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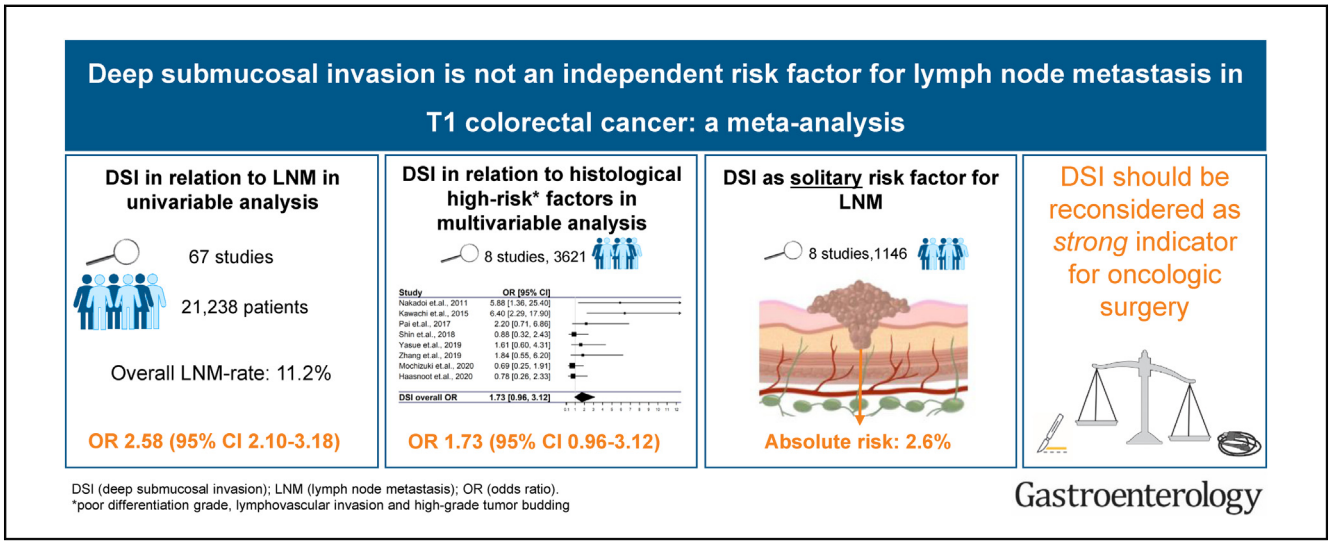
Deep Submucosal Invasion Is Not an Independent Risk Factor for Lymph Node Metastasis in T1 Colorectal Cancer: A Meta-Analysis

Liselotte W. Zwager,[1,2,3] Barbara A. J. Bastiaansen,[1,2,3] Nahid S. M. Montazeri,[4] Roel Hompes,[5] Valeria Barresi,[6] Katsuro Ichimasa,[7] Hiroshi Kawachi,[8] Isidro Machado,[9] Tadahiko Masaki,[10] Weiqi Sheng,[11] Shinji Tanaka,[12] Kazutomo Togashi,[13] Chihiro Yasue,[14] Paul Fockens,[1,2,3] Leon M. G. Moons,[15] and Evelien Dekker[1,2,3]

[1]Amsterdam University Medical Centers location University of Amsterdam, Department of Gastroenterology and Hepatology, Amsterdam, the Netherlands; [2]Amsterdam Gastroenterology Endocrinology Metabolism, Amsterdam, the Netherlands; [3]Cancer Center Amsterdam, Amsterdam, the Netherlands; [4]Biostatistics Unit, Department of Gastroenterology and Hepatology, Amsterdam University Medical Center, University of Amsterdam, Amsterdam, The Netherlands; [5]Department of Surgery, Amsterdam University Medical Center, Amsterdam Cancer Center, University of Amsterdam, Amsterdam, The Netherlands; [6]Department of Diagnostics and Public Health, University of Verona, Verona, Italy; [7]Digestive Disease Center, Showa University Northern Yokohama Hospital, Tsuzuki, Yokohama, Japan; [8]Department of Pathology, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan; [9]Pathology Department, Instituto Valenciano de Oncología and Patologika Laboratory Hospital Quiron Salud, Valencia, Spain; [10]Department of Surgery, Kyorin University, Shinkawa, Mitaka City, Tokyo, Japan; [11]Department of Pathology, Fudan University, Shanghai Cancer Center, Shanghai, China; [12]Department of Endoscopy, Hiroshima University Hospital, Hiroshima, Japan; [13]Coloproctology, Aizu Medical Center, Fukushima Medical University, Aizuwakamatsu, Fukushima, Japan; [14]Department of Gastroenterology, The Cancer Institute Hospital, Japanese Foundation for Cancer Research, Koto-ku, Tokyo, Japan; and [15]Department of Gastroenterology and Hepatology, Utrecht University Medical Center, Utrecht, The Netherlands



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BACKGROUND & AIMS: Deep submucosal invasion (DSI) is considered a key risk factor for lymph node metastasis (LNM) and important criterion to recommend surgery in T1 colorectal cancer. However, metastatic risk for DSI is shown to be low in the absence of other histologic risk factors. This meta-analysis determines the independent risk of DSI for LNM. **METHODS:** Suitable studies were included to establish LNM risk for DSI in univariable analysis. To assess DSI as independent risk factor, studies were eligible if risk factors (eg, DSI, poor differentiation, lymphovascular invasion, and high-grade tumor budding) were simultaneously included in multivariable analysis or LNM rate of DSI was described in absence of poor differentiation, lymphovascular invasion, and high-grade tumor budding. Odds ratios (OR) and 95% CIs were calculated. **RESULTS:** Sixty-seven studies (21,238 patients) were included. Overall LNM rate was 11.2% and significantly higher for DSI-positive cancers (OR, 2.58; 95% CI, 2.10–3.18). Eight studies (3621 patients) were included in multivariable meta-analysis and did not weigh DSI as a significant predictor for LNM (OR, 1.73; 95% CI, 0.96–3.12). As opposed to a significant association between LNM and poor differentiation (OR, 2.14; 95% CI, 1.39–3.28), high-grade tumor budding (OR, 2.83; 95% CI, 2.06–3.88), and lymphovascular invasion (OR, 3.16; 95% CI, 1.88–5.33). Eight studies (1146 patients) analyzed DSI as solitary risk factor; absolute risk of LNM was 2.6% and pooled incidence rate was 2.83 (95% CI, 1.66–4.78).

CONCLUSIONS: DSI is not a strong independent predictor for LNM and should be reconsidered as a sole indicator for oncologic surgery. The expanding armamentarium for local excision as first-line treatment prompts serious consideration in amenable cases to tailor T1 colorectal cancer management.

