Submucosal invasion and risk of lymph node invasion in early Barrett's cancer: potential impact of different classification systems on patient management

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Abstract

Background: Due to the high mortality and morbidity rates of esophagectomy, endoscopic mucosal resection (EMR) is increasingly used for the curative treatment of early low risk Barrett's adenocarcinoma.

Objective: This retrospective cohort study aimed to assess the prevalence of lymph node metastases (LNM) in submucosal (T1b) esophageal adenocarcinomas (EAC) in relation to the absolute depth of submucosal tumor invasion and demonstrate the efficacy of EMR for low risk (well and moderately differentiated without lymphovascular invasion) EAC with sm1 invasion (submucosal invasion $\leq 500 \mu\text{m}$) according to the Paris classification.

Methods: The pathology reports of patients undergoing endoscopic resection and surgery from January 1994 until December 2013 at one center were reviewed and 54 patients with submucosal invasion were included. LNM were evaluated in surgical specimens and by follow up examinations in case of EMR.

Results: No LNM were observed in 10 patients with sm1 adenocarcinomas that underwent endoscopic resection. Three of them underwent supplementary endoscopic eradication therapy with a median follow up of 27 months for patients with sm1 tumors. In the surgical series two patients (29%) with sm1 invasion according to the pragmatic classification (subdivision of the submucosa into three equal thirds), staged as sm2-3 in the Paris classification, had LNM. The rate of LNM for surgical patients with low risk sm1 tumors was 10% according to the pragmatic classification and 0% according to Paris classification.

Conclusion: Different classifications of the tumor invasion depth lead to different LNM risks and treatment strategies for sm1 adenocarcinomas. Patients with low risk sm1 adenocarcinomas appear to be suitable candidates for EMR.

Keywords

Early Barrett's cancer, lymph node metastases, sm1 esophageal adenocarcinoma, endoscopic mucosal resection, Paris classification, submucosal invasion

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Introduction

En bloc esophagectomy, which has been shown to result in better survival for each stage of esophageal adenocarcinoma,¹ is still a major surgical procedure associated with a considerable risk of morbidity and mortality,² and requires a high standard of skills and experience. Endoscopic mucosal resection (EMR) offers an attractive alternative to the removal of early esophageal adenocarcinoma given the lower risk of lymph node metastases (LNM) compared with squamous cell carcinoma.³ It also allows for complete

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histopathological assessment and indirect assessment of the presence of LNM, since the depth of tumor invasion has been shown to correlate strongly with the rate of LNM in adenocarcinoma.⁴

It has to be noted that with EMR the depth of submucosal resection is not well controlled and this poses certain limitations. To overcome this problem, most studies have therefore evaluated surgical resection specimens to assess submucosal (sm) invasion depth instead of EMR specimens. Dividing the submucosa into three equal thirds (pragmatic classification) is considered a reliable subclassification of the submucosa only in surgical specimens. On the other hand, the Paris classification for columnar epithelial tumors of the esophagus defines sm1 invasion as tumor extension into the first 500 μ m of submucosal layer and thereby differentiates sm1 from sm2-3 esophageal adenocarcinomas.⁵

Some studies have attempted to stratify patients into low and high risk groups for LNM and feasibility of EMR based on histopathological features of the EMR specimen.⁶⁻⁸ Poor tumor differentiation and lymphovascular invasion (LVI) always designate a patient to a high risk group, independent of tumor invasion depth. Vieth et al. consider all submucosal cancers to be "high" risk,⁸ while Manner et al. regarded invasion of the upper submucosal third in conjunction with the absence of LVI and good to moderate tumor differentiation as features of "low" risk adenocarcinoma.^{6,7} In recent literature a growing number of researchers share the view that endoscopic therapy for esophageal adenocarcinomas is justified only for selected "low" risk cases.^{9,10}

The primary aim of this study was to assess the prevalence of lymph node metastases in submucosal esophageal adenocarcinomas (T1b) in relation to the absolute depth of submucosal tumor invasion. We further sought to demonstrate both the efficacy of EMR for low risk sm1 adenocarcinomas and the impact of various definitions of sm1 invasion on subsequent clinical management and LNM involvement.

Methods

Patients

The pathology reports of all patients who underwent surgery or EMR for adenocarcinoma of the distal esophagus or the gastroesophageal junction (GEJ) at Erasmus Medical Center during the period from January 1994 until December 2013 were reviewed. Only patients with submucosal invasion were included. Patients with mucosal adenocarcinomas only or tumor invasion beyond the submucosa were excluded. In the event of neoadjuvant chemotherapy or radiotherapy,

patients were excluded because of the potential impact on prognosis and survival. Evidently, patients could not be included when adequate slides or pathology blocks were unavailable for review (Figure 1).

