pT1 Colorectal cancer: histopathologiscal examination update

1. Should we inkt the resection margin?

	Conclusion
ESGE 2017	Inking of margins is recommended
Royal College of Pathologists Dataset for histopathological reporting of colorectal cancer December 2017	The margins of larger, sessile or semi-pedunculated lesions should be painted and the whole of the specimen transversely sectioned into 3 mm slices and submitted for histology in sequentially labelled cassettes. Macroscopic images of the intact and sliced specimen may be helpful to illustrate margin status.
NHS Bowel cancer screening programme Guidance on reporting lesions Maart 2018	If there is any suspicion of malignancy within a local excision specimen at endoscopic procurement or at dissection, it is advisable to paint any identifiable resection margins Macroscopic images are helpful to illustrate margin status and block sampling.

1. **Conclusion**

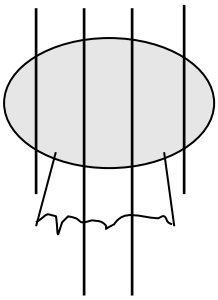
Yes, even in samll poyps (smaller than 1 cm) resection margin should be inkt.

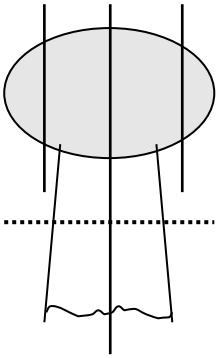
2. **Embedding**

	Conclusion
ESGE 2017	Polypoid lesions Polyps must be sliced and totally embedded. Special attention should be paid to the resection margin, which should be identified and described (dot-like, broad, stalked etc.) and either dissected tangentially into an extra cassette or sliced in a way that allows complete assessment. Mucosal excisions Mucosal excisions need to be pinned out on a cork board or on another suitable type of material, fixed, described and dissected allowing the identification of involvement of the deep and lateral surgical margins.
Royal College of Pathologists Dataset for histopathological reporting of colorectal cancer December 2017	The margins of larger, sessile or semi pedunculated lesions should be painted and the whole of the specimen transversely sectioned into 3 mm slices and submitted for histology in sequentially labelled cassettes. In cases where the margin of normal tissue is less than 3 mm, a 10 mm slice containing the relevant margin should be made and further sectioned at right angles
NHS Bowel cancer screening programme Guidance on reporting lesions Maart 2018	Sectioning should be perpendicular to the polyp base excision margin if this is identifiable. Polyps with a narrow stalk should be trimmed to keep the stalk intact and orientated to allow clear microscopic visualization of the polyp base margin, through multiple levels if necessary. Polyps with a broader stalk ('semi-pedunculated') or sessile polyps should be serially sectioned at 3mm intervals, perpendicular to the base margin if this is identifiable**.** **All tissue should be processed for histological evaluation.** If any mucosal lesion has a surrounding mucosal margin of normal tissue that macroscopically measures less than 3mm, this margin should be examined perpendicularly by taking sections of the margin at right angles from a thicker slice.

Conclusion

Complet examination, the resektion margin preferably examined by perpendiclar slicing of the speciment.





Referenties

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3.Diagnosis of T1 colorectal cancer

Summary of current international guidelines

	Conclusion
European guidelines for quality assurance in colorectal cancer screening and diagnosis. First Edition – Quality assurance in pathology in colorectal cancer screening and diagnosis 2012	Epithelial misplacement of adenomatous epithelium into the submucosa of a polyp is a well-recognised phenomenon [36]. It is commonly seen in prolapsing polyps in the sigmoid colon. Experience suggests that this will be one of the most difficult areas of pathological diagnostic practice in FOBT screening. Sigmoid colonic polyps are particularly prone to inflammation, a feature that tends to enhance the neoplastic changes present. When associated with epithelial misplacement, the potential for misdiagnosis of these lesions as early carcinoma becomes much greater. In cases of epithelial misplacement, surrounding lamina propria and haemosiderin-laden macrophages are found. Submucosal mucinous lakes may be seen. These do not warrant an immediate diagnosis of invasion and must be interpreted in association with the surrounding features.
Royal college of pathologists UK Dataset for histopathological reporting of colorectal cancer December 2017	Given well-recognised difficulties in some polyps of distinguishing stage pT1 adenocarcinoma from epithelial misplacement, and the clinical importance of assessing features within such cancers that may directly impact management, we recommend – the NHSBCSP mandate – that all pT1 cancers be reported by two consultant pathologists.
World Health Organisation, digestive system tumours, 5th edition	Pseudoinvasion/epithelial misplacement, represents prolapse of the adenomatous epithelium into the polyp head, stalk or deeper, often accompanied by extracellular mucin, haemorrhage, and hemosiderin, indicating trauma from peristalsis and prolapse. These appearances can sometimes mimic malignancy. It can be difficult to distinguish pseudoinvasion (or epithelial misplacement), particularly in cases of HGD, from an early stage pT1 colorectal cancer. Such cases usually require histological review by more than one pathologist (often several) or referral to an expert panel of pathologists.

Introduction

In the diagnosis of pT1 colorectal cancer pathologists encounter diagnostic challenges. Epithelial misplacement or pseudo-invasion is one of the main ones. To date epithelial misplacement continues to cause diagnostic difficulties, despite it not being a new phenomenon in colorectal polyps.
(1, 2, 3, 4, 5).

