 2014; Carrara et al., 2020), studies included less than 50 patients. All studies had a prospective design, and one study was a multicentre trial (Andersen et al., 2017). Location of the tumour was either colorectal (Currie et al., 2017; Cahill et al., 2012; Dan et al., 2014; Kusano et al., 2008; Nagata et al., 2006; Carrara et al., 2020) or colon (Andersen et al., 2017; Chand et al., 2018; Hirche et al., 2012; Ankersmit et al., 2019). The definition of the SLN was absent in three studies (Chand et al., 2018; Hirche et al., 2012; Nagata et al., 2006) and differed between the remaining studies: three studies defined the sentinel node(s) as "the first 1–4 lymph nodes to become fluorescent" (Dan et al., 2014; Ankersmit et al., 2019; Carrara et al., 2020), while the other four studies defined the sentinel lymph nodes as "fluorescent spots to become apparent" (Andersen et al., 2017; Currie et al., 2017; Cahill et al., 2012; Kusano et al., 2008). All studies performed in vivo injection of the fluorescence, with only one study using lymphazurin and fluorescein instead of ICG (Dan et al., 2014). Concerning the location of the fluorescence injection, six studies performed subserosal injection (Andersen et al., 2017; Chand et al., 2018; Dan et al., 2014; Kusano et al., 2008; Nagata et al., 2006; Carrara et al., 2020), two studies performed submucosal injection (Currie et al., 2017; Cahill et al., 2012), one study performed both subserosal as well as submucosal injection (Ankersmit et al., 2019) and one study did not report the injection method (Hirche et al., 2012). Concerning pathological analysis, most studies used standard haematoxylin and eosin stain (H&E) analysis for SLNs and lymph nodes. Two studies performed additional immunohistochemistry (IHC) for the SLN (Andersen et al., 2017; Dan et al., 2014) and three studies performed additional IHC for the SLN if the SLN was negative after H&E (Currie et al., 2017; Hirche et al., 2012; Carrara et al., 2020). One paper performed additional IHC if the SLN was negative, but another LN was positive after H&E (Cahill et al., 2012). Finally, one remaining study performed additional IHC if either the SLN or the LN was negative after H&E staining (Ankersmit et al., 2019).

Concerning safety and feasibility, two studies did not report adverse events (Andersen et al., 2017; Cahill et al., 2012). All the other studies did not find any adverse events associated with the use of fluorescence in SLN identification. Concerning practical complications, three studies reported intra-abdominal spilling (Andersen et al., 2017; Currie et al., 2017; Carrara et al., 2020) and one study reported 12 fluorescent LNs after injection of ICG one day prior to surgery (Cahill et al., 2012).

For risk of bias assessment, the QUADAS-2 tool was used (Table 2). One study scored low risk of bias on all risk ratings (Ankersmit et al., 2019), four studies scored more high-risk of bias ratings than low-risk of bias ratings (Cahill et al., 2012; Chand et al., 2018; Kusano et al., 2008; Carrara et al., 2020) and the remaining five studies scored more low-risk of bias ratings than high-risk of bias ratings (Andersen et al., 2017; Currie et al., 2017; Dan et al., 2014; Hirche et al., 2012; Nagata et al., 2006).

3.2. Quantitative analysis

Analysis of more invasive (T3-T4) tumours included five studies, with a total of 118 patients involved. Within this group, 106 successful SLN procedures were reported. Furthermore 21 false negative SLNs were reported. Analysis of the T1-T2 group included six studies, with a total of 139 patients. Within this group 128 successful SLNs were reported, while six false negative SLN were found (Tables 3 and 4).

The pooled estimate of detection rate, accuracy rate and sensitivity were calculated and presented (Tables 3 and 4). A pooled estimate of 90 % and 91 % detection rate was calculated for respectively the T3-T4 group and the T1-T2 group. This difference was not statistically different (Fig. 2). A pooled estimate of 77 % and 98 % accuracy rate was

Table 1
Study characteristics of included studies; *N* number, *SLN* sentinel lymph node, *LN* lymph node, *ICG* indocyanine green, *H&E* haematoxylin and eosin, *IHC* immunohistochemistry, *NR* not reported, *HSA* humane serum albumin.

