Bijlagen bij module Histologische riscofactoren bij T1 CRC

Zoekverantwoording en overzicht geïncludeerde studies per onderwerp

Differentiatie (pubmed: 41 hits)

P: (("colon"(MeSH Terms) OR "colon"(Title/Abstract) OR "rectum"(MeSH Terms) OR "rectum"(Title/Abstract) OR "colorect*"(Title/Abstract) OR "colonic"(Title/Abstract) OR "rectal"(Title/Abstract)) AND ("malignant polyp"(Title/Abstract) OR "malignant polyps"(Title/Abstract))) OR (("colon"(MeSH Terms) OR "colon"(Title/Abstract) OR "rectum"(MeSH Terms) OR "rectum"(Title/Abstract) OR "colorect*"(Title/Abstract) OR "colonic"(Title/Abstract) OR "rectal"(Title/Abstract)) AND ("cancer*"(Title/Abstract) OR "carcinoma"(MeSH Terms) OR "carcinoma*"(Title/Abstract) OR "tumor*"(Title/Abstract) OR "tumour*"(Title/Abstract) OR "adenocarcinoma"(MeSH Terms) OR "adenocarcinoma*"(Title/Abstract) OR "malignan*"(Title/Abstract)) AND ("T1"(Title/Abstract) OR "pT1"(Title/Abstract) OR "submucosa*"(Title/Abstract))) OR ("early"(All Fields) AND ("invasibility"(All Fields) OR "invasible"(All Fields) OR "invasion"(All Fields) OR "invasions"(All Fields) OR "invasive"(All Fields) OR "invasively"(All Fields) OR "invasiveness"(All Fields) OR "invasives"(All Fields) OR "invasivity"(All Fields)) AND "colorectal"(All Fields))

I: ("cell differentiation"(MeSH Terms) OR "differentiation"(Title/Abstract) OR "differentiated"(Title/Abstract) OR "histologic grade"(Title/Abstract)) AND ("poor"(Title/Abstract) OR "poorly"(Title/Abstract) OR "G3"(Title/Abstract) OR "undifferentiated"(Title/Abstract) OR "G4"(Title/Abstract))

C: ("cell differentiation"(MeSH Terms) OR "differentiation"(Title/Abstract) OR "differentiated"(Title/Abstract) OR "histologic grade"(Title/Abstract)) AND ("well"(Title/Abstract) OR "G1"(Title/Abstract) OR "moderated"(Title/Abstract) OR "G2"(Title/Abstract))

O: "lymph node metastasis"(Title/Abstract) OR "lymph node involvement"(Title/Abstract) OR "regional lymph node"(Title/Abstract) OR "lymph node metastases"(Title/Abstract) OR "nodal involvement"(Title/Abstract) OR "LNM"(Title/Abstract)

Overview of included studies

Article	Conclusion	Level of evidence
Kim et al. 2016	N=428, non-pedunculated/pedunculated? Monocenter Method: G1, G2, G3 (G1/2 versus G3) Multivariate analysis revealed that LVI positivity and poorly differentiated histology were independently associated with lymph node metastasis (LNM; P < 0.001 and P = 0.001, respectively).	Retrospective cohort study
Yim et al. 2017	N=252, 64% non-pedunculated Method: not specified. High risk: well to moderate versus poorly differentiated (n=12). Differentiation grade was not associated with LNM.	Retrospective cohort study
Han et al. 2018	N=492, 68% non-pedunculated Method: WHO criteria and categorized groups for the analysis: well-differentiated adenocarci- noma, moderately differentiated adenocarcinoma, and poorly differentiated/mucinous adenocarcinoma (n=11) based on the most predominant histologic feature in the deepest portion of the tumor. High risk: poorly differentiated/mucinous adenocarcinoma Significant, independent predictive factors for LNM included the depth of submucosal invasion >1900 µm (odds ratio (OR) 7.5; 95% confidence interval (CI) 3.1-18.3; p < 0.001), venous invasion (OR 2.4; 95% CI 1.1-5.5; p = 0.03), and poorly differentiated/mucinous adenocarcinoma (OR 6.3; 95% CI 1.3-30.8; p = 0.02). =poor versus well	Retrospective cohort study
Ha et al. 2017	N=745, 94% non-pedunculated Method: Differentiation of adenocarcinomas was classified according to World Health Organization criteria: grade 1 (well differentiated), grade 2 (moderately differentiated), or grade 3 (poorly differentiated, incl. mucinous, signet ring adenocarcinoma with neuroendocrine differentiation). (G3 n=19) (Five patients with G3 as single risk factor (taking budding and LVI into account), one had lymph node metastasis.) Grades 1 and 2 were defined as histologic low grade, and grade 3, mucinous carcinoma, signet ring cell carcinoma, and carcinoma with neuroendocrine differentiation were defined as histologic high grade	Retrospective cohort study

	Both univariate (Table 3) and multivariate (Table 4) analyses indicated that histologic high grade (P < 0.001), vascular invasion (P < 0.001), deep submucosal invasion (P = 0.010), and budding (P = 0.034) were significantly associated with LNM	
Yasue et al. 2019	N=846, only non-pedunculated, Method: poorly differentiated adenocarcinoma/signet-ring cell carcinoma/mucinous carcinoma (POR) histological differentiation. POR was deemed as a risk factor when present in the main tissue type and area of invasion. (POR n=93) OR: 2.09	Retrospective cohort study
Oh et al. 2019	N=833, 20% non-polypoid, validation N=722, 15% non-polypoid Method: Differentiation of adenocarcinomas was classified according to World Health Organization criteria: grade 1 (well differentiated), grade 2 (moderately differentiated), or grade 3 (poorly differentiated, incl. mucinous, signet ring adenocarcinoma with neuroendocrine differentiation). (G3 n=20, 2,4%, G3 n=26, 3,6%) Vascular invasion and high-grade histology were the strongest risk factors (odds ratio (OR), 8.45; 95% confidence interval (CI), 4.56 to 15.66); p < 0.001 and OR, 7.89; 95% CI, 2.89 to 21.52; p < 0.001, respectively).	Retrospective cohort study
Barel (2019)	Method: For the grade of differentiation, we used the 4 grades classification given by the World Health Organization: grade 1 for well-differentiated adenocarcinoma with more than 95% gland formation, grade 2 for moderately differentiated adenocarcinoma with 50–95% gland formation, grade 3 for poorly differentiated adenocarcinoma with less than 50% gland formation and grade 4 for undifferentiated carcinoma lacking any gland formation or mucin production. Mucinous, signet-ring cells and micropapillary adenocarcinomas were individualized when the percentages of the corresponding tumor components were greater than 50%24. “High grade” tumors included the poorly differentiated adenocarcinoma, signet ring cells carcinoma, micropapillary and undifferentiated tumors. Low-grade (G1-G2) versus high-grade (G3-4) In multivariate analysis, only the presence of vascular invasion on HES slides (Odds Ratio: 9.32, CI:2.83–31.86, p = 0.0002) and poor differentiation (Odds Ratio:16.87, CI:4.16–70.90, p < 0.0001) were independent factors associated with LNM OR 16.87	
Kudo (2021)	Method: Histologic grade was examined with hematoxylin and eosin (HE)-stained specimens and based on the least differentiated tumor component. Poor/mucinous/signet versus tub/papillary Adjusted OR: 1.81	