The classical epithelial misplacement features are lobulated glands, lamina propria accompaniment, haemosiderin deposition and muscular proliferation. Mimicry is particularly a problem when glands showing high grade dysplasia are misplaced and when epithelial misplacement is associated with rupture, mucin extravasation, secondary inflammatory changes, epithelial disruption and stromal reaction. Evaluation of the architecture of the misplaced glands (organoid or

haphazard) might aid in the distinction. Continuity between surface and deeper glands, misplaced adenomatous epithelium accompanied by lamina propria and non-adenomatous epithelium and accompanying muscular proliferation of the type associated with mucosal prolapse are features which favor benignity. Glandular angulation, single cell infiltration ('tumour budding') and convincing desmoplastic stromal reaction are all features which support a diagnosis of malignancy. Lymphatic or venous invasion clearly confirms malignancy (2,3).

Summary of literature

One of the most challenging diagnostic areas of difficulty in bowel cancer screening pathology has been reported to be distinguishing epithelial misplacement from invasive adenocarcinoma (2,3).

In UK bowel cancer screening programs, it has triggered mandatory double reporting of all stage pT1 colorectal cancers (2). Pathologists can access an 'expert board' whereby these difficult diagnostic problems are assessed by 3 specialist gastrointestinal pathologists. The results for the first 5 years of these assessments have shown substantial levels of agreement between the three expert board pathologists, whereby the ultimate diagnosis has been changed, from that of the original referral diagnosis, by the expert board for half of all the polyps, in the substantial majority from malignant to benign. In 3% of polyp cases, the expert board consensus has been the dual diagnosis of both epithelial misplacement and adenocarcinoma, further illustrating the diagnostic difficulties (5).

In a Dutch study on pedunculated polyps in the pre-screening era the percentage of misdiagnosis due to epithelial misplacement was 6% (6). This percentage is only expected to increase with the introduction of the bowel cancer screening program on the Netherlands (3). In the same Dutch study, it was concluded that generalist and expert pathologists experience diagnostic difficulty distinguishing pseudo-invasion and high-grade dysplasia from T1 colorectal cancer and recommends considering review of the histology of pedunculated T1 colorectal cancers by a second pathologist with discussion at a multidisciplinary meeting to prevent overtreatment (6).

Conclusion: Considering the diagnostic difficulty double reading of all T1 CRC's by a GI pathologist is recommended by most guidelines.

Literature

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Definitions and individual predictive value of histological high-risk parameters for metastasis

Differentiation grade

Question:

What is the diagnostic value of a histologically poor differentiation grade for the presence of lymph node metastases in T1 CRC patients?

Summary of current international guidelines

	Conclusion	Level of evidence
College of American Pathologists	Grade 1 Well differentiated (>95% gland formation) Grade 2 Moderately differentiated (50-95% gland formation) Grade 3 Poorly differentiated (<50% gland formation) Grade 4 Undifferentiated (no gland formation or mucin; no squamous or neuroendocrine differentiation)	
ESGE 2017	Grading of colorectal carcinomas should be performed according to the WHO classification, and tumors are graded as well-differentiated (> 95% gland formation), moderately differentiated (50%– 95% gland formation), or poorly differentiated (< 50% gland formation). Carcinomas may be heterogeneous, so the tumor should be graded according to the least differentiated component. The interobserver agreement between pathologists when grading colorectal adenocarcinoma specimen is fair at best, and it has been suggested that use of the high grade and low-grade categories should be standardized.	
Royal college of pathologists Dataset for histopathological reporting of colorectal cancer December 2017	Differentiation is based primarily on architecture and specifically gland or tubule formation. The criteria for poorly differentiated tumours are either irregularly folded, distorted and often small tubules or the absence of any tubular formation. Poorly differentiated adenocarcinomas should be separated from well/moderately differentiated adenocarcinomas but only if this forms the predominant area of the tumour. Although poor differentiation is identified by the same criteria as in major resection specimens, it is unclear from the literature whether this should be based on the predominant area or the worst area. For stage pT1 colorectal cancers, poor differentiation should be based on the worst area until the situation is clarified by further research.	Level of Evidence C
Japanese Guideline, JSCCR 2016	Tumor grade is assessed at the deepest part of the tumor containing the most unfavorable histologic feature, and is classified as favorable grade (well and moderately differentiated adenocarcinoma) or unfavorable grade (poorly differentiated adenocarcinoma and mucinous carcinoma)	
World Health Organisation, digestive system tumours, 5th edition	Grading of CRC is based on gland formation: low-grade (formerly well- to moderately differentiated) and high-grade (formerly poorly differentiated) tumours. Grading is based on the least differentiated component. The invasive front, where formation of tumour budding and poorly differentiated clusters occur, should not be taken into account when grading the tumour, but should be reported separately. In mucinous adenocarcinomas grading should be based on glandular formation.	