Keywords: T1 Colorectal Cancer; Deep Submucosal Invasion; Lymph Node Metastasis; Risk Stratification.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Ample evidence suggests a low risk for lymph node metastasis (LNM) in T1 colorectal cancer (CRC) with deep submucosal invasion (DSI) when other risk factors are absent.

NEW FINDINGS

This meta-analysis shows that DSI is not an independent risk factor for LNM. Furthermore, the absolute risk for LNM in DSI cancers as sole risk factor is low (2.6%).

LIMITATIONS

This meta-analysis is mainly based on retrospective cohorts using different inclusion and exclusion criteria, which are more sensitive to confounding variables.

IMPACT

DSI should be reconsidered as sole indicator for surgery. The expanding endoscopic armamentarium is expected to lead to a higher number of patients that can be spared radical surgery.

GI CANCER

The detection of T1 colorectal cancer (CRC) has increased significantly since the implementation of screening programs.[1] The risk for LNM in T1 CRC varies between 1% and 34% and depends on the presence of histologic risk factors.[2–6] Established histologic criteria to predict LNM in T1 CRC include deep submucosal (SM) invasion $\geq$1000 μm or SM2–3 (deep submucosal invasion [DSI]), poor differentiation (PD), lymphovascular invasion (LVI), and high-grade tumor budding (TB). If 1 or more of these risk factors are present, the patient is deemed "high risk" for LNM and oncologic surgery with adequate mesocolic lymphadenectomy is considered the reference treatment standard.[7–9] Although 70%–80% of patients are classified as high risk using these criteria, the vast majority (>90%) will end up lymph node–negative on histologic evaluation of the surgical specimen.[10] Surgical overtreatment remains a major issue in T1 CRC and optimal management must strike the right balance between oncologic safety and minimizing treatment-associated morbidity and mortality.[11,12]

Guidelines consider DSI a high-risk factor for LNM and strong indicator for radical surgery.[7–9] Because DSI is the only factor that can be assessed optically before resection, its presence shapes management decisions. Currently, DSI is the most prevalent criterion to refrain from endoscopic resection or refer for additional surgery.[13,14] However, studies have shown conflicting results on its predictive value, and accumulating evidence suggests DSI is only a weak predictor for LNM in the absence of other risk factors, with rates of approximately 1.6%–2.2%.[15–17] This limited risk may outweigh surgery-related mortality and recurrence despite oncologic surgery.[10,11,18]

Availability and technical improvements of local excision techniques like endoscopic submucosal dissection (ESD), endoscopic full-thickness resection (eFTR), and transanal minimal invasive surgery are evolving and enable complete local excision as first-line treatment, also when deeper submucosal invasion is present.[19] A total excisional biopsy can be a viable option to allow for histopathologic risk assessment and guide further treatment. Moreover, high-quality evidence shows that a local excision does not affect surgical or oncologic outcomes in patients who need completion surgery.[20–23] To optimize T1 CRC management and increase chances for organ preservation, it is important to know whether DSI significantly predicts LNM. This meta-analysis aimed to study DSI as an independent risk factor for LNM in T1 CRC.

Materials and Methods

This meta-analysis was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement.[24] The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO registration number: CRD42020145938).

Search Strategy

The literature search was designed with assistance of a medical sciences librarian. Electronic literature databases MEDLINE (PubMed), EMBASE (Ovid), and the Cochrane Library (Cochrane Central Register of Controlled Trials) were searched from inception till 19 July 2021. The full search strategy is detailed in the Supplementary Material. Bibliographies of key articles, review articles, and meta-analyses were manually searched to identify additional studies.

Study Selection

All studies reporting on the association between LNM and specific histologic risk factors as DSI, PD, LVI, and TB in patients with T1 CRC treated with primary endoscopic resection, primary radical surgery, or completion surgery from the year 2000 up to July 2021 were assessed for eligibility.

In order to describe DSI as a risk factor for LNM, all studies analyzing DSI in univariable analysis were included, regardless of presence of other risk factors. To assess DSI as independent risk factor for LNM in relation to the other main risk factors (PD, LVI, and TB), the following studies were considered:

Abbreviations used in this paper: **CRC, colorectal cancer; DSI, deep submucosal invasion; eFTR, endoscopic full-thickness resection; ESD, endoscopic submucosal dissection; LNM, lymph node metastasis; LVI, lymphatic and/or vascular invasion; OR, odds ratio; PD, poor differentiation; SM, submucosa; TB, tumor budding.**

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1. studies in which the above-mentioned 4 main histologic risk factors were simultaneously included in a multivariable analysis and
2. studies reporting the rate of LNM in T1 CRC with DSI as the only present high-risk factor while the other 3 risk factors (PD, LVI, and TB) were assessed and negative.

Excluded were studies reporting on: 1) lesions of pedunculated morphology only, 2) lesions with tumor stages other than T1 CRC without data separation, 3) endoscopic-resected lesions without additional surgery and information on LNM status during follow-up, 4) fewer than 10 patients, and those that were 5) not available in English language, 6) not available in full text, and 7) published as conference abstracts only. In case of overlapping patient data, results of the most recent study or most relevant to our aim were included.

Definitions of Deep Submucosal Invasion

Various definitions and measuring methods have been used to evaluate DSI (see Table 1 for an overview). For studies performing univariable analysis, all definitions of DSI used were taken into account, except for studies using a mean measured value of DSI. For the purpose of determining the independent risk of DSI for LNM, only studies in which DSI was defined as SM2–3 and/or $\geq$1000 μm were included.

Other Included Risk Factors for Lymph Node Metastasis

Other established histologic risk factors for the prediction of LNM assessed in our study were PD, LVI, and TB. Despite lack of standardization and considerable variation in measurement methods, we included all studies reporting on their presence. Studies that evaluated LVI as 2 individual separate parameters—lymphatic and vascular invasion—could not be included in multivariable analysis, as the inclusion and correction for the same number of parameters is obligatory to assess the independent risk of DSI in meta-analysis.

Data Extraction

Two reviewers (L.Z., B.B.) independently assessed titles and abstracts of all references retrieved by our search. Irrelevant studies and duplicates were excluded. Remaining studies were retrieved in full text and screened by the same 2 reviewers. Disagreement regarding inclusion on abstract or full-text level was resolved by consensus. Consensus was obtained via discussion and agreement among 3 authors (L.Z., B.B., E.D.). If data were incomplete or multivariable analysis was not performed for our included parameters, the authors were contacted to share additional data in a standardized extraction form (Supplementary Material) or to share individual patient data. After receipt, additional data were checked on completeness and consistency. Extracted data from each study included the following: first author, year of publication, country, recruitment period, study design, total number of patients, number of patients with LNM, location, morphology, type of treatment, reported definition of DSI, risk of DSI and LNM, presence of specific histologic risk factors, and risk of LNM. The assessment of study quality and risk of bias is reported in the Supplementary Material.