In case of tumor positive vertical resection margins after EMR, the specimen could not be evaluated with regard to the depth of infiltration. If such patients underwent subsequent surgical resection, the surgical specimen was used for assessment of tumor invasion depth and the presence of LNM.

Initial evaluation and management

Patients were initially evaluated in Erasmus Medical Center with standard and high resolution endoscopy at a later date and endoscopic ultrasound (EUS) to assess the depth of infiltration and lymph node involvement. Biopsies were obtained and EUS with fine needle aspiration (FNA) was performed in the case of a suspicious lymph node to exclude LNM. In the latter case, additional CT scanning was also performed.

Surgical excision of adenocarcinoma was decided for patients with cancer invading the submucosal layer, lesions deemed too large for endoscopic resection and in case of suspected or proven lymph node involvement. If a patient refused to undergo surgical excision or was unfit for surgery, EMR was performed. Patients with mucosal cancers and elevated lesions without endoscopic signs of invasive features usually underwent EMR, which was introduced in 1999 in the Erasmus Medical Center.

Endoscopic resection

Patients underwent endoscopic resection either with "capped-EMR" or with multiband mucosectomy (MBM).

All specimens were retrieved and pinned down on cork without any attempt to reconstruct the lesions. In piecemeal resections, the pathologist evaluated only the vertical margins, while the lateral margins were already endoscopically estimated.

Histological evaluation

Resected specimens were fixated (8% formaldehyde), step-sectioned by 2–5 mm intervals (EMR and surgical resection specimens respectively), cut in 4 μ m thick slides, and stained with hematoxylin and eosin (H-E).

All slides were revised and evaluated by two independent gastrointestinal pathologists, according to the latest World Health Organization (WHO) classification. The deepest levels of invasion of the tumor in the submucosa (sm levels 1–3) and the total width of the sm were measured. In cases where the lamina muscularis

Figure 1. Flowchart of patients with T1b tumors that underwent review of their medical records and pathological review of their EMR and surgical specimens. EAC, esophageal adenocarcinoma; T1b, submucosal tumors; T1a, intramucosal tumors; sm, submucosal invasion.

mucosae (mm) was duplicated, submucosal invasion was calculated under the deepest layer of mm (true lamina muscularis mucosae).¹¹ In the surgical resection specimens without residual tumor after EMR, the total width of the sm was measured above the Squamocolumnar junction. The mean value of three measurements in three different slides is reported. Additionally, features such as presence of LVI, tumor size and differentiation grade (classified as good [G1], moderately [G2], and poorly differentiated [G3] adenocarcinoma in accordance with the WHO classification 2010), lymph node status (in the surgical specimens), and vertical margin (in the EMR specimens) were evaluated. The vertical margins in the EMR specimens were measured in the central region of the slides, because at that point the artifacts due to the surgical procedure were less visible or absent. In case of EMR followed by surgery, the deepest level of tumor invasion in either specimens determined the T stage of the tumor. Specimens (surgical or EMR) in which the deepest tumor front could not be properly revised were excluded.

Subsequent management

Further treatment was tailored for each patient depending on the histopathological analysis of the EMR specimen, the biopsy results from residual Barrett's

mucosa and fitness for surgery. Patients were treated surgically in case of non-radical EMR, G3 tumors, and lymphovascular or submucosal invasion.

Endoscopic eradication therapy using argon plasma coagulation (APC), photodynamic therapy (PDT), radiofrequency ablation (RFA), and stepwise EMR was applied to the rest of the patients when there were residual suspicious for neoplastic lesions, high grade dysplasia (HGD) or residual areas of Barrett's mucosa.

Follow up

Follow up data were obtained from reviewing patients' medical records. The date of recurrence, death and last follow up were noted. Follow up time was calculated from the date of first medical procedure, either surgery or EMR, to date of death or date of the most recent clinical, endoscopic or radiologic investigation. Patients were followed up after a complete EMR, every 3–6 months during the first year and annually thereafter. Follow-up investigations included endoscopy with high-resolution endoscopes and biopsies in residual Barrett's mucosa. An EUS examination was included to assess lymph-node status. In case of missing follow up data, the general practitioner was contacted for additional information.