Lymfangioinvasie

P: (("colon"(MeSH Terms) OR "colon"(Title/Abstract) OR "rectum"(MeSH Terms) OR "rectum"(Title/Abstract) OR "colorect*"(Title/Abstract) OR "colonic"(Title/Abstract) OR "rectal"(Title/Abstract)) AND ("malignant polyp"(Title/Abstract) OR "malignant polyps"(Title/Abstract))) OR (("colon"(MeSH Terms) OR "colon"(Title/Abstract) OR "rectum"(MeSH Terms) OR "rectum"(Title/Abstract) OR "colorect*"(Title/Abstract) OR "colonic"(Title/Abstract) OR "rectal"(Title/Abstract)) AND ("cancer*"(Title/Abstract) OR "carcinoma"(MeSH Terms) OR "carcinoma*"(Title/Abstract) OR "tumor*"(Title/Abstract) OR "tumour*"(Title/Abstract) OR "adenocarcinoma"(MeSH Terms) OR "adenocarcinoma*"(Title/Abstract) OR "malignan*"(Title/Abstract)) AND ("T1"(Title/Abstract) OR "pT1"(Title/Abstract) OR "submucosa*"(Title/Abstract))) OR ("early"(All Fields) AND ("invasibility"(All Fields) OR "invasible"(All Fields) OR "invasion"(All Fields) OR "invasions"(All Fields) OR "invasive"(All Fields) OR "invasively"(All Fields) OR "invasiveness"(All Fields) OR "invasives"(All Fields) OR "invasivity"(All Fields)) AND "colorectal"(All Fields))

I: "lymphovascular invasion"(Title/Abstract) OR "LVI"(Title/Abstract) OR "lymphatic invasion"(Title/Abstract) OR "venous invasion"(Title/Abstract) OR "vascular invasion"(Title/Abstract) OR "angioinvasion"(Title/Abstract)

C:

O: "lymph node metastasis"(Title/Abstract) OR "lymph node involvement"(Title/Abstract) OR "regional lymph node"(Title/Abstract) OR "lymph node metastases"(Title/Abstract) OR "nodal involvement"(Title/Abstract) OR

"LNM"(Title/Abstract)

Totaal (254 hits Pubmed):
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Tanaka (1995)	177 T1 CRCs (CHI) 1983-1993 Multicenter 21 LNM (12%)	Lymphatic invasion present: 24% LNM Absent: 5%	Lymphatic invasion
Bayar (2002)	59 patients 1970-1990 Tis-T1 Rectum (CHI)	A significantly higher rate of lymph node metastasis occurs in the presence of venous invasion (P < 0.01).	Lymphatic invasion Venous invasion
Nascimbeni (2002)	353 sessile T1 CRCs (CHI) 46 LNM (13%) 1979-1995	LVI present: 32% LNM LVI absent: 11% LNM Multivariable analysis: OR 3.5	Lymphovascular invasion
Yamamoto (2004)	301 T1 CRCs (CHI) 1970-2001 19 LNM (6.3%)	Depth of submucosal invasion (sm3) and presence of lymphovascular invasion were significant risk factors for lymph node metastasis both univariately and multivariately	Lymphovascular invasion
Ueno (2004)	292 T1 CRCs (CHI & ENDO)	LVI present: 30.7% LNM LVI absent: 5.7% LNM Adjusted OR: 2.7	Vascular invasion (lymphatic vessels and/or venous vessels)
Okabe (2004)	428 T1 CRCs (CHI) 2 centers LNM 10%	LVI present: 21% LNM LVI absent: 5.1% LNM Adjusted OR: 4.4	Lymphovascular invasion
Tominaga (2004)	155 nonpedunculated T1 CRCs (CHI) 1985-2001 monocenter 19 (12.3%) LNM	Multivariate analysis showed lymphatic invasion (P = 0.014 to be an independent factor predicting lymph node metastasis. Multivariable OR 4.33	Lymphatic invasion (presence of cancer cells within endothelial-lined channels without significant numbers of red blood cells) Venous invasion (tumor emboli within endothelial-lined channels surrounded by a smooth muscle wall)
Choi (2008)	168 T1 CRCs 1989-2004 Monocenter LNM 14.3%	Lymphovascular invasion was a risk factor for LN metastasis in univariate analysis (p = 0.019); however, in multivariate analysis, lymphovascular invasion could not predict LN metastasis.	Lymphovascular invasion
Yamauchi (2008)	164 T1 CRCs (CHI) Two centers 16 LNM (9.8%)	Multivariate analysis adjusting for all fi ve pathological factors showed that TB and pathological differentiation were still signifi cantly associated with LN Metastasis ➔ Lymphatic invasion en venous invasion dus niet	Lymphatic channel involvement Venous invasion