Statistical Analysis

Descriptive analysis was used to summarize study findings. To evaluate the impact of DSI on LNM across the included studies, a univariable meta-analysis was performed. The overall odds ratio (OR) and 95% CI was provided to show association.

To assess the overall impact of DSI on LNM in presence of other risk factors, multivariable meta-analysis was performed in which all 4 histologic risk factors (DSI, PD, LVI, and TB) were included simultaneously. If the required data for our analysis were not reported in the original publication, the authors were contacted to provide multivariable analysis for these 4 specific factors or to provide raw patient data. Finally, meta-analysis was performed to determine the incidence rate of LNM in studies where DSI was described as the only present risk factor in the absence of PD, TB, and LVI. The overall OR and 95% CI were provided to show the association for each risk factor separately. Heterogeneity among studies was captured by the random-effects model and was assessed by means of I^2 statistics. Publication bias was assessed by a funnel plot. All analyses were performed using R statistical software (version 3.6.1) using the *Meta* package and $P < .05$ was considered as statistically significant.

Sensitivity Analysis

In total, 5 sensitivity analyses were performed. These aimed to assess the impact of variations of information. For univariable meta-analysis, we performed a sensitivity analysis for studies using only a cutoff value of $\geq$1000 μm for the definition of DSI, as this is the most commonly used definition. For both univariable and multivariable meta-analyses, additional sensitivity analysis for studies that included only nonpedunculated lesions was performed to check for differences in results. Another sensitivity analysis was performed for multivariable analysis regarding studies from Asian countries. Final sensitivity analysis for multivariable analysis included only studies with lesions treated by primary radical surgery to check for changes in results when possible less advanced lesions treated by primary endoscopic resection were excluded from analysis.

Results

Search Results and Study Characteristics

Our search identified 3042 articles, as outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis flow diagram (Figure 1). After removal of 1032 duplicates, titles and abstracts of 2010 records were relevant for further analysis and 1813 were excluded. After full-text evaluation, 67 studies (21,238 patients) met our inclusion criteria.[2–6,13–17,23,25–81]

Detailed study characteristics are shown in Supplementary Table 1. No randomized trials were identified and only 5 studies were prospective cohort studies. Three studies (241 patients) included data on T1 rectal cancer only.[17,31,43] In total, 4254 patients (20.0%) had rectal cancer, 8455 patients (39.8%) had colon cancer, and this distinction could not be made in 8529 patients (40.2%). Regarding morphology, 9220 lesions were described as nonpedunculated (43.4%) and morphology was not described clearly for 9955 lesions (46.9%).

Table 1. Overview of Definitions and Methods of Measuring of Deep Submucosal Invasion

Study, year	Definition of DSI	Methods of measuring DSI
Pedunculated		
Haggitt, 1985[99]	DSI is defined as level 4 (invasion into the submucosa to a level deeper than the stalk)	Depth of submucosa invasion is divided into 5 levels of invasion: level 0 (noninvasive disease without invading the m. mucosae), level 1 (tumor invading through the m. mucosae into the submucosa but limited to the head of the lesion, level 2 (tumor invasion extending into the neck of the lesion), level 3 (tumor invading any part of the stalk), and level 4 (tumor invading into the submucosa to a level deeper than the stalk but above the m. propria).
Kitajima, 2004[3]	DSI is defined as $\geq$1000 μm	Depth of submucosal invasion is measured as the distance between Haggitt's level 2 and the deepest invasion point.
Ueno, 2004[67]	DSI is defined as $\geq$2000 μm	Depth of submucosal invasion is measured as the distance between the tumor surface and the deepest invasion point.
JSCCR 2010,[100] 2014,[101] 2016,[102] and 2019[8]	DSI is defined as $\geq$1000 μm	For pedunculated lesions with tangled m. mucosae, depth of submucosal invasion is measured as the distance between the point of deepest invasion and the reference line, starting between the head and the stalk of the tumor. Tumors are classified as head invasion (invasive cancer tissue was confined to the head of the polyp; corresponding to Haggitt's level 1) or stalk invasion (cancer invaded into the stalk of the polyp; corresponding to Haggitt's level 2 or deeper).
Nonpedunculated		
Kudo, 1993[103]	DSI was defined as a submucosal invasion depth $\geq$SM2	Depth of submucosal invasion is divided into upper third (SM1), middle third (SM2), and lower third (SM3).
Kikuchi, 1995[104]	DSI was defined as a submucosal invasion depth $\geq$SM2	Depth of submucosal invasion is divided into slight submucosal invasion from the m. mucosa to the depth of 200 to 300 μm (SM1), intermediate between SM1 and SM3 (SM2) and carcinoma invasion near the inner surface of the m. propria (SM3).
Nascimbeni, 2002[2]		Depth of submucosal invasion is divided into upper third (SM1), middle third (SM2), and lower third (SM3).
Kitajima, 2004[3]	DSI is defined as $\geq$1000 μm	Depth of submucosal invasion is measured for tumors with an identifiable m. mucosae from the lowest border of the m. mucosae to the deepest invasive front. If the m. mucosae is not identifiable, the depth is measured from surface to the invasive front.
Ueno, 2004[67]	DSI is defined as $\geq$2000 μm	Depth of submucosal invasion is measured as the distance between the tumor surface and the deepest invasion point.
JSCCR 2010,[100] 2014,[101] 2016,[102] 2019[8]	DSI is defined as $\geq$1000 μm	Depth of submucosal invasion is measured from the lower border of the m. mucosae, if it is possible to identify the m. mucosae of the lesion. When it is not easy to identify the m. mucosae, the depth of submucosal invasion is measured from the surface of the lesion.

JSCCR, Japanese Society for Cancer of the Colon and Rectum; m. mucosae, muscularis mucosae; m. propria, muscularis propria.

Fifty studies were performed in Asia (17,772 patients), 14 in Europe (2293 patients), 2 in North America (143 patients), and 1 study included a combined Asian and North American cohort (400 patients). Of all 67 studies, 63 included patients treated by primary radical and/or completion surgery and 4 included patients treated with primary radical surgery, completion surgery, and/or endoscopic resection with follow-up.