Evidence table (method used to assess grade of differentiation)

Article	Conclusion	Level of evidence
Kim et al. 2016	N=428, non-pedunculated/pedunculated? Method: JSCCR (see above)	Retrospective cohort study
Yim et al. 2017	N=252, 64% non-pedunculated Method: not specified. High risk: well to moderate vs. poorly differentiated (n=12). Differentiationgrade 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 adenocarcinoma, 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	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.)	Retrospective cohort study
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)	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%)	Retrospective cohort study

Conclusion

Poor differentiation grade is associated with a significantly higher risk of developing lymph node metastases in T1 colorectal cancer compared to well or moderate differentiation grade.

Differentiation grade must be based on gland formation according to the WHO and defined as low grade (≥ 50% gland formation) and high grade (<50% gland formation).

Differentiation grade should be based on the most predominant component and not on the worst component as the lower limit of such component is not clearly defined.

The invasive front should not be considered when grading.

Lymphovascular invasion

Question: is lymphovascular invasion important for the risk stratification in pT1 CRC?

	Conclusion LVI	Level of evidence
ESGE, 2017	Presence of lymphovascular invasion or poor differentiation of the tumor are associated with increased risk of lymph node metastasis, independently of the depth	

	or morphology of the tumor, and are an indication for surgery.) Surgery is recommended when lymphovascular invasion, deeper infiltration than sm1, positive/nonevaluable vertical margins, or poorly differentiated tumor with submucosal invasion is diagnosed.	
JGES 2015	In the case of complete endoscopic resection, pT1 (SM) carcinoma when vascular invasion is present, the estimated rate of lymph node metastasis of the lesion and the background of the patient are comprehensively evaluated and the indication for additional surgical resection is considered. In histological diagnosis, special staining and immunostaining of vascular invasion are informative. Elastica van Gieson staining or Victoria blue/HE double staining can be used to confirm venous invasion. To verify lymphatic vessel invasion, immunostaining with anti-lymphatic vessel endothelial antibody (D2-40) in combination with other staining methods is preferred.	[III, B]/ [II, A]
JSCCR 2016	If vascular invasion is observed during histological examination of the resected specimen, intestinal resection with lymph node dissection is considered as an additional treatment: Vascular invasion consists of lymphatic and venous Invasion	(level of evidence: IVb, grade of recommendation: B).
Oncoline, 2014	Chirurgische resectie dient te worden overwogen bij aanwezigheid van (lymf)angio-invasie). Lymfangio invasie moet opgenomen worden in het standaard verslag van de patholoog. De vasculaire of lymfatische invasie is goed onderbouwd maar nog niet in alle standaarden opgenomen. Een probleem bij het beoordelen van vasculaire of lymfatische invasie is de reproduceerbaarheid.	Recommendation: Category B
SIGN 2016	Colonic (and some rectal) cancers may be excised by polypectomy at colonoscopy (polyp cancers), and cohort studies indicate that such lesions do not require further surgery unless there is histopathological evidence of tumour at the margin (incomplete excision), lymphovascular invasion or if the invasive tumour is poorly differentiated.	
Cancer NSAG summary of evidence 2013	The risk on lymfnode involvement can be summarised as; a) Lymphovascular invasion absent: 11% risk of nodal metastasis lymphovascular invasion present: 32% risk of nodal metastasis b) Lymphatic invasion absent: 1% risk of nodal metastasis lymphatic invasion present: 25% risk of nodal metastasis c) Venous permeation absent: 7% risk of nodal metastasis Venous permeation present: 31% risk of nodal metastasis	

Evidencetabel

Article	Conclusion	Level of evidence
Beaton et al. 2013	- LVI: The impact of lymphovascular invasion on the risk of lymph node metastasis: OR: 4.81 [3.14, 7.37] (P < 0.00001) (studies >200 cases: OR: 4.01 [2.43, 6.63] (P < 0.00001)) - LI: The impact of lymphatic invasion on the risk of lymph node metastasis. OR: 7.66, [4.73–12.39] (P < 0.00001) - VI: The impact of vascular invasion on the risk of lymph node metastasis. OR: 4.03, [2.60–6.25] (P < 0.00001)	Systemic review and meta-analysis
Bosch et al. 2013	- Risk of LVI on LNM: RR 3.9 [2.7–5.6] - LI: Lymphatic invasion was the most powerful predictor of LNM, RR 5.2 [4.0–6.8] - VI: vascular invasion is a much weaker predictor of LNM, RR 2.2 [1.4–3.2] Definitions were provided in 3 of the 10 studies,	Systemic review and meta-analysis
Ueno et al. 2014	Association between risk factors and lymph node metastasis in early invasive colorectal cancer: Vascular invasion: OR 4.8 (3.8-6.0, p<0.0001) Vascular invasion (definite cancer involvement of lymphatic vessels and/or venous vessels)	Systemic review and meta-analysis Retrospective cohort study

Table of evidence (definitions used)

Article	Conclusion	Level of evidence
Kim et al. 2016	Vascular invasion and lymphatic invasion assessed. Definition not specified. Lymphovascular invasion (LVI) used as factor in uni- and multivariate analysis. Multivariate analysis revealed that LVI positivity was independently associated with lymph node metastasis	Retrospective cohort study
Yim et al. 2017	Terms used: lymphatic invasion, venous invasion, vascular invasion, lymphovascular invasion 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. Vascular invasion as 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. Only tumor cell nests in spaces lined by endothelial cells were counted as lymphovascular invasion. Additional immunohistochemical staining with Podoplanin (clone D2-40) to detect lymphatic invasion, and with CD34 or CD31, to detect venous invasion were performed in those sections in which it was difficult to judge the presence or absence of lymphovascular invasion. Multivariate; the most powerful clinicopathological parameter for predicting LNM was lymphatic invasion	Retrospective cohort study
Han et al. 2018	Terms used: lymphatic invasion, venous invasion, vascular invasion Definition used: lymphovascular invasion was identified as the presence of cancer cells within endothelial lined channels. Method for assessing lymphatic and venous invasion were not further specified.	Retrospective cohort study