Choi (2009)	87 T1 CRCs (CHI & END) 6/30 met high risk factor had LNM (20%)	Venous invasion univariate risk factor maar niet multivariate	Venous invasion Angiolymphatic invasion
Ishii (2009)	136 T1 CRCs (CHI) 18 LNM (13.2%)	Both univariate and multivariate analyses revealed that lymphatic vessel invasion detected by D2-40 and a poorly differentiated histology at the invasion front were independent risk factors of lymph node metastasis. Blood vessel invasion dus niet Adjusted OR: 7.12	Lymphatic vessel invasion (met D2-40) Blood vessel invasion
Suzuki (2009)	124 T1 CRCs (CHI) 1990-2004 monocenter 18 LNM (14.5%)	Multivariate analysis showed that venous invasion by EVG and tumor budding by HE showed significance as predictors of LNM Dus niet op HE en ook niet D2-40 voor lymphatic invasion Multivariate analysis showed only venous invasion by EVG stain as being significantly associated with distant metastases (P=0.001) Dus niet op HE en ook niet D2-40 voor lymphatic invasion	Lymphatic channel invasion (D2-40 & H&E) Venous invasion (EVG & H&E)
Huh (2010)	224 T1-T2 CRC (CHI) 1999-2008 monocenter 14.5% LNM in T1 groep	the presence of lymphovascular invasion (P < 0.001) or perineural invasion (P = 0.004) was an independent predictor for lymph node metastasis. Adjusted OR: 15.79	Lymphovascular invasion
Tateishi (2010)	322 T1 CRCs (CHI) 46 LNM (14.3%)	Multivariate analysis showed that lymphatic invasion (P<0.01), tumor differentiation (P<0.01), and tumor budding (P<0.01) were significantly associated with lymph node metastasis. Adjusted OR: 3.19 Venous invasion dus niet	Lymphatic invasion Venous invasion
Akishima-Fukasawa (2011)	111 T1 CRCs Case-cohort approach 36 LNM cases	Lymphatic invasion adjusted OR: 15.6 Blood vessel invasion dus niet	Lymphatic invasion (Cancer cells in a LYVE-1-positive vessel structure were evaluated as lymphatic invasion) Blood vessel invasion (stained by victoria blue and vWF)
Nakadoi (2012)	499 T1 CRCs (CHI) 1981-2008 41 LNM (8.2%)	The incidence of lymph node metastasis was significantly higher in lesions featuring poorly differentiated/mucinous adenocarcinoma, submucosal invasion ≥ 1800 μm, vascular invasion, and high-grade tumor budding than in other lesions. Adjusted OR: 2.84	Vascular invasion

Chang (2012)	943 T1-T2 CRC 188 LNM (19.9%) T1 CRC LNM: 31 (11.7%)	In multivariate analysis, lymphovascular invasion (LVI; P < 0.001, hazard ratio 11.472), poor differentiation (PD; P = 0.007, hazard ratio 3.218), and depth of invasion (presence of pT2; P = 0.032, hazard ratio 1.694) were significantly related to nodal involvement. Adjusted OR: 11.4	Lymphovascular invasion
Wada (2013)	120 T1 CRCs (CHI) 1995-2005 monocenter 12 LNM (10%)	Only D2-40-LVI was identified to be a significant independent predictive factor for nodal metastasis of T1 colorectal cancer (odds ratio 6.048, p = 0.018, CI 1.360–26.89; Table 1) in the multivariate logistic regression analysis	Lymphatic invasion (H&E & D2-40) Lymphatic vessels were distinguished from blood vessels by the absence of luminal red blood cells or smooth muscle within the vessel wall Venous invasion (H&E & VWF)
Yim (2017)	252 T1 CRCs (CHI) 2000-2015 31 LNM (12.3%)	the most powerful clinicopathological parameter for predicting LNM was lymphatic invasion Venous invasion was not	Lymphatic invasion (the presence of at least one tumor cell cluster within vascular space lined by a single layer of endothelial cells with no supporting smooth muscle, elastic lamina and/or red blood cells, whose lumens are sometimes filled with lymphocytes.) Venous invasion Vascular invasion (tumor cell nests in spaces that were lined by endothelium and filled with red blood cells, located in the vicinity of an artery and distant from the main lesion.) D2-40, CD34 or CD31 used in case it was difficult
Ha (2017)	745 T1 CRCs 2001-2015 Monocenter 91 LNM (12.2%)	Univariate and multivariate analyses identified deep submucosal invasion (P = 0.010), histologic high grade (P < 0.001), budding (P = 0.034), and vascular invasion (P < 0.001) as risk factors for LNM. Adjusted OR: 6.6	**Vascular invasion** was defined as the presence of cancer cells within endothelial-lined channels, including angiolymphatic invasion and venous invasion. **= LVI** Vascular invasion of small vessels without a vascular smooth muscle layer was defined as angiolymphatic invasion, and vascular invasion of large vessels with a vascular smooth muscle layer was defined as venous invasion.
Han (2018)	492 T1 CRCs (CHI) 2008-2012	Univariate; venous invasion (OR 3.1) and lymphatic invasion (OR 3.0) were shown to be significant predictive factors for LNM. Multivariate analysis; significant, independent predictive factors for LNM included venous invasion (OR 2.4; 95% CI 1.1–5.5; p = 0.03).	Lymphatic invasion Venous invasion Lymphovascular invasion was identified as the presence of cancer cells within endothelial-lined channels.
Yasue (2019)	846 T1 CRCs Monocenter Niet-gesteeld 2005-2016	Significant risk factors for LNM in multivariate analysis were lymphovascular invasion (odds ratio (OR) 8.09; 95% confidence interval (CI) 3.84-17.1), tumor budding (OR 1.89; 95% CI 1.09-3.29), and histological	Lymphovascular invasion Additional D2-40 staining and Victoria blue-H&E staining were performed