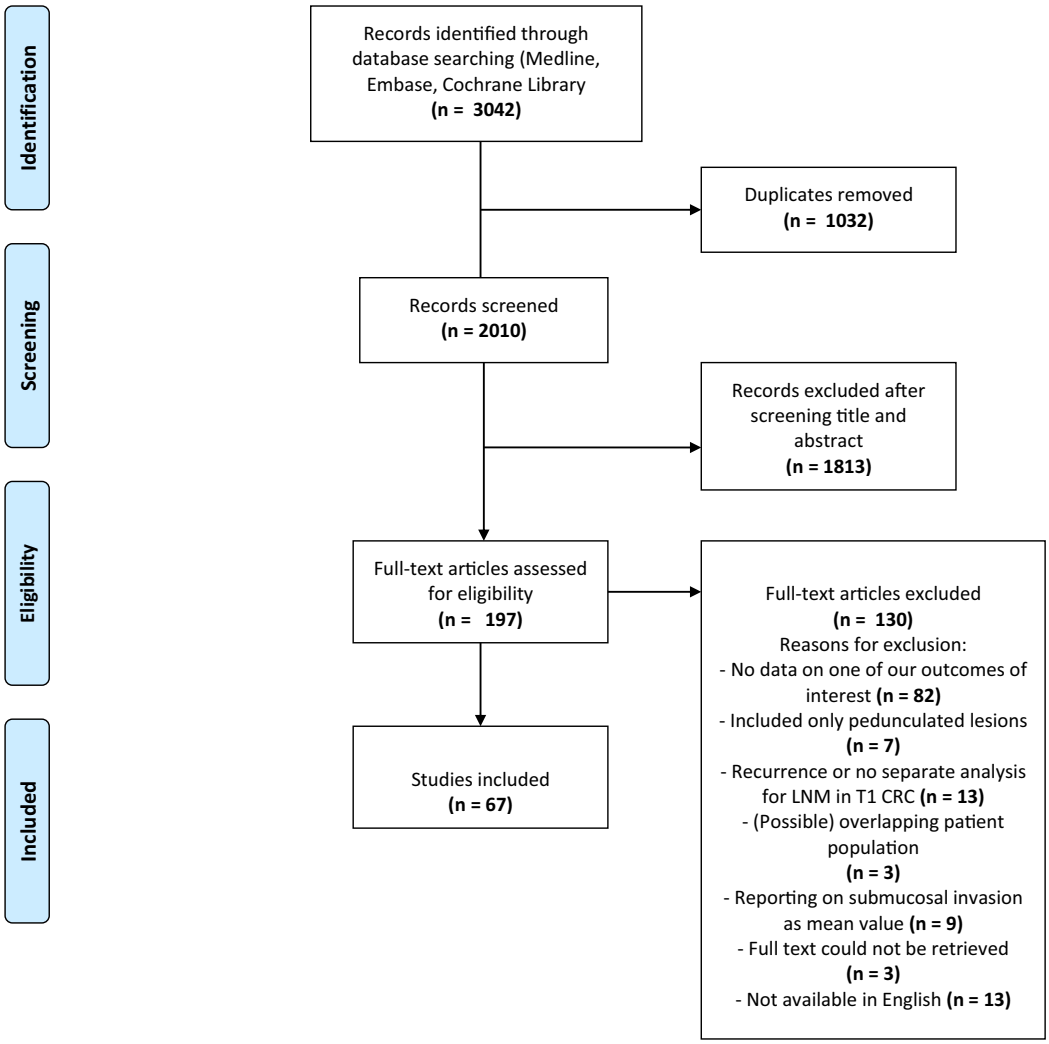

Figure 1. Flow chart of selection process.

Study Selection

All 67 studies analyzed the risk of DSI for LNM irrespective of the presence of other risk factors, and all were included in univariable meta-analysis. In 3 studies, DSI was simultaneously included in a multivariable analysis with PD, LVI, and TB and could be included in our multivariable meta-analysis.[15,57,62] In another 29 studies, multivariable analysis for LNM was performed, but included additional risk factors or did not include all 4 risk factors of interest. After contacting all 29 authors, we received additional data regarding the risk factors of interest in relation to LNM from 8.[15,16,26,39,47,49,51,73] Five studies provided their results in a standardized data extraction form[16,39,49,70,73] and 3 shared raw patient data.[26,33,47] After analyzing data of those 8 studies, 3 could not be included: 2 did not include any cases containing PD and in 1 the OR of DSI could not be assessed, as none of the cases with superficial invasion had LNM.[26,47,70] In total 8 studies (3621 patients) could be included in multivariable analysis.[15,16,33,39,51,57,62,73]

For sensitivity analysis of studies including only lesions treated with primary radical surgery in multivariable analysis, we requested additional data from 6 studies that were already included in multivariable analysis and received additional patient data from 4.[15,16,33,51] Finally, 8 studies (1146 patients) provided a detailed description of the relationship between each histologic risk factor or combination of risk factors and rate of LNM. In these studies, the risk of DSI as sole risk factor could be analyzed.[15–17,29,31,32,39,42,67] All included studies were judged according to quality in prognosis studies (Supplementary Material). In total, 13 studies were at high risk of bias.[14,17,34,35,38,40,46,52,54,64,69,78,79] The risk of bias assessment did not lead to exclusion of studies. There was no evidence of publication bias, with all studies lying within the 95% CI of the funnel plot (Supplementary Figure 1).

Deep Submucosal Invasion in Relation to Lymph Node Metastasis

In all 67 studies (21,238 patients), univariable analysis was performed to determine the risk of DSI in relation to LNM. The overall rate of LNM was 11.2% (2363 of 21,025), excluding 1 study (213 patients) that did not report the overall rate of LNM. Univariable meta-analysis showed DSI

is a significant risk factor for the presence of LNM (OR, 2.58; 95% CI, 2.10–3.18; 67 studies, Figure 2). Notably, the definition for DSI varied among studies. When studies reported both quantitative and qualitative definitions of DSI, we used the quantitative definition for analysis. Except for 1 study using a cutoff level of 1900 μm, we used Kudo's classification. Quantitative cutoff values for DSI varied between 300 and 3000 μm. Sensitivity analysis including only studies using a cutoff level of 1000 μm for DSI (43 studies) showed no changes with significant association between DSI and LNM (OR, 2.32; 95% CI, 1.80–2.97) (Supplementary Figure 2). Another sensitivity analysis was performed including only studies on nonpedunculated lesions (16 studies), which also demonstrates a significant association between DSI and LNM (OR, 2.86; 95% CI, 1.87–4.38) (Supplementary Figure 3).

Deep Submucosal Invasion in Presence of Other Risk Factors Simultaneously Included in Multivariable Analysis

In total, 8 studies (3621 patients) were included in our multivariable analysis. Concerning the definitions of risk factors, 7 studies used a similar cutoff level of 1000 μm for DSI. One study primary reported a cutoff level of 2000 μm, but it could be included in our multivariable analysis after we received additional data using a cutoff level of 1000 μm. For TB, all 8 studies described budding as foci of isolated cancer cells or clusters at the invasive front of the lesion. Seven studies regarded 5 or more foci as positive and 1 study used 10 foci as positive. LVI was reported as lymphatic, vascular, and/or venous invasion, and PD was classified according to the World Health Organization criteria and Japanese guidelines. For detailed description of all definitions used see Table 2.