	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).	
Ha et al. 2017/ Oh et al. 2019	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. Univariate and multivariate analyses identified vascular invasion as a risk factor for LNM.	Retrospective cohortstudies
Yasue et al. 2019	Lymphovascular invasion Assessment method: additional D2-40 staining and Victoria blue-H&E staining were performed using the samples of endoscpic resections 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. Mutlivariate analysis; LVI was a significant risk factor (OR 8.09; 95% CI 3.84–17.1), with the highest OR.	Retrospective cohort study

Conclusion

Lymphovascular invasion has an independent predictive value for development of lymph node metastasis.

Venous invasion should be reported separately.

Podoplanin (clone D2-40) to detect lymphatic invasion, and CD34 or CD31 to detect vascular invasion, are recommended.

Depth of submucosal invasion

Summary of current international guidelines

Guideline	Conclusion
JGES, 2015	The therapeutic course should be determined in accordance with the 2014 JSCCR Guidelines. -In case of SM invasion depth ≥ 1000 μm, the estimated rate of lymph node metastasis of the lesion and the background of the patient are comprehensively evaluated and the indication for additional surgical resection is considered. -In cases in which only the SM invasion depth does not satisfy the criteria for a radical cure, and where no other risk factors for metastasis are observed, the lymph node metastasis rate has been reported to be extremely low.
ESGE, 2015	In sessile lesions depth of invasion should be additionally be measured (in micrometers from the muscularis mucosae) and the limit for sm1 has to be defined as equal to or less than 1000 micrometers. For a sessile/flat lesion, depth of invasion is an important factor since the risk of lymph node metastasis appears significant only in lesions with more than 1mm. submucosal invasion. -In pedunculated lesions the Haggitt classification should be applied. The criteria for surgery are only Haggitt level 4 or positive vertical margins. -In the case of invasive carcinoma with massive submucosal invasion (>1000 u below the muscularis mucosae) (…) additional surgical intervention with removal of regional lymph nodes should be recommended.
JSCCR, 2016	-Additional treatment is considered with depth of SM invasion ≥ 1000 μm -When it is possible to identify or estimate the location of the muscularis mucosae, depth of SM invasion is measured from the lower border of the muscularis mucosae. -When it is not possible to identify or estimate the location of the muscularis mucosae, the depth of SM invasion is measured from the surface of the lesion. -The phrase 'possible to identify or to estimate' means that there is no 'deformity' of the muscularis mucosae as a result of SM invasion. -For pedunculated lesions with a tangled muscularis mucosae, depth of SM invasion is measured as the distance between the point of deepest invasion and the reference line, which is defined as the boundary between the tumor head and the stalk. Invasion by pedunculated lesions that is limited to within the head is defined as 'head invasion'.
Oncoline, 2014	Does not include depth of invasion as risk predictor in T1 CRC.
UK-guideline, 2013	"There are many methods for measuring the depth of invasion into the submucosa that can substage pT1 lesions and each has its advantages and disadvantages." "Haggitt concluded that only in level 4 lesions was there a significant risk of nodal involvement (27%). Although level 3 had no involved nodes some developed recurrence." "The absolute depth of invasion has been proposed as a more accurate method of assessing invasion. (…) A submucosal invasion depth of 3mm for pedunculated tumours is significantly associated with an increased risk of lymph node metastasis." "Matsuda et al. reported a large series of pedunculated polyps (n=384) using Haggitt lines and came to the same conclusion, putting the risk for level 3 & 4 at 6%."
SICCR, 2014	Measurement of depth of submucosal invasion, according to the Haggitt or Paris classification, is highly predictive of the risk of lymph node metastases, whereas there are no other adverse factors, the risk of lymph node metastases is low for pedunculated polyps with malignancy confined to the head or the upper part of the stalk (Haggitt 1, 2, 3).