Author, year	Study design	N patients T1-T4	Location of tumour	Tumour staging	Definition of SLN	In vivo or ex vivo	Tracer	Location of injection	Mode of	Histopathological technique SLN	Histopathological technique LN	Adverse events	Practical complications
Andersen, 2017	Two institutions prospective	29	Colon	T1-T4	Fluorescent spots after 20min.	In vivo (ICG-HSA) Ex vivo (methylene blue)	ICG-HSA (25 mg ICG in 9 mL water and 1 mL 20% HSA)	0.5 mL 2 cm distal + proximal of the tumour	Subserosal	H&E IHC	H&E	NR	Intra-abdominal spillage (n=7)
Carrara, 2020	Single Institution prospective	95	Colon and rectum	T1-T4	The first LN that lights up after injection of fluorescent dye	In vivo	ICG	Two injections cranially and caudally	Subserosal	H&E IHC [if SLN (-),	NR	No adverse events	Intra-abdominal spillage (n=3)
Cahill, 2012	Single institution prospective	14	Colon and rectum	T1-T3	Fluorescent sentinel nodes lying within the intended field of resection.	In vivo	ICG	Three or four aliquots (2.8 mL in total) proximal + distal of the tumour	Submucosal	H&E IHC [if SLN (-), LN (+)]	H&E	NR	One case: injection one day before surgery: identification of 12 fluorescent LNs.
Currie, 2017	Single institution prospective	30	Colon and rectum	T1-T4	All fluorescent sentinel nodes lying within the intended field of resection	In vivo	ICG	Four aliquots of 1 mL around the tumour	Submucosal	H&E IHC [if SLN (-)]	H&E	No adverse events	ICG extravasated into peritoneum (n=7)
Chand, 2018	Single institution prospective	10	Colon	T1-T4	NR	In vivo	ICG (5mg/ 10 mL, 5mg/ 5 mL, 5mg/ 3 mL)	Four sites with 1 mL ICG	Subserosal	NR	NR	No adverse events	No practical complications
Dan, 2004	Single institution prospective	120	Colon and rectum	T1-T4	First 1–4 lymph nodes to become fluorescent	In vivo	1 % Lymphazurin 10 % Fluorescein	Surrounding the tumour (0.5−2 mL)	Subserosal	H&E IHC	H&E	No adverse events	No practical complications
Hirche, 2011	Single institution Prospective	26	Colon	T1-T4	NR	In vivo	ICG (5mg/mL)	2.0 mL	NR	H&E IHC [if SLN (-)]	H&E	No adverse events	No practical complications
Kusano, 2008	Single institution prospective	26	Colon and rectum	T1-T2	Lymph nodes draining ICG appeared as round spots of clear fluorescence	In vivo	0.5 % ICG solution	4 sites surrounding the tumour (0.5 mL)	Subserosal	NR	NR	No adverse events	No practical complications
Nagata, 2006	Single institution prospective	48	Colon and rectum	T1-T3	NR	In vivo	25 mg ICG diluted with 5 mL of distilled water	Proximal and distal to the tumour	Subserosal	H&E	H&E	No adverse events	No practical complications
Ankersmit 2019	Single institution prospective	29	Colon	T2-T3	First 1–4 lymph nodes to become fluorescent	In vivo	ICG-HSA (25 mL of ICG diluted in 1.0 mL of HSA (20 %)) and 1.0 mL NaCl 0.9 %	1−3 peritumoral injections	Subserosal (first 14) Submucosal (last 15)	H&E IHC [if SLN (-)]	H&E IHC [if SLN (-)]	No adverse events	No practical complications

Table 2
Risk of bias assessment according to QUADAS-2 tool (low risk: ☺, high risk: ☹, unknown risk:?).