Our multivariable analysis reveals DSI is not a significant predictor for LNM (OR, 1.73; 95% CI, 0.96–3.12) in the presence of other risk factors, including PD, TB, and LVI. In contrast, multivariable meta-analysis showed a significant association between LNM and PD (OR, 2.14; 95% CI, 1.39–3.28), TB (OR, 2.83; 95% CI, 2.06–3.88), and LVI (OR, 3.16; 95% CI, 1.88–5.33) (Figure 3). Sensitivity analysis over 3 studies considering exclusively nonpedunculated morphology did not change our findings (OR, 1.32; 95% CI, 0.70–2.46). In addition, sensitivity analysis for studies with Asian origin (OR, 1.92; 95% CI, 0.91–4.05) and for lesions treated with primary radical surgery (OR, 1.26; 95% CI, 0.66–2.41) did not change the outcome (Supplementary Figures 4–6).

Deep Submucosal Invasion in Absence of Other High-Risk Factors

In total 8 studies (1146 patients) analyzed the risk of DSI as sole risk factor for LNM. In the absence of PD, LVI, and TB, the absolute risk of LNM for DSI was 2.6% (30 of 1146), with a pooled incidence rate of 2.83 (95% CI, 1.66–4.78) (Figure 4). The proportion of all DSI cancers without other histologic high-risk factors was 37.9% (95% CI, 36.2%–39.7%) (Supplementary Table 2). Nonpedunculated lesions were reported in 5 studies, and in the other 3 studies morphology was not specified. Sensitivity analyses were not performed because only 2 studies included nonpedunculated lesions exclusively.

Discussion

This meta-analysis was conducted to investigate the independent predictive value of DSI for the presence of LNM in T1 CRC in relation to other established histologic risk factors (ie, PD, TB, and LVI). In multivariable analysis, no significant association between LNM and DSI was found and, according to these results, DSI does not classify as an independent risk factor for LNM. Moreover, our study demonstrates that the absolute risk for LNM in deep submucosal invasive cancer is low (2.6%) in the absence of PD, TB, and LVI. These findings are in contrast to previously published meta-analyses and may have important implications for clinical practice and future research.[82–85]

Many studies have reported an array of histologic factors associated with an increased risk of LNM, of which DSI, PD, LVI, and TB have shown to be consistent and strong predictive factors.[82–85] Whereas others can only be assessed on pathologic examination, SM invasion depth can be evaluated optically before treatment using high-definition chromoendoscopy (virtual or dye-based) and validated classification systems, such as the Japan Narrow Band Imaging Expert Team, Narrow-Band Imaging International Colorectal Endoscopic system, and/or Kudo.[86,87] En-bloc local resection is only recommended for lesions at high risk for superficial submucosal invasion.[88] Therefore, optical assessment of invasion depth influences treatment selection. For lesions with optical signs of deeper submucosal invasion, international guidelines recommend radical surgery.[7–9,89] This recommendation is based on a considerable body of evidence, including several meta-analyses describing DSI as a significant risk factor for LNM in T1 CRC.[82–85] Similar to these findings, our univariable meta-analysis showed a significantly higher rate of LNM in DSI-positive cancers. However, to correct for the confounding effect of concomitant presence of other risk factors, all 4 established risk factors should be included simultaneously in multivariable analysis, and this was not done in any of the meta-analyses performed previously.[82–85,90]

Our multivariable analysis showed that DSI is not an independent risk factor for LNM and its strength lies in the collection of additional raw patient data from Asian and Western centers, which results in a large number of patients (n = 3621) to allow for statistically significant analysis. These results are further highlighted in our meta-analysis for DSI cancers lacking other histologic criteria, showing a low absolute risk for LNM of 2.6%, questioning the advantage of radical surgery. As the risk for recurrent disease in T1 CRC is never zero and even a radical oncologic resection for low-risk T1 CRC harbors a risk of recurrent disease, this absolute risk for LNM must be balanced against surgery-related mortality (1.7%) and recurrence, despite oncologic surgery (0.7%–1.0%).[11,12,21,91] Until now, focusing on DSI has shaped treatment decisions, and endoscopic treatment