Evidence table

Article	Conclusion	Level of evidence

Beaton et al. 2013	4 studies, gedefinieerd volgens Kudo (Nascimbeni 2002), SM3 hoger risico op LNM vs. SM1, geen budding meegenomen (Sohn 2007), non-sessiel, diepte invasie geen associatie met LNM (Son 2008), SM2/SM3 risicofactor voor LNM, geen multivariaat analyse, geen budding meegenomen (Choi 2008), SM3 hoger risico op LNM 4 studies (N= >200) quantitatief Kitajima 2004, (1/77 LN+ >/= 1 mm zonder andere risicofactoren, 0 LN+ <1 mm ondanks andere risicofactoren). 85% van de T1 CRC's heeft een invasiediepte van >/= 1 mm. Okabe 2004 Significant association on MV analysis (the 3.0 mm breakpoint showed the strongest significance and was selected for multivariate analysis) Ueno 2004, grens >/= 2 mm, geen significante associatie MV Tateishi 2010, Univariate analysis; invasion depth had a significant influence on lymph node metastasis. Multivariate analysis; depth of invasion was not significantly associated with lymph node metastasis.	Systemic review and meta-analysis
Bosch et al. 2013	4 studies semi quantitatief; Sm1/2 vs. sm3, RR 3.3 [95 %CI 1.8 – 6.2]); sm1 vs. sm2/3, RR 3.6 [95 %CI 1.3 – 9.8]) Onafhankelijke factor in 1/3 multivariable tests (sm1 vs. sm3, Nascimbeni), geen budding meegenomen. 5 studies quantitatief; Invasiediepte ≥ 1 mm > strong increase in relative risk for LNM (RR 5.2 [95 %CI 1.8 – 15.4]), onafhankelijke factor in 2/ 3 multivariable analyses. Yamamoto 2004, geen budding Ueno 2004, grens >/= 2 mm, geen significante associatie in multivariate analyse Kitajima 2004, (1/77 LN+ >/= 1 mm zonder andere risicofactoren, 0 LN+ <1 mm ondanks andere risicofactoren, wel is dit 85% van de patienten met T1 CRC) Masaki 2006, geen significante associatie in univariate analyse, kleine serie Okabe 2004, Significant association on MV analysis (the 3.0 mm breakpoint showed the strongest significance and was selected for multivariate analysis)	Systemic review and meta-analysis
Mou et al. 2013	4 studies Pooled analysis showed a significant association between submucosal invasion </= 1,000 µm with absence of LNM (RR 1.15, 95 % CI 1.11–1.18), without significant heterogeneity (P = 0.91, I2 = 0 %), when compared to the tumors with submucosal invasion >1,000 µm Well-differentiated nonpedunculated T1 colorectal cancer invasive into the submucosa ≤1,000 µm, without lymphovascular involvement or tumor budding, has the lowest risk of nodal metastasis (1.9 %)	systematic review and meta-analysis
Ueno et al. 2014	Submucosal invasion depth <1000 µm was significantly relevant to the incidence of LNM - false-negative rate (the incidence of positive LNM in the no-risk group) was most favorable. Submucosal invasion depth demonstrated to have the lowest ability to identify the risk of LNM. 85% >/= 1mm, 12,4% LNM+ (18 (3,4%) missed), 60% (differentiatie, VI, budding or PDC), 15,9% LNM+ (52 (3,7%) missed) 85% (differentiatie, VI, budding or PDC +ID), 12% LNM+ (6 (1,6%) missed)	Systemic review and meta-analysis Retrospective cohort study

Article	Conclusion	Level of evidence
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
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 µmwas 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 (vs. 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

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 vs. T1a	Retrospective cohort study
Oh et al. 2019	N=833, 20% non-polypoid Method: Polypoid, Sm2 Haggitt line-<3mm, Sm3= >3mm from Haggitt line. Non-polypoid, Sm1 <1mm, Sm2 1-2mm, Sm3 >2mm. High risk Sm >/= 2 (vs. Sm1) 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

Summary of literature

The measurement of submucosal invasion depth (SID) in early colorectal cancer was first described by Haggitt et al. (1985) and Kudo et al., who divided the submucosa into anatomical compartments for pedunculated lesions (Haggitt level 1-4) and third parts for sessile lesion (Sm1-3) respectively, using the muscularis mucosae and propria as its boundaries. Given the absence of the m. propria in local resections of early colorectal cancer subsequent modifications to these methods have been introduced resulting in different measuring schemes (Kikuchi 1995, Nascimbeni 2002). In 2004 Ueno et al. and Kitajima et al. established quantitative methods for measuring SID, providing an alternative way of measuring in cases where the muscularis mucosae could not be identified. A combination of both methods was adopted in the Japanese guidelines as method for measuring SID, including the use of Haggitt level 2 as baseline in pedunculated polyps with tangled m. mucosae. At present SID is regarded as a risk factor for lymph node metastases in early invasive colorectal cancer and it has been integrated in international guidelines (JSCCR, ESGE) as criteria to determine the indication for (additional) radical surgery, however the measurement of SID still faces practical difficulties and is subject to high interobserver variation. (Kouyama 2016, Ueno 2014). In literature a heterogenous population of polyp types and different measurement schemes are used with different cut-off rules for determining the relation of SID to lymph node metastases (Ueno14, Kim, Han, Yim, Yasue, Ha, Oh). When a relation was established, it was mostly not independent of other risk factors. SID is a factor that could fairly identify a group with very low risk of having lymph node metastases, however with the cost of a high rate of unnecessary radical surgery when considered a risk factor for LNM (Ueno14, Oh, Yasue, Ha).

Depth of invasion in non-pedunculated polyps

Invasiedepth >= 1000um is a risk factor for development of lymph node metastasis

Depth of invasion in <u>pedunculated polyps</u>

Question

How does submucosal invasion depth in pedunculated polyps with pT1 CRC relate to the degree of risk of lymph node metastasis and how should it be measured?