	Risk of bias				Applicability concerns		
Author, year	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Andersen, 2017	?	☺	?	☹	☺	☺	☹
Cahill, 2012	?	☹	?	☹	☺	☺	☹
Carrara, 2020	☺	?	?	☹	☺	?	?
Currie, 2017	☺	?	?	☹	☺	☺	☹
Chand, 2018	☺	☹	☹	☹	☺	☹	☹
Dan, 2004	?	☺	?	☹	☺	☺	☹
Hirche, 2011	?	☺	?	☹	☺	☺	☹
Kusano, 2008	☹	☹	☹	?	☺	?	?
Nagata, 2006	☹	☹	☹	☺	☺	☺	☺
Ankersmit, 2019	☺	☺	☺	☺	☺	☺	☺

calculated for respectively the T3-T4 and the T1-T2 group (Tables 3 and 4). The T1-T2 group had a 1.25 [CI: 1.05–1.47] higher accuracy rate compared to the T3-T4 group (Fig. 3). Finally a pooled estimate of 30 % and 80 % sensitivity was calculated for the T3-T4 and the T1-T2 group. Sensitivity was 2.31 [CI 1.14–4.67] times higher in the T1-T2 group (Fig. 4). Sensitivity analyses for submucosal injection, and ICG-HSA was not possible due to the low amount of studies in these subgroups. Further sensitivity analyses showed no differences in outcomes.

4. Discussion

The concept of the SLN procedure as a diagnostic and prognostic tool in colon cancer has been thoroughly studied (van der Pas et al., 2011; Cahill et al., 2008). Regardless, sensitivity and accuracy rates remain relatively unsatisfying, calling for a need to optimize the procedure. Notably, most studies include more invasive tumours, which are known to alter lymph drainage patterns (Cahill et al., 2008, 2009b). Furthermore, visibility of generally used dyes such as patent blue is not sufficient due to the adipose mesocolon surrounding lymph nodes (Bembenek et al., 2007; Lim et al., 2008; Stojadinovic et al., 2007). Fluorescent markers such as ICG have been suggested to optimise the SLN procedure. The main focus of this review is to investigate the implementation and performance of the in vivo SLN procedure using fluorescent tracers in early stage colon cancer, while looking for elements that need to be improved for increasing the performance of the procedure.

For patients with T3-T4 colon cancer that underwent an in vivo SLN procedure using a fluorescent tracer, a pooled accuracy rate of 77 % and a pooled sensitivity rate of 30 % was found. For patients with T1-T2 colon cancer a pooled accuracy rate of 98 % and a pooled sensitivity rate of 80 % was found. Meaning that both the number of correct predictions of the nodal status using the SLN procedure (accuracy rate) and the rate of correct predictions of the lymph positive nodes using the SLN procedure (sensitivity) increases in patients with T1-T2 colon cancer compared to patients with T3-T4 colon cancer. The suggested improvement of sensitivity rates in small tumours (T1-T2) could be explained by the idea that more invasive tumours (T3-T4) alter the lymph drainage patterns, resulting in lower accuracy rate, lower

Table 3
Quantitative assessment of T3-T4 patients; *N* number, *SLN* sentinel lymph node, [a] Pooled estimate with random effects model.

Author, year	N patients T3-T4	N of successful SLN identification	Detection rate T3-T4	Accuracy rate T3-T4	False negatives T3-T4	Sensitivity T3-T4
Andersen, 2017	21	14	14/21 (67 %)	10/14 (71 %)	4	1/5 (20 %)
Carrara,2020	47	46	46/47 (98 %)	43/46 (93 %)	3	6/9 (67 %)
Currie, 2017	16	14	14/16 (88 %)	10/14 (71 %)	4	3/7 (43 %)
Kusano, 2008	–	–	–	–	–	–
Nagata, 2006	19	18	18/19 (95 %)	13/18 (72 %)	5	0/5 (0 %)
Ankersmit 2019	15	14	14/15 (93 %)	9/14 (64 %)	5	3/8 (38 %)
Total	118	106	106/118 (90 %)[a]	85/106 (77 %)[a]	21	13/34 (30 %)[a]

Table 4
Quantitative assessment of T1-T2 patients; *N* number, *SLN* sentinel lymph node, [a] Pooled estimate with random effects model.