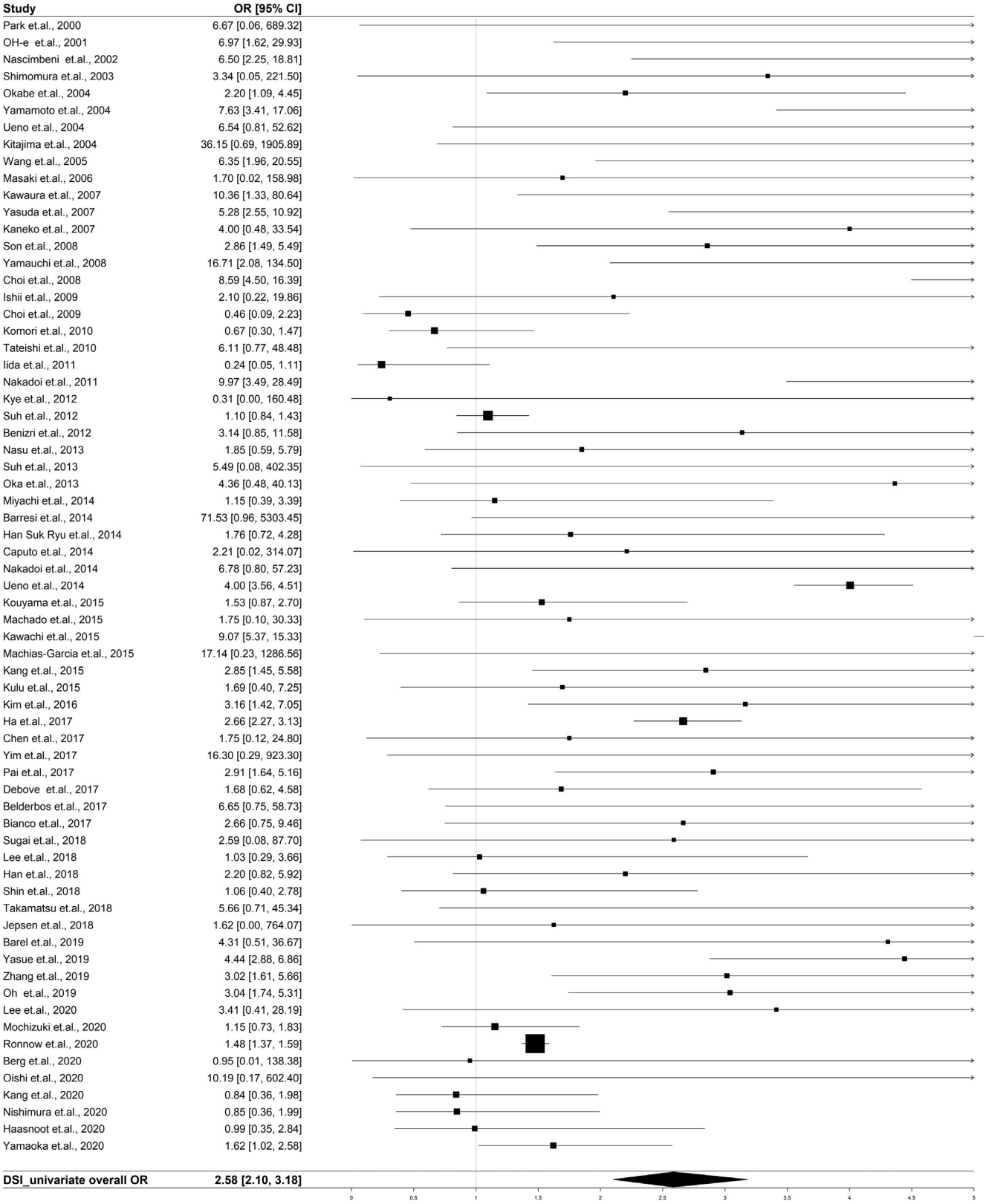

Figure 2. Forest plot with odds ratios of risk of DSI in relation to LNM.

Table 2. Studies Describing Deep Submucosal Invasion in Presence of Other Histologic Risk Factors in Multivariable Analysis

First author, year	Total included patients, n[a]	Nonpedunculated cases, n (%)	Treatment method	Definition of DSI	Definition of PD	Definition of LVI	Definition of TB
Haasnoot, 2020[33]	225	225 (100)	Primary surgery and additional surgery	Deep invasion was defined as invasion depth $\geq$1000 μm by Kitajima or Kikuchi level SM2–3.	Histologic grade was classified in view of the World Health Organization criteria.[105]	LVI was performed via H&E staining and defined as the presence of cancer cells within endothelial-lined channels.	TB was measured, defined, and scored using the standardized, evidence-based method for TB assessment as described previously: a cancer cell nest consisting of 1 or $<$5 cells that infiltrates the interstitium at the invasive margin of the tumor; after selecting 1 field where budding is the most intensive, the number of buds is counted in a field measuring 0.785 mm^2. Depending on the number of buds, the grade of budding is defined as grade 1 (0–4 buds), grade 2 (5–9 buds), or grade 3 ($>$10 buds). Grade 1 is considered low-grade TB, and grades 2 and 3 are considered high-grade TB.
Mochizuki, 2020[51]	745	NA	Primary surgery and additional surgery	Depth of submucosal invasion was evaluated according to the JSCCR classification 2019 as $<$1000 μm (T1a) and $\geq$1000 μm (T1b).	Histologic grade was classified in view of the World Health Organization criteria.	Vascular invasion was diagnosed by double staining with H&E and Victoria blue and lymphatic invasion was diagnosed by H&E staining and immunostaining with D2-40 antibody.	Cancer cell nest consisting of 1–5 cells at the invasive margin of the carcinoma. After selecting the field where budding was the most intensive, the number of buddings was counted with a 20$\times$ objective lens. Budding grade was scored as follows: grade 1: 0–4; grade 2: 5–9; and grade 3: $\geq$10, grade 2–3 was defined as TB positivity.

Table 2. Continued

First author, year	Total included patients, n[a]	Nonpedunculated cases, n (%)	Treatment method	Definition of DSI	Definition of PD	Definition of LVI	Definition of TB
Yasue, 2019[15]	846	846 (100)	Endoscopy, primary surgery, and additional surgery	Depth of submucosal invasion was evaluated according to the JSCCR classification 2020 as $<$1000 μm (T1a) and $\geq$ 1000 μm (T1b).	Histologic grade was classified in view of the JSCCR guidelines 2016.	Pathological investigation was performed for all these samples via H&E staining, additional D2-40 staining and Victoria blue-H&E staining were performed to evaluate lymphatic invasion and venous invasion, respectively. Surgical resection samples underwent lymphovascular evaluation using only H&E staining; immunostaining was not performed.	Cancer cell clusters made up of 1–4 constituent cells present at the stroma of invasive front. TB was graded according to the number of budding foci in a field of a 20$\times$ objective lens: grade 1: 0–4, grade 2: 5–9, and grade 3: $\geq$10, grade 2–3 was defined as TB positivity.
Zhang, 2019[73]	172	172 (100)	Primary surgery	Submucosal invasion depth was evaluated by the JSCCR guidelines 2016 as $<$1000 μm and $\geq$ 1000 μm.	Histologic grade was classified in view of the World Health Organization criteria.	For LVI evaluation immunohistochemical staining of D2–40 and special staining of elastic fiber to facilitate the evaluation was performed.	The numbers of budding in a hotspot area with the densest budding were counted. The presence of 5 or more budding foci under a 20$\times$ objective lens was defined as positive state.
Shin, 2018[62]	213	155 (72.8)[b]	Additional surgery	Submucosal invasion was classified as SM1, SM2, and SM3. In the sessile lesions, the cutoff limit was between SM1–2 was a submucosal depth of 1000 and $>$2000 was SM3, SM2, and SM3 were defined as deep submucosal invasion. In pedunculated tumors, the cutoff limit between SM1 and SM2 was the level of the neck, and submucosal depth $>$ 3000 μm from the neck was defined as SM3.	Histologic grades were classified as low or high. High-grade included poorly differentiated adenocarcinoma, undifferentiated adenocarcinoma, signet ring cell carcinoma, mucinous adenocarcinoma, and small cell carcinoma.	Vascular invasion was defined as the presence of cancer cells within endothelial-lined channels.	An isolated cell or a small cluster of $<$ 5 tumor cells in the invasive front was defined as a “budding” focus, and $>$ 10 budding foci viewed at 200 $\times$ magnification was defined as budding positive.