Summary of literature

In 1985 Haggitt classified submucosal invasion depth for pedunculated tumors into 5 levels of invasion (0-4). To date Haggitt's is the most widely used for the classification of invasion depth in pedunculated T1 CRC. In the method proposed by Kitajima 2004, for pedunculated lesions, the depth of the submucosal invasion was measured as the distance between Haggitt's level 2 and the deepest invasion point. In the method proposed by Ueno 2004, depth of submucosal invasion is simply measured as the distance between the tumor surface and the deepest invasion point. The latter step is modified in the method proposed by Kawachi 2015 and recommended by the JSCCR guidelines 2016. The JSCCR states that for pedunculated tumors with a tangled muscularis mucosae, depth of submucosal invasion is measured in micrometers starting from the line between the polyp head and stalk ('Haggitt line' or reference line) to the point of deepest invasion of the tumor. Tumors with invasion limited to the head are considered to have submucosal invasion of 0 µm in depth, or are defined as 'head invasion'.

As mentioned above several methods have been proposed for measuring submucosal invasion depth, both specific and nonspecific for pedunculated tumors. According to one study comparing three methods, the JSCCR 2016 guidelines approach is most predictive of lymph node metastasis. (*Yim 2017).* Haggitt's classification was not included in the latter study. Using Haggitt's classification, risk of lymph node metastasis in levels 1 and 2 is reported to be 0%. For level 3, risk ranges from 0% to 25%. For level 4, risk ranges from 14.6% to 30.8%. Levels 3-4 vs levels 1-2, and level 4 vs levels 1-3 invasion were significantly associated with lymph node metastasis. (*Ueno 2004, Backes 2018*)

Conclusion

There is evidence of moderate quality that submucosal invasion depth is a risk factor for lymph node metastasis in malignant pedunculated polyps (retrospective studies, low number of cases, differing methods of measuring, pooled results from pedunculated and sessile tumors). (niveau 2).

Recommendations

1. For malignant pedunculated lesions with submucosal invasion limited to the head, or Haggitt levels 1 and 2, risk of lymph node metastasis is considered low.
2. Haggitt level 4 the risk of lymph node metastasis is elevated
3. The risk of lymph node metastasis can not estimated sufficiently in malignant pedunculated lesions with submucosal invasion Haggitt level 3 based on the current literature

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Tumorbudding

Introduction

Tumor budding has been primarily reported in Japanese studies and is included as a high-risk feature in early CRC in the Japanese guidelines. It refers to the presence of single cells of small groups of cells in the stroma at the invasive front of the tumor. Until recently standardized international criteria on how to assess tumorbudding have been lacking.

Question

What is the diagnostic value of tumorbudding for the presence of lymph node metastases in T1 CRC patients?

Summary of current international guidelines

Richtlijn	Conclusion
ESGE 2017	Prospective studies, and a consensus definition for the reporting of tumor budding are required for the inclusion of this characteristic in standard histopathological reporting of T1 cancer.
Royal College of Pathologists Dataset for histopathological reporting of colorectal cancer December 2017	There is emerging evidence that identification of the phenomenon of tumour budding in local excision specimens may be of prognostic importance in predicting outcome and/or predictive of nodal metastatic disease. This is not yet considered sufficient to justify its inclusion as a core data item
JSCCR 2016	If any of the following findings is observed during histological examination of the resected specimen, intestinal resection with lymph node dissection is considered as an additional treatment (evidence level B). Poorly differentiated adenocarcinoma, signet-ring cell carcinoma, or mucinous carcinoma, Depth of SM invasion ≥1000 μm, vascular invasion positive and/or ***Budding (G2/3).*** Method of assessment and grading: after selecting one field where budding is the most intensive, number of buddings is counted in a field measuring 0.785 mm2 observed through a 20× objective lens (WHK 10× ocular lens). Depending on the number of buddings, Grade of budding is defined as follows: Grade 1: 0–4, Grade 2: 5–9, Grade 3: 10 or more. The lymph node metastasis rate by Grade 2/3 tumors is significantly higher than by Grade 1 tumors.

Summary of literature

Multiple different systems to assess tumorbudding has been described in literature (1). Despite lack of standardization high grade tumorbudding has been identified as a strong and independent predictor of LNM in early colorectal cancer in many meta-analyses. (2-6). Recently, during the International Tumor Budding Consensus Conference (ITBCC) (2016), international consensus has been reached on an evidence-based, standardized scoring system for tumor budding to be used in international CRC guidelines and routine practice. (7). The agreed definition for tumor budding is a single tumor cell or a cell cluster of up to 4 tumor cells.

Conclusion

Tumor budding is recommended to be assessed on HE in one hotspot (in a field measuring 0.785 mm2) at the invasive front. A three-tier system should be used along with the budding count. 0–4 buds—low budding (Bd 1). 5–9 buds—intermediate budding (Bd 2). 10 or more buds—high budding (Bd 3). In pT1 colorectal cancer, Bd2 and Bd3 are associated with an increased risk of lymph node metastasis (7).

Aanbevelingen

1. Tumor budding wordt gescoord zoals beschreven in de aanbeveling van de internationale tumor budding consensus conferentie. (strong recommendation)
2. De aanwezigheid van tumor budding GR2/3 wordt beschouwd als een significante risico voor het hebben van lymfkliermetastase in T1 CRC (strong recommendation)

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Interobserver variation for histological assessment

Introduction

Current risk stratification for lymph node metastasis is solely based on the presence of known histological risk factors for lymph node metastasis, such as lymphovascular invasion, tumor budding, poorly differentiated clusters, grade of differentiation and depth of invasion (Haggitt level for pedunculated polyps). This risk stratification is hampered by a significant interobserver variability for the different histological parameters.