Author, year	N patients T1-T2	N of successful SLN identification	Detection rate T1-T2	Accuracy rate T1-T2	False negatives T1-T2	Sensitivity T1-T2
Andersen, 2017	8	5	5/8 (63 %)	5/5 (100 %)	0	1/1 (100 %)
Carrara, 2020	48	46	46/48 (96 %)	46/46 (100 %)	0	2/2 (100 %)
Currie, 2017	14	13	13/14 (93 %)	11/13 (85 %)	2	0/2 (0 %)
Kusano, 2008	26	23	23/26 (89 %)	19/23 (83 %)	4	2/6 (33 %)
Nagata, 2006	29	29	29/29 (100.0 %)	29/29 (100 %)	0	4/4 (100 %)
Ankersmit, 2019	14	12	12/14 (86 %)	12/12 (100 %)	0	1/1 (100 %)
Total	139	128	128/139 (91 %)[a]	122/128 (98 %)[a]	6	10/16 (80 %)[a]

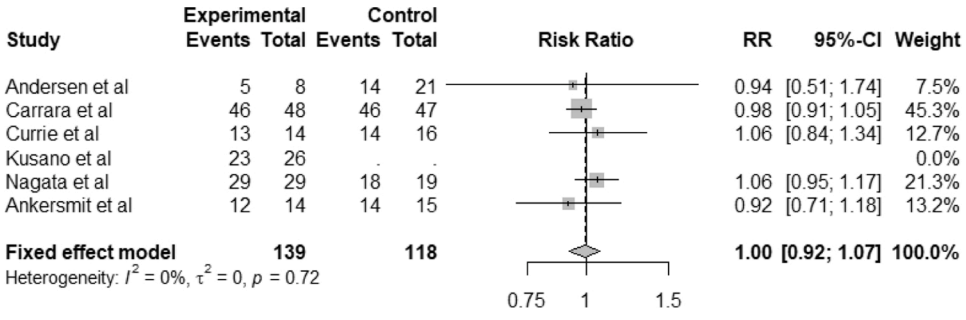

Fig. 2. T1-T2 vs T3-T4 detection rate.

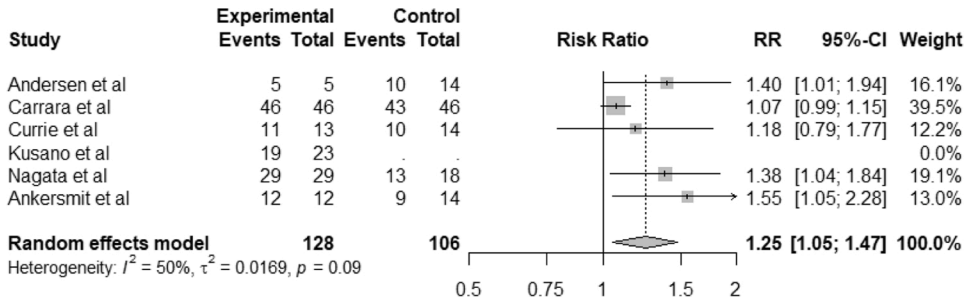

Fig. 3. T1-T2 vs T3-T4 accuracy rate.