Table 2. Continued

First author, year	Total included patients, n[a]	Nonpedunculated cases, n (%)	Treatment method	Definition of DSI	Definition of PD	Definition of LVI	Definition of TB
Pai, 2017[57]	115	84 (72.4)	Primary surgery	Submucosal invasion depth was evaluated according to the JSCCR guidelines 2014 as $<$1000 μm and $\geq$1000 μm.	Histologic grade was classified in view of the World Health Organization criteria.	Lymphatic invasion	Tumor buds were defined as isolated cancer cells or a cluster of $<$5 neoplastic cells at the invasive front of the tumor. The tumor invasive front was assessed at a scanning (10$\times$ objective) magnification for the area with maximal tumor budding. Tumors were classified as having low TB if 0 to 4 tumor buds were identified per 0.95 mm^2 and high tumor budding if $\geq$5 tumor buds were identified per 0.95 mm^2.
Kawachi, 2015[39]	806	667 (82.8)	Primary surgery and additional surgery	Submucosal invasion depth was evaluated according to the JSCCR 2010 guidelines as $<$1000 μm and $\geq$1000 μm.	Histologic grade was classified in view of the JSCCR 2010 guidelines. Histologic grade was classified into 2 levels, low grade (well differentiated to moderately differentiated) or high grade (poorly differentiated, mucinous carcinoma, or signet-ring cell carcinoma), and the most predominant component was considered the histologic grade of each tumor.	Lymphatic and venous invasion within the tumor as well as in the adjacent tissue was evaluated based on H&E-stained sections and graded as positive or negative.	TB was assessed based on the number of foci of isolated cancer cells or a cluster comprising $<$5 cells in the invasive frontal region. Budding was counted in a field measuring 0.95 mm^2 using a 20$\times$ objective lens and 10$\times$ ocular lens, and classified as grade 1 (0–4 foci in the field), grade 2 (5–9 foci), or grade 3 ($\geq$10 foci). Grade 2–3 was defined as TB-positivity.
Nakadoi, 2012[16]	499	NA	Primary surgery and additional surgery	Submucosal invasion depth was evaluated according to the JSCCR 2010 guidelines as $<$1000 μm and $\geq$1000 μm.[c]	Histologic grade was classified in view of the World Health Organization criteria.	Vascular invasion	A bud was defined as a single cancer cell or a cluster of $<$5 cells along the invasive margin, and budding was graded per microscopic field at 200$\times$ magnification: grade 1, 0–4 buds; grade 2, 5–9 buds; or grade 3, 10 or more buds. Grade 2–3 was defined as TB positivity.

JSCCR, Japanese Society for Cancer of the Colon and Rectum; NA, not applicable.
[a]Only the total number of cases included in our study were included in the total number of patients
[b]Defined as non-polypoid or sessile.
[c]Received additional data with 1000 μm as cutoff level.

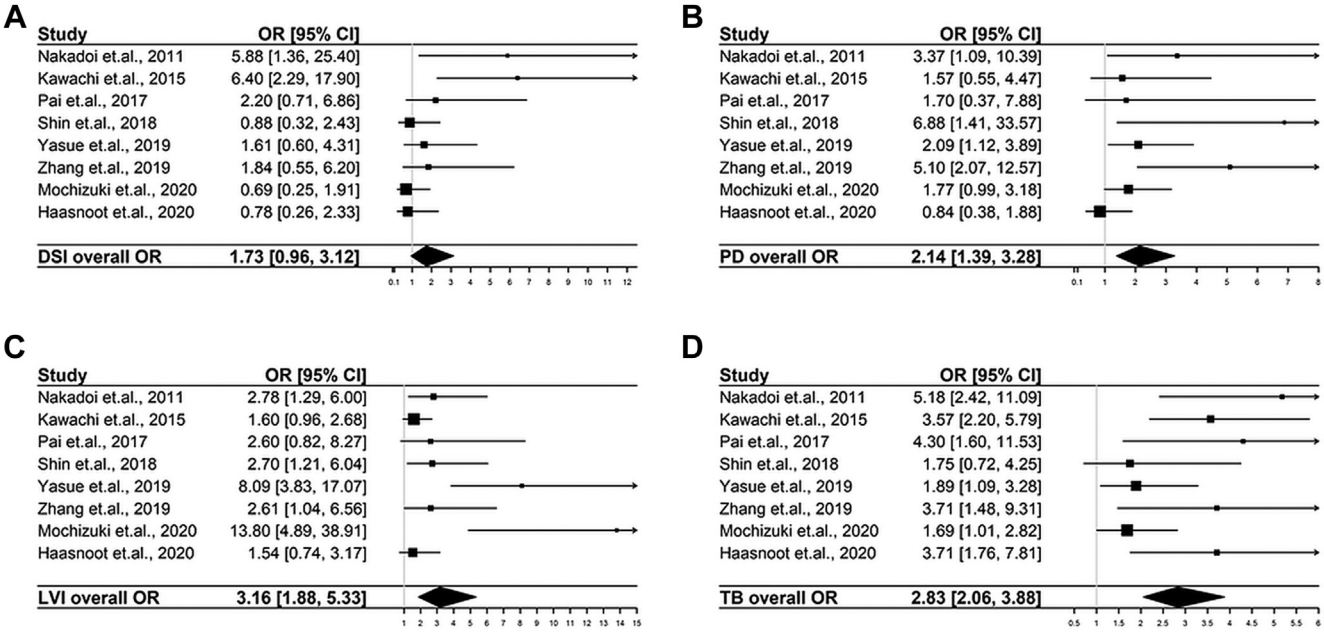

Figure 3. Forest plots with odds ratios of accepted histologic risk factors simultaneously included in multivariable analysis. (*A*) DSI. (*B*) PD. (*C*) LVI. (*D*) TB grade 2 or 3.

has been performed exclusively for suspect superficial invasive T1 cancers. However, optical assessment of invasion depth remains challenging and invasion depth frequently turns out to be deeper than expected after complete endoscopic resection. Detailed histologic assessment in multiple large cohorts have confirmed DSI to be present in up to two-thirds of cases after endoscopic resection for a suspect superficial submucosal cancer.[10,13,15,92] This puts DSI as the most frequent encountered criterion to refer for oncologic surgery.

Novel advanced local resection techniques, such as ESD, eFTR, and transanal minimal invasive surgery, have expanded the therapeutic armamentarium available for T1 CRC.[19,93,94] These minimal invasive techniques have been shown to allow a high rate of R0 resections, even when deeper invasion is present. For ESD, R0 resection rates of 62%–65% for deep submucosal invasive T1 CRC have been reported.[92,95] Although reasonable considering the low rate of complications (2.9%), this R0 rate is significantly lower than the 97% R0 for superficial T1 CRC and is mainly attributable to a tumor-positive deep resection plane.[95] In this regard, eFTR has the potential strong advantage of including the muscularis propria. Recent prospective eFTR registry data demonstrated R0 rates of 82% in a large number of T1 CRCs, of which 60% showed DSI.[19] For nonexposed eFTR, current size restriction of the resection device allow lesions up to approximately 2 cm amenable for radical resection, which is a serious constraint, as opposed to ESD. However, as the maximum diameter of the invasive front in T1 CRC rarely exceeds 15 mm, logic would suggest eFTR might have therapeutic potential in a proper subset of T1 CRC.[67,96]

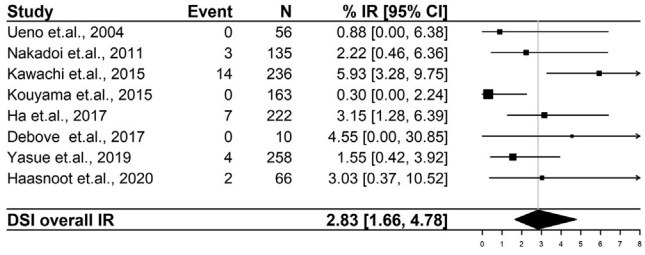

Figure 4. Forest plots with incidence rates of DSI in absence of other risk factors.