		differentiation (OR 2.09; 95% CI 1.12-3.89).	using the samples of ER to evaluate lymphatic invasion and venous invasion, respectively. Meanwhile, the surgical resection samples underwent lymphovascular evaluation using only H&E staining; immunostaining was not performed.
Oh (2019)	833 T1 CRCs (CHI&END) Validation: 722 T1 CRCs	Multivariate: OR 8.45	Vascular invasion **= LVI** (Vascular invasion was defined as the presence of cancer cells within endothelial-lined channels, including angiolymphatic invasion and venous invasion. Vascular invasion of small vessels without a vascular smooth muscle layer was defined as angiolymphatic invasion, and vascular invasion of large vessels with a vascular smooth muscle layer was defined as venous invasion.)
Barel (2019)	312 T1 CRCs (CHI&END) 2009-2013 multicenter 19 LNM	Poor tumor differentiation, vascular invasion and high grade tumor budding on HES slides were notably identified as strong risk-factors of lymph node metastases In multivariate analysis, only the presence of **vascular invasion on HES slides** (Odds Ratio: 9.32, CI:2.83–31.86, p = 0.0002) and poor differentiation (Odds Ratio:16.87, CI:4.16–70.90, p < 0.0001) were independent factors associated with LNM	Vascular invasion (both, on H&E) Lymphatic invasion (D2-40) Venous invasion (CD31) Lymphatic invasion was diagnosed in case of cancer cells seen within endothelial cell-lined small vessels and venous invasion when tumor cells were seen in the lumen of large vessels with a muscle layer.
Rönnow (2020)	1439 T1 CRCs (CHI) 2009-2017 2016-2018 Multicenter 150 LNM (10%)	LVI (P < 0.001), perineural invasion (P < 0.001), mucinous subtype (P = 0.006), and age <60 years (P < 0.001) were identified as independent risk factors LVI present: 39.1% LNM Absent: 8.1%	Lymphovascular invasion (LVI was identified by use of hematoxylin/eosin staining and comprise both intramural and extra mural vascular invasion as well as lymphatic invasion.)
Kudo (2021)	3134 T1 CRCs (CHI&END) 1997-2017 Multicenter 319 LNM (10.2%)	Multivariate: Lymphatic invasion: OR 4.57 Vascular invasion: OR 1.86	Lymphovascular invasion Lymphatic invasion (Lymphatic invasion was evaluatedusing HE staining adding immunostaining with D2–40 antibody(D2–40) as needed) Vascular invasion (Vascular invasion, which is defined as invasion of tumor cells into blood vessels, was also evaluated using HE staining adding Victoria blue or Elastica Van Giesonstain as needed.)

Tumor budding (120 hits)

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Overview of included studies

Article	Conclusion	Study design
Akishima-Fukasawa 2011	N = 111 < 5 = absent >4 = present By multivariate analysis, lymphatic invasion, NIC and MMP-7 expression at the invasive front were independent predictors of LN metastasis. TB alleen in univariate analyse	Case cohort
Suh 2012	N = 435 Method: An isolated cell or a small cluster of < 5 carcinoma cells in the invasive front was defined as a budding focus, **with positive tumor budding defined as > 10 budding foc**i viewed at × 200 magnification Grade 3, angiolymphatic invasion, budding, and the absence of BGA were identified as factors associated with LNM in univariate and multivariate analyses (P < 0.05). OR 2.35	Retrospective cohort
Ueno 2014	N = 3556 Tumors with <5 budding foci were classified as low-grade and those with ≥5 budding foci as high-grade 25.4% LNM in Bd positive Multivariable OR 3.8 The incidence of LNM was higher in PDC-positive tumors (17.4 %) than in PDC-negative tumors (6.9 %; P < 0.0001), and PDCs had an adverse impact on LNM irrespective of the degree of submucosal invasion. Grade 3, vascular invasion, budding, and submucosal invasion depth were also significant factors (all, P < 0.0001).	Retrospective cohort
Kawachi 2015	N=806 Univariate budding 2 and budding 3 both risk factor, no differences in metastasis --> after that they combined 2 and 3 Multivariate G2/G3 OR 3.14 (1.91-5.21)	Retrospective cohort
Miyachi 2015	N= 653 Budding = 5 or more = positive Multivariate OR positive budding 1.80	Retrospective cohort
Yim et al. 2017	N=252, 64% non-pedunculated Parameters included: depth and width of the submucosal invasion, tumor budding, poorly differentiated clusters (PDCs), histological grade, lymphatic invasion, venous invasion, perineural invasion, peritumoral inflammation, and desmoplasia Method: - Presence/absence - G1 versus Gr 2/3 Both predictive, but present/absent most (but lesser specificity) Outcome: Univariate; The depth and width of the submucosal invasion, lymphatic invasion, tumor budding, and the presence of poorly differentiated clusters (PDCs) were significantly associated with the incidence of LNM. Multivariate; The most powerful clinicopathological parameter for predicting LNM was lymphatic invasion, followed by the presence or absence of tumor budding, presence of PDCs and tumor budding graded by the Ueno method.	Retrospective cohort study

Ha et al. 2017	N=745, 94% non-pedunculated Parameters included: depth of submucosal invasion, histologic grade, budding, vascular invasion, and background adenoma. Method: 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 magnification was defined as budding positive** OR 1.76 Outcome: Univariate and multivariate analyses identified deep submucosal invasion (P = 0.010), histologic high grade (P < 0.001), budding (P = 0.034), and vascular invasion (P < 0.001) as risk factors for LNM. Among the patients with one, two, three, and four risk factors, 6.0%, 18.7%, 36.4%, and 100%, respectively, were positive for LNM..	Retrospective cohort study
Pai 2017	N=116 surgically treated Multivariate OR 4.03	Case control
Lee 2018	N= 133 surgically treated Low grade = <5 foci (in 200x field) High grade = 5 or > foci Grade 1 versus Grade 2/3 Our results were consistent with previous findings indicating that the presence of tumor budding and specifically, a higher number of tumor budding foci, correlated strongly with lymph node metastasis (P b .05). Our data indicated that choosing a tumor budding value of 3.5 as the cut-off between LN+ and LN− metastasis groups yielded the ROC curve with optimal sensitivity and specificity for predicting nodal metas- tasis (87.5% and 81.1%, respectively) and revealed that tumor budding ≥3.5 was an independent risk factor for the prediction of LN metastasis in our cohort of patients with T1 CRC.	Retrospective cohort
Yasue et al. 2019	N=846, only non-pedunculated, Parameters included: depth of invasion, differentiation grade, lymphovascular invasion and tumorbudding. Tumor budding was graded according to the number of budding foci in a field of a 20 × objective lens, as follows: Grade 1: 0–4, Grade 2: 5–9, and Grade 3: 10 or more. Outcome: significant risk factors in mutlivariate analysis were LVI (OR 8.09; 95% CI 3.84–17.1), TB (OR 1.89; 95% CI 1.09–3.29), and POR (OR 2.09; 95% CI 1.12–3.89); among these variables, LVI had the highest OR.	Retrospective cohort study
Oh et al. 2019	N=833, 20% non-polypoid, validation N=722, 15% non-polypoid Parameters included: vascular invasion, deep submucosal invasion, histological grade and tumorbudding. Method: > 10 budding foci viewed at 200× magnification was defined as budding positive OR 1.70 Vascular invasion and high-grade histology were the strongest risk factors. Deep submucosal invasion (sm2/3) and tumor budding were also statistically significant predictors of LNM.	Retrospective cohort study
Barel 2019	N= 312 G1 versus G2/G3 In univariate analyses, the pres- ence of vascular invasion on HES slides, perineural invasion, positive lateral margin on endoscopically-resected samples, poor tumor differentiation and high tumor budding on HES slides were significantly associated with LNM. In multivariate analysis, only the presence of vascular invasion on HES slides (Odds Ratio: 9.32, CI:2.83– 31.86, p = 0.0002) and poor differentiation (Odds Ratio:16.87, CI:4.16–70.90, p < 0.0001) were independent fac- tors associated with LNM. Every	Retrospective cohort