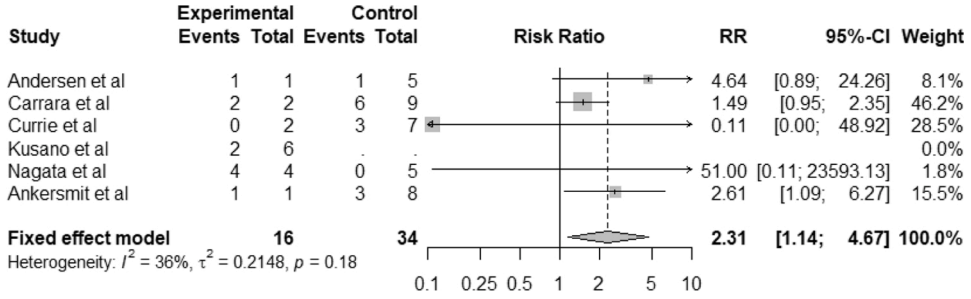

Fig. 4. T1-T2 vs T3-T4 sensitivity.

sensitivity and more skip lesions (Joosten et al., 1999; Patten et al., 2004; Doekhie et al., 2006; Grinnell, 1966; Cahill et al., 2009a). Although some authors suggested the influence of tumour stage on success rate of the SLN procedure, this association has not yet been established (van der Pas et al., 2011; Carrara et al., 2020).

A sensitivity rate of 80 % for the SLN procedure using fluorescence in T1-T2 colon cancer reported in this systematic review is higher than the sensitivity rate reported in a subanalysis for fluorescent tracers in a large systematic review (van der Pas et al., 2011). However they only included two studies using a fluorescent tracer. A more recent systematic review, included five studies using a fluorescent tracer, and reported a pooled sensitivity of 34 % (Qiao, 2020). Although these results appear disappointing, in contrast to our systematic review, certain studies were not included (Cahill et al., 2012; Chand et al., 2018; Dan et al., 2014; Nagata et al., 2006). Furthermore, no distinction between colon and rectum, or size of the tumor (T1-T2 vs T3=-T4) was made, which might explain the difference. Nevertheless, a sensitivity rate of 80 % in T1-T2 tumours is still not satisfying. We suggest this to be an effect of small studies, with low experience of the surgeon influencing the results, as it has been suggested that experience of the surgeon is of importance for the performance of the fluorescent SLN procedure (Cahill et al., 2009a; Bembenek et al., 2007). Furthermore, since the T1-T2 group consisted of a small amount of patients, sensitivity is a rather inaccurate value due to the low rates of events. Accuracy rate might therefore be a better parameter resembling a trustworthy SLN procedure. Clearly, this analysis showed that accuracy rate increases in the T1-T2 group. However, in order to adequately investigate the performance of the SLN procedure in T1-T2 colon cancers, a larger group of patients is needed with more events.

Besides the performance, safety and feasibility of the SLN is an important issue. No adverse events associated with fluorescent tracers were described in the included articles. Furthermore, studies primarily focusing on adverse events regarding ICG reported a very low number of adverse events (Murawa et al., 2014; Summary of product characteristics of indocyanine green, 2016). Therefore, using ICG seems to be relatively safe. Concerning practical complications of the procedure, three articles reported intra-abdominal leakage of ICG, leading to the inability to adequately assess SLN status intra-abdominally (Andersen et al., 2017; Currie et al., 2017; Carrara et al., 2020). This could be prevented by injecting the fluorescent tracer submucosally instead of subserosally, as performed by several authors as well (Currie et al., 2017; Cahill et al., 2012; Ankersmit et al., 2019). Nevertheless, this requires a complex logistical planning, since intra-operative colonoscopy is required for submucosal injection of the fluorescent tracer.

Furthermore, the method of fluorescent tracer injection might influence accuracy rate and sensitivity as well. Unfortunately, we could not perform sensitivity analysis due to the low amount of studies in this subgroup. Lymphatic networks of the colon are composed of two non-communicating parts: one containing the lacteals draining the villi and connecting submucosal lymphatic network, and the second containing the lymphatics draining the intestinal muscular layer. These systems deliver lymph into a common network of lymphatics vessels assembling near the mesenteric border (Miller and Newberry, 2021). Most studies inject the tracer in the serosal layer of the colon. However, injecting into the submucosal layer would theoretically seem to be the most beneficial, since colorectal tumours most commonly appear in the mucosal layer. Ankersmit et al. showed a sensitivity of 80 % while injecting in the submucosal layer, while having a sensitivity of 0 % if the ICG was injected into the subserosal layer (Ankersmit et al., 2019). Furthermore, Cahill et al. showed promising results with the submucosal injection of ICG (Cahill et al., 2012). However, Currie et al. showed a low sensitivity, perhaps this is explained by the fact they included relatively large tumours in their study (Cahill et al., 2009a; Currie et al., 2017).