Essentially, obtaining a radical resection for DSI cancers would only be justified if it leads to a potential curative resection in a relevant proportion of patients. Our study showed that the proportion of all DSI cancers lacking other histologic high-risk criteria was 37.9% (95% CI, 36.2%–39.7%). This indicates that the curative resection rate for T1 CRC after radical local excision will increase significantly when DSI would be waived as risk factor. Indisputably, detailed histologic assessment in good-quality intact specimen remains the most reliable approach to predict the risk for LNM. In this regard, a complete local excision for amenable cases could be seen as an important step forward to aid clinical decision making and discriminate those who truly have high-risk disease and sparing others radical surgery, considering factors, such as age, comorbidity, and patient preference. Moreover, several high-quality studies have shown that prior endoscopic resection did not unfavorably affect long-term outcomes of those in need for oncologic surgery.[20–23] To further refine risk stratification and, given the important limitations of preoperative staging, future research should establish more reliable predictive criteria to select patients likely to benefit from local excision as first-line treatment and reduce surgical overtreatment. New quantitative markers, such as the maximum width or

total area of SM invasion, might prove to be better predictors for the presence of LNM than the absolute depth of SM invasion, which could be explained by the larger number of vessels in the superficial submucosa.[67,97] Furthermore, molecular markers or noninvasive liquid biopsy might have potential, but prospective studies are necessary to define their role in current riskmodels.[98]

In line with previous studies, our results show that TB and LVI are both strong independent predictors for LNM.[82,83,90] Most included studies did not provide an accurate definition of LVI and histopathologic techniques varied among studies (eg, some studies used immunohistochemistry, which is thought to be more accurate than H&E staining). This lack of standardization might have caused some bias. Moreover, some studies suggest LVI should be investigated as 2 separate variables, that is, lymphatic invasion and vascular invasion combined into a single factor might be less informative and could present a lower risk for LNM.[83,84] To include and correct for the same number of risk factors in our multivariable meta-analysis, we only included studies that reported LVI as 1 variable. As a result, not all studies with multivariable analyses could be included. Same applied for TB, as some studies lack data on TB in multivariable analysis. Despite these limitations, our results confirm that both LVI and TB are powerful predictive parameters for LNM and confirm the significance of TB as a novel high-risk feature.

Another limitation to address is the retrospective design in almost all included studies using different inclusion and exclusion criteria, which are more sensitive to confounding variables. Histopathology might not have been assessed uniformly, as endoscopic and surgical resected specimens are handled differently in terms of sectioning thicknesses and use of immunostaining. For this, we cannot rule out that presence of certain histologic risk factors are underestimated. In addition, there was a considerable variation in definitions of DSI used. In current guidelines, 1000 μm and SM1 vs SM2–3 are established as cutoff levels for DSI.[7–9,89] Unfortunately, retrieved data did not allow us to differentiate between other absolute cutoff levels or to check for differences between SM1–2 vs SM3. Further prospective studies should be undertaken to study whether other cutoff levels would meaningfully affect our results. Lastly, we were unable to study other potential risk factors that could influence the risk for LNM, for example, tumor location (colon vs rectum). No usable data could be retrieved divided in colon vs rectal location and our outcome of interest, which is a potential weakness of our analysis that deserves future study.

In conclusion, this meta-analysis is the first to reveal no significant independent association between DSI and LNM. These results challenge the early perspective and oncologic dogma of DSI as a strong indicator for oncologic surgery. In light of the expanding spectrum of local resection methods and increasing interest in organ preservation, a management shift toward local excision as the initial approach for amenable DSI cases to guide shared decision making is expected. Active surveillance instead of radical suzrgery for DSI as sole risk factor may be a reasonable approach considering the low risk for LNM. Future prospective large-scale studies should establish refined risk-stratification models to optimize treatment in T1 CRC.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://doi.org/10.1053/j.gastro.2022.04.010.

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Correspondence
Address correspondence to: Barbara A. J. Bastiaansen, MD, Department of Gastroenterology and Hepatology, Amsterdam University Medical Center, Academic Medical Center, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands. e-mail: b.a.bastiaansen@amsterdamumc.nl.

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Data Availability
Data are available on reasonable request.

CRediT Authorship Contributions
Liselotte W. Zwager, MD (Conceptualization: Equal; Data curation: Lead; Methodology: Equal; Project administration: Lead; Writing – original draft: Equal; Writing – review & editing: Lead).

Barbara A. J. Bastiaansen, MD (Conceptualization: Equal; Data curation: Equal; Investigation: Equal; Methodology: Equal; Supervision: Equal; Writing – original draft: Equal; Writing – review & editing: Lead).

Nahid S. M. Montazeri, MS, PhD (Formal analysis: Lead; Methodology: Equal; Writing – review & editing: Equal).

Roel Hompes, MD, PhD (Conceptualization: Equal; Writing – review & editing: Equal).

Valeria Barresi, MD, PhD (Data curation: Supporting; Writing – review & editing: Equal).

Katsuro Ichimasa, MD, PhD (Data curation: Supporting; Writing – review & editing: Equal).

Hiroshi Kawachi, MD, PhD (Data curation: Supporting; Writing – review & editing: Equal).

Isidro Machado, MD, PhD (Data curation: Supporting; Writing – review & editing: Equal).

Tadahiko Masaki, MD, PhD (Data curation: Supporting; Writing – review & editing: Equal).

Weiqi Sheng, MD, PhD (Data curation: Supporting; Writing – review & editing: Equal).

Shinji Tanaka, MD, PhD (Data curation: Supporting; Writing – review & editing: Equal).

Kazutomo Togashi, MD, PhD (Data curation: Supporting; Writing – review & editing: Equal).

Chihiro Yasue, MD, PhD (Data curation: Supporting; Writing – review & editing: Equal).

Paul Fockens, MD, PhD (Conceptualization: Equal; Writing – review & editing: Equal).

Leon M. G. Moons, MD, PhD (Conceptualization: Equal; Writing – review & editing: Equal).

Evelien Dekker, MD, PhD (Conceptualization: Equal; Data curation: Supporting; Investigation: Equal; Methodology: Supporting; Supervision: Lead; Writing – original draft: Supporting; Writing – review & editing: Lead).

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