PDC's (8 hits)

((("colon"(MeSH Terms) OR "colon"(Title/Abstract) OR "rectum"(MeSH Terms) OR "rectum"(Title/Abstract) OR "colorect*"(Title/Abstract) OR "colonic"(Title/Abstract) OR "rectal"(Title/Abstract)) AND ("malignant polyp"(Title/Abstract) OR "malignant polyps"(Title/Abstract))) OR (("colon"(MeSH Terms) OR "colon"(Title/Abstract) OR "rectum"(MeSH Terms) OR "rectum"(Title/Abstract) OR "colorect*"(Title/Abstract) OR "colonic"(Title/Abstract) OR "rectal"(Title/Abstract)) AND ("cancer*"(Title/Abstract) OR "carcinoma"(MeSH Terms) OR "carcinoma*"(Title/Abstract) OR "tumor*"(Title/Abstract) OR "tumour*"(Title/Abstract) OR "adenocarcinoma"(MeSH Terms) OR "adenocarcinoma*"(Title/Abstract) OR "malignan*"(Title/Abstract)) AND ("T1"(Title/Abstract) OR "pT1"(Title/Abstract) OR "submucosa*"(Title/Abstract))) OR ("early"(All Fields) AND ("invasibility"(All Fields) OR "invasible"(All Fields) OR "invasion"(All Fields) OR "invasions"(All Fields)

OR "invasive"(All Fields) OR "invasively"(All Fields) OR "invasiveness"(All Fields) OR "invasives"(All Fields) OR "invasivity"(All Fields)) AND "colorectal"(All Fields))) AND (("poorly"(All Fields) AND ("cell differentiation"(MeSH Terms) OR ("cell"(All Fields) AND "differentiation"(All Fields)) OR "cell differentiation"(All Fields) OR "differentiated"(All Fields) OR "differentiation"(All Fields) OR "differential"(All Fields) OR "differentials"(All Fields) OR "differentiate"(All Fields) OR "differentiates"(All Fields) OR "differentiating"(All Fields) OR "differentiational"(All Fields) OR "differentiations"(All Fields) OR "differentiative"(All Fields)) AND ("cluster analysis"(MeSH Terms) OR ("cluster"(All Fields) AND "analysis"(All Fields)) OR "cluster analysis"(All Fields) OR "clustering"(All Fields) OR "clusterings"(All Fields) OR "cluster"(All Fields) OR "cluster s"(All Fields) OR "clustered"(All Fields) OR "clusterization"(All Fields) OR "clusters"(All Fields))) OR "PDC"(All Fields)) AND ("lymph node metastasis"(Title/Abstract) OR "lymph node involvement"(Title/Abstract) OR "regional lymph node"(Title/Abstract) OR "lymph node metastases"(Title/Abstract) OR "nodal involvement"(Title/Abstract) OR "LNM"(Title/Abstract))

Muscularis mucosae (137 hits)

(((("colon"(MeSH Terms) OR "colon"(Title/Abstract) OR "rectum"(MeSH Terms) OR "rectum"(Title/Abstract) OR "colorect*"(Title/Abstract) OR "colonic"(Title/Abstract) OR "rectal"(Title/Abstract)) AND ("malignant polyp"(Title/Abstract) OR "malignant polyps"(Title/Abstract))) OR (("colon"(MeSH Terms) OR "colon"(Title/Abstract) OR "rectum"(MeSH Terms) OR "rectum"(Title/Abstract) OR "colorect*"(Title/Abstract) OR "colonic"(Title/Abstract) OR "rectal"(Title/Abstract)) AND ("cancer*"(Title/Abstract) OR "carcinoma"(MeSH Terms) OR "carcinoma*"(Title/Abstract) OR "tumor*"(Title/Abstract) OR "tumour*"(Title/Abstract) OR "adenocarcinoma"(MeSH Terms) OR "adenocarcinoma*"(Title/Abstract) OR "malignan*"(Title/Abstract)) AND ("T1"(Title/Abstract) OR "pT1"(Title/Abstract) OR "submucosa*"(Title/Abstract))) OR ("early"(All Fields) AND ("invasibility"(All Fields) OR "invasible"(All Fields) OR "invasion"(All Fields) OR "invasions"(All Fields) OR "invasive"(All Fields) OR "invasively"(All Fields) OR "invasiveness"(All Fields) OR "invasives"(All Fields) OR "invasivity"(All Fields)) AND "colorectal"(All Fields))) AND ("mucous membrane"(MeSH Terms) OR ("mucous"(All Fields) AND "membrane"(All Fields)) OR "mucous membrane"(All Fields) OR ("muscularis"(All Fields) AND "mucosa"(All Fields)) OR "muscularis mucosa"(All Fields) OR ("m"(All Fields) AND ("mucosa s"(All Fields) OR "mucosae"(All Fields) OR "mucosas"(All Fields) OR "mucous membrane"(MeSH Terms) OR ("mucous"(All Fields) AND "membrane"(All Fields)) OR "mucous membrane"(All Fields) OR "mucosa"(All Fields))) OR ("mucous membrane"(MeSH Terms) OR ("mucous"(All Fields) AND "membrane"(All Fields)) OR "mucous membrane"(All Fields) OR ("muscularis"(All Fields) AND "mucosae"(All Fields)) OR "muscularis mucosae"(All Fields)) OR ("m"(All Fields) AND ("mucosa s"(All Fields) OR "mucosae"(All Fields) OR "mucosas"(All Fields) OR "mucous membrane"(MeSH Terms) OR ("mucous"(All Fields) AND "membrane"(All Fields)) OR "mucous membrane"(All Fields) OR "mucosa"(All Fields)))) AND ("lymph node metastasis"(Title/Abstract) OR "lymph node involvement"(Title/Abstract) OR "regional lymph node"(Title/Abstract) OR "lymph node metastases"(Title/Abstract) OR "nodal involvement"(Title/Abstract) OR "LNM"(Title/Abstract))