Question

What is the interobserver variation in the assessment of high-risk features in T1 CRCs?

Summary of current international guidelines

Richtlijn	Conclusion vertical margin	Level of evidence
UK guideline	Histological assessment of malignant polyps is open to considerable interobserver variation, particularly with regard to the important risk factors of degree of differentiation of the malignant component and the presence or absence of lymphatic invasion. Pathologists should be prepared to seek a second opinion from another colleague where there is any doubt about histological findings, especially where surgery may be contemplated	Evidence obtained from at least one well-designed controlled study without randomization

Summary of literature

A study by Harris et al. showed that when H&E slides of stage I and II CRC were randomly assigned to 6 different pathologists, the kappa for small and large vessel invasion were 0.28 and 0.18 respectively. The kappa only improved slightly with the use of immunohistochemistry (CD31 or D2-40) for detection of large vessel invasion to a kappa of 0.4. Ueno et al. described that interobserver agreement between observers from different institutes for differentiation grade, (lympho-)vascular invasion and tumor budding in T1 CRCs was moderate (kappa 0.48) and fair (kappa 0.33 and 0.29) respectively. (Ueno 2014) In a more recent publication, H&E slides of 56 cases were assigned to 4 GI expert pathologists working within the UK bowel screening program. This study showed kappa's varying between 0.15 for the Haggitt level (poor agreement) to 0.35 for lymphovascular invasion (fair agreement) and 0.44 for tumor budding (moderate agreement).

Considerations

Given the reported interobserver variation in the assessment of high-risk features in T1 CRCs pathologists should have a low threshold for seeking a second opinion from another colleague where there is any doubt in the presence or absence of high risk features, especially in cases where surgery may be considered.

Pathological tumor free margin

Introduction

T1 CRCs can be removed by local resection. However, in 6.8-17.8% of the submucosal invasive carcinomas lymph node metastasis occur.[1] Furthermore, the local resection may not have removed the lesion adequately, with a risk of local recurrence.[2] Margin status is generally accepted as a predictor of adverse outcome (local recurrence, lymph node metastasis, distant metastasis), but the margin needed for a 'clear resection margin' is unclear.

Question

What pathological tumor free margin is a risk factor for disease recurrence after local resection of T1 CRC?

Summary of current international guidelines

Guideline	Conclusion	Level of evidence
ASGE, 2013 https://www.asge.org/docs/default-source/education/practice_guidelines/doc-role-of-endoscopy-in-the-staging-and-management-of-colorectal-cancer.pdf?sfvrsn=6	We recommend surgical management of all malignant polyps with unfavorable histological features (including <1 mm cancer-free margin) if the patient is an appropriate surgical candidate. We recommend surgery for sessile or flat colonic neoplasia that demonstrates submucosal invasion if the patient is an appropriated surgical candidate.	Moderate quality
ESGE, 2017 https://www.esge.com/colorectal-polypectomy-and-endoscopic-mucosal-resection-emr-esge.html	Clearance of ≤1 mm is associated with similar outcomes to definite margin involvement, and clearance >1 mm appears to be helpful in defining low risk patients. Other European guidelines currently recommend a level of ≤1 mm as equivalent of margin involvement	
ESMO, 2013 https://www.esmo.org/Guidelines/Gastrointestinal-Cancers/Early-Colon-Cancer	Unfavourable histological findings include lymphatic or venous invasion, grade 3 differentation, level 4 invasion (invades the submucosa of the bowel wall below the polyp) or involved margins of excision. When unfavourable histological features are present in a polyp from a patient with an average operative risk, resection is recommended	Level of evidence IV (retrospective cohort studies or case-control studies) Grade of recommendation B (strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended)
Oncoline, 2014 https://www.oncoline.nl/index.php?pagina=/richtlijn/item/pagina.php&id=37098&richtlijn_id=933	Polypectomy alone is sufficient in case of complete resection (resection margin >1 mm) of a good-moderate differentiated T1 colorectal carcinoma without (lymph)angioinvasion. In all other cases an additional surgical resection should be considered.	Low
UK Guideline, 2014 https://www.nice.org.uk/guidance/cg131/chapter/1-Recommendations	Offer further treatment to patients whose tumour had involved resection margins (less than 1 mm)	

Summary of literature

Only one retrospective cohort study was published on the relationship between a pathological tumor free margin of different distances (involved, 0.1-1 and >1 mm) and adverse outcomes (residual disease or lymph node/distant metastases).[2] The authors reported no adverse outcomes in both 21 patients with a clear resection margin between 0.1 and 1 mm and in 25 patients with a clear resection margin >1 mm.

Three additional studies reported on the occurrence of adverse outcomes comparing the use of both a margin of >0 mm and of >1 mm as an R1 resection in the same population. In one of these studies no additional patients with adverse outcomes were seen if a margin of >0 mm was used.[3] The other two studies both found 2 additional patients (2-4%) with adverse outcomes if a margin of >0 mm was used instead of a margin ≥1 mm.[4, 5] Two other studies reported on a margin of >0 mm versus a margin of >2 mm in the same population and found 1 and 2 additional patients (2-4%) with adverse outcomes if a margin of >0 mm was used.[6, 7] One study reported on a margin of >1 mm versus a margin of >2 mm in the same population and found no additional patients with adverse outcomes if a margin of >1 mm was used.[8] These results were not adjusted for the presence of other unfavorable histological features.