Although the results of this systematic review and meta-analysis appear to be promising, certain things should be taken into consideration. First, only a limited amount of studies could be included in the quantitative analysis, thereby increasing the risk of bias in general. More specifically, the risk on publication bias is plausible. By only including articles in the quantitative analysis, a distinction between T1-T2 patients and T3-T4 patients could be made. However, despite contacting all of the authors, some studies had to be excluded. The limited amount of studies combined with the low amount of patients per study, resulted in a low event rate for sensitivity, making this a rather inaccurate parameter. Therefore, accuracy rate might better represent the performance of the SLN procedure in small datasets. Taken into account the above,

confirmation of sensitivity and accuracy rates in larger datasets is necessary. Secondly, as all of the included studies in the quantitative analysis were small studies, bias due to mastering the technique is introduced, which is known to influence the outcomes (Cahill et al., 2009a; Bembenek et al., 2007). Lastly, the quality of most studies, as assessed by the QUADAS-2 tool was low-moderate, underlining the urge for more large, high quality studies.

Despite these limitations, this study provides a clear overview of the in vivo SLN procedure in colon cancer using fluorescent tracers. The SLN procedure seems safe and feasible, and it appears that small colon tumours (T1-T2) result in higher accuracy rate and sensitivity rate. In addition, studies reporting on submucosal injection of ICG suggest that this technique might result in higher accuracy rate and sensitivity rates. In order to adequately report on the sensitivity of the SLN procedure, a large cohort of patients should be included in a prospective study investigating SLN identification by submucosal injection of ICG in small (T1-T2) colon tumours.

4.1. *Future perspectives*

Currently, the standard surgical procedure is segmental resection including removal of surrounding lymph nodes, and bares the risk of high postoperative morbidity rate. If the SLN procedure would prove to be an adequate staging technique for lymph nodes in colon carcinoma, local resection using minimal invasive surgery or endoscopic resection with an additional SLN excision after submucosal injection of indocyanine green around the tumour could be performed. Minimal invasive surgery can be performed using robot-assisted surgery, which provides a set of new technologies that can easily be applied, such as fluorescence guided surgery with the Firefly camera on the da Vinci Robotic Surgical Systems (Intuitive Surgical, Inc, Sunnyvale, CA, USA). Imaginably, this could be applied in patients with small (T1-T2) colon tumours using a hybrid minimal invasive procedure in which indocyanine green will be injected submucosally around the tumour through endoscopy. Meanwhile, the surgeon will be able identify the SLN intra-abdominally using the near-infrared Firefly of the Robotic system. After ICG injection and SLN identification, an endoscopic transmural resection can be performed under the direct intra-abdominal robot-assisted surveillance. The surveillance will prevent damage to other structures, while enabling surgical closure of the colonic defect with sutures. This hybrid procedure could be the new minimal invasive procedure replacing the standard segmental resection for small (T1-T2) colon tumours.

Funding

No funding was received for this study.

CRediT authorship contribution statement

T.A. Burghgraef: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Visualization, Writing - original draft, Writing - review & editing. **A.L. Zweep:** Data curation, Formal analysis, Investigation, Writing - original draft, Writing - review & editing. **D.J. Sikkenk:** Formal analysis, Methodology, Validation, Visualization, Writing - review & editing. **M.H.G.M. van der Pas:** Conceptualization, Methodology, Supervision, Writing - review & editing. **P.M. Verheijen:** Conceptualization, Methodology, Supervision, Writing - review & editing. **E.C.J. Consten:** Conceptualization, Methodology, Supervision, Writing - review & editing.

Declaration of Competing Interest

The authors report no declarations of interest.

Acknowledgments

There are no acknowledgments.

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