Overview of included studies

Tominaga et al. Diseases of the colon and rectum 2005	2-tier, HE (type A) and Desmin (type B), non-pedunculated T1 CRCs, N=155(19LN+)	type A1 (well preserved m. mucosae) type A2 (disrupted m. mucosae) type B1 (muscularis mucosa that could be identified by desmin immunohistochemistry) type B2 (disrupted muscularis mucosa)	Univariate +, Multivariate -. Type A1 0%, Type B1 5.3% (1/19) Type A2 10.5%, Type B2 84.2%	Level 3
Tateishi et al. Modern Pathology 2010	2-tier, HE, all T1 CRCs, N=322(46LN+)	type A (preserved or incompletely disrupted by tumor invasion) type B (completely disrupted by tumor invasion)	Type B Univariate +, Multivariate-, Type B 16%, Type A 2% (1/40)	Level 3
Nakadoi et al. Surgical Endoscopy 2013	3-tier, HE and Desmin, all T1 CRCs, N=322(38LN+)	A. m. mucosae present on HE B. Deformity of m. mucosae by HE, C. Complete rupture of the m. mucosae by HE. Desmin performed when in doubt between B. and C. on HE.	Type C Univariate+, Multivariate+ Negative: only in B and C LN+ Type A 0%, Type B 7,2%, Type C 17,3%	Level 3
Myachi et al. J Gastroenterol Hepatol 2016	2-tier, HE and Desmin, all T1 CRCs N=653(60LN+)	grade 1, muscular fibers maintained; the muscular fibers of a lesion maintained their original directionality and continuity but had disappeared only a small part (within 3–4 normal glands wide) due to carcinoma invasion; if there were any controversial points on these conditions, all cases fell into grade 2. grade 2 when the muscle fibers had fragmented or disappeared; if the muscular fibers were fragmented and had lost their original alignment or showed wider disappearance.	Grade 2 Univariate +, Multivariate?, 10%, Grade1 0% Combination MM grade 2 with LVI or Budding or poor differentiation	Level 3

Backes et al. Gastroenterology 2018	2-tier, HE, pedunculated T1 CRCs, N=148(37LN+, matched)	Type A: shattered but aligned muscularis mucosa Type B: incompletely or completely disrupted muscularis mucosa	Type B Univariate+, Multivariate+, 31%, Type A 3% (1/31)	Level 3

Invasiediepte (pubmed 260 hits, 20-07-2021)

(((("colon"(MeSH Terms) OR "colon"(Title/Abstract) OR "rectum"(MeSH Terms) OR "rectum"(Title/Abstract) OR "colorect*"(Title/Abstract) OR "colonic"(Title/Abstract) OR "rectal"(Title/Abstract)) AND ("malignant polyp"(Title/Abstract) OR "malignant polyps"(Title/Abstract))) OR (("colon"(MeSH Terms) OR "colon"(Title/Abstract) OR "rectum"(MeSH Terms) OR "rectum"(Title/Abstract) OR "colorect*"(Title/Abstract) OR "colonic"(Title/Abstract) OR "rectal"(Title/Abstract)) AND ("cancer*"(Title/Abstract) OR "carcinoma"(MeSH Terms) OR "carcinoma*"(Title/Abstract) OR "tumor*"(Title/Abstract) OR "tumour*"(Title/Abstract) OR "adenocarcinoma"(MeSH Terms) OR "adenocarcinoma*"(Title/Abstract) OR "malignan*"(Title/Abstract)) AND ("T1"(Title/Abstract) OR "pT1"(Title/Abstract) OR "submucosa*"(Title/Abstract))) OR ("early"(All Fields) AND ("invasibility"(All Fields) OR "invasible"(All Fields) OR "invasion"(All Fields) OR "invasions"(All Fields) OR "invasive"(All Fields) OR "invasively"(All Fields) OR "invasiveness"(All Fields) OR "invasives"(All Fields) OR "invasivity"(All Fields)) AND "colorectal"(All Fields))) AND ("depth of invasion"(Title/Abstract) OR "submucosal invasion"(Title/Abstract) OR "SM invasion"(Title/Abstract) OR "invasion depth"(Title/Abstract) OR "Haggitt"(Title/Abstract) OR "Kikuchi"(Title/Abstract)) AND ("lymph node metastasis"(Title/Abstract) OR "lymph node involvement"(Title/Abstract) OR "regional lymph node"(Title/Abstract) OR "lymph node metastases"(Title/Abstract) OR "nodal involvement"(Title/Abstract) OR "LNM"(Title/Abstract))

Overview of included studies

Article	Conclusion	Study design
Kawachi, 2016	N= 806, 139 pedunculated Method: First, each tumor was classified as one of the following three tumor types according to the tumor shape and status of the muscularis mucosa: pedunculated tumor, nonpedunculated tumor with identifiable muscularis mucosa, and nonpedunculated tumor without identifiable muscularis mucosa. The depth of submucosal invasion was measured according to the criteria for each tumor type. In pedunculated tumors, the depth of submucosal invasion was 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).17 In tumors with head invasion, the depth of submucosal invasion was considered to be 0 µm. In tumors with stalk invasion, the vertical distance from the line between the head and stalk (named 'Haggitt's line' by Matsuda et al18) to the invasive front was measured as the depth of submucosal invasion. In nonpedunculated tumors with identifiable muscularis mucosa, the depth of submucosal invasion was defined from the bottom line of the muscularis mucosa to the invasive front. In nonpedunculated tumors without identifiable muscularis mucosa, the depth of submucosal invasion was defined as the tumor thickness measured from the surface of the tumor to the invasive front at the deepest invasive site. Multivariabele OR > 1000 micrometer = 5.56	
Kim et al. 2016	N=428, non-pedunculated/pedunculated? Method: JSCCR 2010 High risk: submucosal invasion of ≥ 1000 µm Parameters included: negative lateral/vertical margins; submucosal invasion depth within 1000mm; no lymphovascular invasion (LVI); well or moderately differentiated. Outcome: Univariate analysis submucosal invasion depth >1000mm was not significantly associated with LNM. Submucosal invasion depth >1500mm was. Multivariate analysis revealed that depth of invasion was not independently associated with lymph node metastasis, LVI positivity and poorly differentiated histology were (LNM; P<0.001 and P=0.001, respectively).	Retrospective cohort study
Pai, 2017	N= 116, 32 pedunculated Method: Briefly, each tumor was classified into three categories based on histological review: pedunculated, non-pedunculated with identifiable muscularis mucosae, or non-pedunculated without identifiable muscularis mucosae. For pedunculated tumors, the depth of submucosal invasion was measured in micrometers (µm) starting from the line between the polyp head and stalk ('Haggitt line') to the invasive front of the tumor. Tumors with invasion limited to the head of a pedunculated polyp were considered to	Case cohort