There are many studies that report on the occurrence of adverse outcomes in patients with a resection margin of >0 mm. In four of these studies we were able to separate the results in patients with other unfavorable histological features (poor differentiation and/or (lymph)angioinvasion). No adverse outcomes were seen in any of the in total 166 patients with an R0 resection without other unfavorable histological features.[9-12] Unfortunately, exact resection margins are not reported in these publications.

The same results are found in studies that report on the occurrence of adverse outcomes in patients with a margin of >1 mm without other unfavorable histological features (no adverse outcomes in 7 patients with an R0 resection)[13] and in studies that report on patients with a margin of >2 mm (no adverse outcomes in in total 58 patients with an R0 resection without other unfavorable histological features in three studies).[14-16] Also in these studies, exact resection margins are unknown.

One study described that presence of cancer at or near the margin (≤1 mm) was significantly associated with the occurrence of adverse outcomes, even in the absence of other unfavorable parameters ($p<0.002$).[17] The exact margins (involved or 0.1-1 mm) of the patients with adverse outcomes are not described in this study.

Considerations

Evidence on tumor free margin is limited. Only one study compares different pathological tumor free margins (0.1-1 mm and >1 mm). In this study (including 65 polyps) the authors conclude that a clear resection margin of any distance can be considered low risk and therefore managed non-surgically.

However, the results of some studies suggest a lower risk of adverse outcomes in patients with a complete resection if only resections with a margin of >1 mm or even >2 mm are considered R0 resections. However, these results are not corrected for the presence of other unfavorable histological features. In addition, in these studies patients with involved margins and with margins 0.1-1 mm are analyzed as one group. Therefore, we cannot exclude that the patients with adverse outcomes were actually the patients with involved margins and not the patients with margins of 0.1-1 mm.

In all studies that were adjusted for other unfavorable histologic features, no adverse outcomes are found in low risk patients (no poor differentiation or lymphatic or venous invasion) with an R0 resection, irrespective of the distance of the resection margins.

One study suggests that cancer at or near the margin (<1 mm) is significantly associated with the occurrence of adverse outcomes, even in the absence of other unfavorable histologic features. However, again, in this study patients with involved margins and with margins 0.1-1 mm are analyzed as one group. Therefore, we cannot exclude that the patients with adverse outcomes were actually the patients with involved margins and not the patients with margins 0.1-1 mm. [17]

Currently no distinction is made between macroscopically radical vs. macroscopically irradical margins, en-bloc versus piecemeal resections and lateral versus deep margin, and their relation with separate components of adverse outcome are not consistently specified, which also potentially impedes to draw clear conclusions on which resection margins are to be considered safe or on when completing local resection alone might be satisfactory.

Conclusies

T1 CRC with positive resektion margin is considered as high risk.

Pathological free resection margin is considerd as low risk.

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B6. When to consider adjuvant surgery in T1 CRC

Introduction

Er is bewijs van lage tot matige kwaliteit dat een aantal histologische kenmerken geassocieerd zijn met het optreden van een ongunstige uitkomst (lokaal recidief kanker, lymfkliermetastasen, afstand metastasen, CRC gerelateerd overlijden). Deze kenmerken bestaan uit; pathologisch positieve laterale of diepe resectiemarge, slechte differentiatie, (lympho-)vasculaire invasie. In enkele richtlijnen worden ook de submucosale invasiediepte en tumor budding genoemd. In enkele internationale richtlijnen wordt tevens gesuggereerd dat gesteelde poliepen een lager risico hebben dan sessiele poliepen, zie ook "summary of current international guidlines. (ASGE, 2013; ESGE, 2015; ESMO, 2013; JSCRC, 2015; Oncoline, 2014; UK guideline, 2013)

Summary of current interational guidelines

	Conclusion	**Level of evidence**
ASGE , 2013 (1)	Surgery is recommended when: Haggitt 4 poor histological differentiation vascular or lymphatic invasion <1 mm cancer-free margin	Moderate: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
ESGE, 2015 (2)	Surgery is recommended when: Haggitt 4 positive/nonevaluable vertical margins	Strong recommendation, moderate quality evidence
ESMO 2013, (3)	Surgery is recommended when: Haggitt 4 grade 3 differentiation lymphatic or venous invasion involved margins of excision	Level of evidence: Retrospective cohort studies or case–control studies Grade of recommendation: Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
JSCCR, 2016 (4)	Depth of SM invasion ≥1000 µm Vascular invasion positive Poorly differentiated adenocarcinoma, signet-ring cell carcinoma, or mucinous carcinoma Grade 2/3 budding at the site of deepest invasion	
Oncoline, 2014 (5)	slecht gedifferentieerd (lymf)angio-invasie resectiemarge ≤1 mm Het is onbekend of gesteelde T1 CRCs een lagere kans op LNM hebben, wat wel gesuggereerd wordt	Niveau: Laag
UK guideline, 2013 (6)		