	have submucosal invasion of 0 µm in depth. For non-pedunculated tumors with identifiable muscularis mucosae, submucosal invasion was measured from the bottom of the muscularis mucosae to the invasive front of the tumor. For non-pedunculated tumors without identifiable muscularis mucosae, submucosal invasion was measured from the surface of the tumor to the invasive front of the tumor. To more accurately measure the depth of invasion, a photograph was taken of the deepest point of invasion and the depth was measured digitally (cellSens standard, Olympus). Tumor grade, depth of submucosal invasion, and lymphatic invasion were not independent predictors of lymph node metastasis (all with P>0.05).	
Yim et al. 2017	N=252, 64% non-pedunculated High risk: submucosal invasion of ≥ 1000 µm Method: JSCCR, Kitajima, Ueno Outcome: Univariate; The depth and width of the submucosal invasion, lymphatic invasion, tumor budding, and the presence of poorly differentiated clusters (PDCs) were significantly associated with the incidence of LNM. Multivariate; The most powerful clinicopathological parameter for predicting LNM was lymphatic invasion, followed by the presence or absence of tumor budding, presence of PDCs and tumor budding.	Retrospective cohort study
Han et al. 2018	N=492, 68% non-pedunculated High risk: depth of submucosal invasion >1900 Method: depth of submucosal invasion was measured at the deepest portion according to the Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines; when the muscularis mucosae could be confirmed, it was applied as the baseline and the vertical distance from this line to the deepest extent of invasion was defined as the submucosal depth. When the muscularis mucosae could not be confirmed because of carcinomatous invasion, the most superficial side of the submucosal invasive cancer was used as the baseline and the vertical distance from this line to the deepest portion represented the depth of submucosal invasion. And Kudo. Outcome: Depth of submucosal invasion >1900 µm was an independant predicitve factor for LNM. Sm3 was one of the significant risk factors for LNM (p<0.001) in univariate analysis. However, multivariate analysis showed that Kudo's classification could not predict LNM.	Retrospective cohort study
Ha et al. 2017	N=745, 94% non-pedunculated Method: surgical resections; Kudo Sm1, Sm2, Sm3. Endoscopic resection (61%); cut-off for Sm1 1mm. Pedunculated lesions; Sm2 Haggitt line-<3mm, Sm3= >3mm from Haggitt line. High risk Sm >/= 2 (versus Sm1) Outcome: Both univariate and multivariate analyses indicated that deep submucosal invasion was significantly associated with LNM. *Positief voorspellende waarde van de conventionele risicofactoren (differentiatiegraad, lymfphovasculaire invasie en budding) 22%, negatief voorspellende waarde 98%.* *Positief voorspellende waarde van de conventionele risicofactoren (differentiatiegraad, lymfphovasculaire invasie en budding) in combinatie met de invasiediepte 15%, negatief voorspellende waarde 99%.* ***In 80% van de gevallen indicatie voor chirurgie als invasiediepte wordt beschouwd als een risicofactor, in plaats van 51% met conventionele factoren.***	Retrospective cohort study
Miyachi 2018	N= 653, pedunculated? Method: The vertical invasion depth was measured according to the JSCCR guidelines > 1000 mm was no independent risk factor Moreover, 189 of these 196 cases had no pathological factors but showed an invasion depth of ≥ 1000 µm, which means that 189 unnecessary surgeries might have been performed merely because of the "1000-µm rule."	
Yasue et al. 2019	N=846, only non-pedunculated, Method: The pathological diagnosis was made according to the Japanese Society for Cancer of the colon and rectum guidelines. When it is possible to identify the location of the muscularis mucosae, DI is measured from the lower border of the muscularis mucosae. When it is not possible to identify the location of the muscularis mucosae, DI is measured from the surface. Submucosal invasion less than 1000 lm is classified as T1a and submucosal invasion of 1000 lm or deeper is classified as T1b. High risk: T1b ID >/= 1 mm versus T1a Multivariate analyse: invasiediepte is geen onafhankelijke risicofactor voor LNM. *Positief voorspellende waarde van de conventionele risicofactoren (differentiatiegraad, lymfphovasculaire invasie en budding) 16%, negatief voorspellende waarde 99%.*	Retrospective cohort study

	Positief voorspellende waarde van de conventionele risicofactoren (differentiatiegraad, lymfphovasculaire invasie en budding) in combinatie met de invasiediepte 11%, negatief voorspellende waarde 100%. ***In 80% van de gevallen indicatie voor chirurgie als invasiediepte wordt beschouwd als een risicofactor, in plaats van 51% met conventionele factoren.*** In fact, the rate of LNM with only DI was 1.6% (4/258)	
Lee, 2018	N= 133, only 12 pedunculated Method: In the non-pedunculated type, depth of submucosal invasion was measured with a micrometer, according to two methods used in early gastric cancer which have been previously described (16). The first, involved the calculation of the distance from the lowest point of the muscularis mucosa (or surface of ulceration) to the point of deepest tumor penetration as previously reported ("classic" method). The alternative method measured the distance from the lowest point of the imaginary line of the plane of the muscularis mucosa to the point of deepest tumor penetration in cases of irregular (discontinuous or hypertrophic) or absent muscularis mucosae. In the pedunculated type, we measured both SID from muscularis mucosa and neck invasion depth from the imaginary line between the tumor head and the stalk to deepest area of invasion front, as previously described There was no significant difference in the methods of SID measurement between the LN− and LN+ groups and a depth of invasion ≥1000 µm was not associated with LN metastasis in T1 CRC	
Oh et al. 2019	N=833, 20% non-polypoid Method: For endoscopically resected sessile and flat tumors, the cut-off between sm1 and sm2 was 1,000 µm, according to the Paris classification, with an SM depth > 2,000 µm defined as sm3. For endoscopically resected pedunculated tumors, the cut-off between sm1 and sm2 was at the level of the neck, and an SM depth > 3,000 µm from the neck was defined as sm3. Deep submucosal invasion was defined as an SM depth ≥ sm2. Sm1 versus sm2/3: Multivariabele OR 2.14 Vascular invasion and high-grade histology were the strongest risk factors. Deep submucosal invasion (sm2/3) and tumor budding were also statistically significant predictors of LNM.	Retrospective cohort study
Berg, 2020	N= 216 T1 CRCs from 213 patients ➔ 162 low-risk patients There was a significantly increased rate of lymph node metastases in ≥ 2000-µm depth group compared to the < 2000-µm group (p = 0.01). There was no significant difference between width classes of < 4 mm and ≥ 4 mm with respect to residual carcinoma or lymph node metastases.	
Rönnow, 2020	N=1439, ? pedunculated? Method: Depth of submucosal invasion was classified according to Kudo, dividing the submucosal layer into, Sm1: upper third, Sm2: middle third, and Sm3: lower third of the submucosa. In cases where local excision was performed before surgical resection, depth of submucosal invasion is only stated in the SCRCR when it can be reliably assessed and for flat and sessile lesions only. Geen onafhankelijke voorspeller in multivariabele analyse	Retrospective cohort study

Resectiemarge

	PubMed	
P	((colon(MESH) OR colon(tiab) OR rectum(MESH) OR rectum(tiab) OR colorect*(tiab) OR colonic(tiab) OR rectal(tiab)) AND ("malignant polyp" (tiab) OR "malignant polyps" (tiab))) OR ((colon(MESH) OR colon(tiab) OR rectum(MESH) OR rectum(tiab) OR colorect*(tiab) OR colonic(tiab) OR rectal(tiab)) AND (cancer* (tiab) OR carcinoma(MESH) OR carcinoma*(tiab) OR tumor*(tiab) OR tumour*(tiab) OR adenocarcinoma(MESH) OR adenocarcinoma*(tiab) OR malignan*(tiab)) AND (T1 (tiab) OR pT1 (tiab) OR submucosa*(tiab)))	#1
I	("margins of excision"(MeSH) OR margin(tiab) OR radical(tiab) OR radicality(tiab) OR irradical(tiab) OR irradicality(tiab))	#2
C		
O	("neoplasm, residual"(MeSH) OR "residual neoplasm*"(tiab) OR "residual disease*"(tiab) OR "residual cancer*"(tiab) OR recurrence(MeSH) OR recurrence(tiab) OR "recurrent disease*"(tiab) OR relapse(tiab) OR relapsing(tiab) OR recidive*(tiab) OR "lymphatic metastasis"(MeSH) OR "lymphnode metastases"(tiab) OR "lymphnode metastasis"(tiab) OR "lymphatic metastases*"(tiab) OR "lymphatic metastasis"(tiab) OR "lymph node metastasis"(tiab) OR "lymph node metastases"(tiab))	#3

	#1 AND #2 AND #3	19-8-2018: 456 hits
	Embase	
P	(((colon/exp OR colon:ti,ab OR rectum/exp OR rectum:ti,ab OR colorect*:ti,ab OR colonic:ti,ab OR rectal:ti,ab) AND (colorectal tumor/exp OR colon tumor/exp OR cancer*:ti,ab OR carcinoma/exp OR carcinoma*:ti,ab OR tumor*:ti,ab OR tumour*:ti,ab OR adenocarcinoma/exp OR adenocarcinoma*:ti,ab OR malignan*:ti,ab) AND (T1:ti,ab OR pT1:ti,ab OR submucosa*:ti,ab)) OR ((colon/exp OR colon:ti,ab OR rectum/exp OR rectum:ti,ab OR colorect*:ti,ab OR colonic:ti,ab OR rectal:ti,ab) AND ('malignant polyp':ti,ab OR 'malignant polyps':ti,ab)))	#1
I	('surgical margin'/exp OR margin:ti,ab OR 'radical resection'/exp OR radical:ti,ab OR radicality:ti,ab OR irradical:ti,ab OR irradicality:ti,ab)	#2
C		
O	('minimal residual disease'/exp OR 'residual neoplasm*':ti,ab OR 'residual disease*':ti,ab OR 'residual cancer*':ti,ab OR 'recurrent disease'/exp OR 'recurrent disease*':ti,ab OR recurrence:ti,ab OR relapse:ti,ab OR relapsing:ti,ab OR recidive*:ti,ab OR 'lymph node metastasis'/exp OR 'lymph node metastasis':ti,ab OR 'lymphnode metastasis':ti,ab OR 'lymph node metastases':ti,ab OR 'lymph node metastases':ti,ab OR 'lymphatic metastasis':ti,ab OR 'lymphatic metastases':ti,ab)	#3
	#1 AND #2 AND #3 excluding conference abstracts	19-8-2018: 511 hits
	Cochrane	
P	((colon:ti,ab OR rectum:ti,ab OR colorect*:ti,ab OR colonic:ti,ab OR rectal:ti,ab) AND (cancer*:ti,ab OR carcinoma*:ti,ab OR tumor*:ti,ab OR tumour*:ti,ab OR adenocarcinoma*:ti,ab OR malignan*:ti,ab) AND (T1:ti,ab OR pT1:ti,ab OR submucosa*:ti,ab)) OR ((colon:ti,ab OR rectum:ti,ab OR colorect*:ti,ab OR colonic:ti,ab OR rectal:ti,ab) AND ("malignant polyp":ti,ab OR "malignant polyps":ti,ab))	#1
I	(margin:ti,ab OR radical:ti,ab OR radicality:ti,ab OR irradical:ti,ab OR irradicality:ti,ab)	#2
C		
O	("residual neoplasm*":ti,ab OR "residual disease*":ti,ab OR "residual cancer*":ti,ab OR "recurrent disease*":ti,ab OR recurrence:ti,ab OR relapse:ti,ab OR relapsing:ti,ab OR recidive*:ti,ab OR "lymph node metastasis":ti,ab OR "lymphnode metastasis":ti,ab OR "lymph node metastases":ti,ab OR "lymph node metastases":ti,ab OR "lymphatic metastasis":ti,ab OR "lymphatic metastases":ti,ab)	#3
	#1 AND #2 AND #3	19-8-2018: 1 hit