Outcome of the study

The primary outcome of the study was the occurrence of LNM. This was assessed by examining the presence or absence of LNM in surgical resection specimens whenever available and by follow-up during which time CT scan and/or EUS with or without FNA were performed on indication. In our study low risk adenocarcinomas are defined as tumors with G1-2 differentiation and no LVI.

Statistical methods

The data were analyzed descriptively by using absolute and relative frequencies, means, ranges, minimum and maximum values. The interquartile range (IQR) and median were used to describe data with a skewed distribution.

Results

The study population consisted of 54 patients with a T1b adenocarcinoma. Seven patients had undergone only EMR, 17 patients underwent first EMR and subsequent surgery mainly because of the submucosal tumor invasion, and 30 patients underwent surgery only. Transthoracic excision was performed in five patients, while trans hiatal resection was carried out in 42 of the 47 patients. The median number of resected lymph nodes was 12, ranging from 3 to 28, which is the recommended minimum LN count for a greater than 90% staging sensitivity.¹² The capped-EMR technique was used in 19 patients and the MBM technique in 5 patients.

Histopathological analysis of EMR specimens

The width of the submucosal layer in EMR specimens ranged from 400 μ m to 4180 μ m with a median of 1715 μ m (IQR 1017.5–2262.5 μ m). The infiltration depth in sm1 adenocarcinomas ranged from 30 μ m to 400 μ m with a median of 85 μ m (IQR 52.5–210 μ m). Sm2-3 tumor invasion was observed in 14 patients with depth of infiltration ranging from 560 μ m to 2910 μ m with a median of 970 μ m (IQR: 705–1232.5 μ m).

Outcome-histopathological analysis of patients that underwent EMR and subsequent surgery. Seventeen patients that were initially treated with EMR, underwent additional surgery because of tumor invasion into the submucosal layer. Three out of seven patients with positive vertical resection margins in EMR specimens had no residual tumor in the surgical specimens. This is probably explained by a positive vertical cauterization plane from the lesional side but not from the resection site.

Resection occurred exactly at the level of the deepest invasion. The results are displayed in Table 1. The median number of resected lymph nodes per patient was 15 (IQR 11–20).

Outcome of patients that underwent only EMR. Four patients with sm1 invasion and three patients with sm2-3 invasion underwent only EMR and did not proceed to surgery because of significant comorbidity and an estimated high surgical mortality risk (Table 2). The median follow up period of these patients was 18 months (IQR 13–49 months). No patient was diagnosed with local or distant cancer recurrence during this period.

Among sm1 patients, RFA and PDT were applied in two after EMR with complete eradication of Barrett's mucosa. A complementary EMR was performed for the remaining patient who had a suspicious lesion, which proved to be HGD. One patient with sm1 invasion (T1sm1 G1) had a follow up endoscopy which showed complete eradication of dysplasia and metaplasia, but died of a tumor unrelated cause 4 months later. Unfortunately no imaging or autopsy findings are available for this patient. Two of the patients with sm2-3 tumors died of other causes 12 and 132 months after EMR, while one patient with sm2-3 neoplasia died of an unknown cause 14 months later.

Histopathological analysis of surgical specimens

Patients included in our study underwent surgery because of the submucosal invasion of adenocarcinoma (Table 3). The width of the submucosal layer in the surgical specimens ranged from 1030 to 7400 μ m with a median of 3225 μ m (IQR 1980–4085 μ m). In the surgical specimens sm1 tumors were detected according to the pragmatic classification in seven patients; according to Paris classification, three were classified into the sm2-3 group and four were classified into the sm1 group. Sm1 tumors had a median depth of tumor infiltration of 350 μ m (IQR 205–695 μ m). Two out of seven patients with sm1 invasion (29%) had lymph node involvement; interestingly both patients had tumor infiltration beyond 500 μ m into the submucosa and would have been staged as sm2-3 in the Paris classification; a poorly differentiated tumor was detected in one of them. Neither of these two patients had LVI.

Twenty-three patients presented sm2 and sm3 tumors according to the pragmatic classification with a median tumor infiltration depth of 2130 μ m (IQR 1535–3525 μ m); all had tumor infiltration beyond 500 μ m into the submucosa and thus according to the Paris classification were classified into the sm2-3 group. LNM was observed in 11 of the 23 of patients (48%) with sm2 and sm3 tumors. If a subdivision to sm2 and 3

Table 1. Histopathology of patients that underwent EMR followed by surgery

No	Initial management	Sm invasion (μm)	Sm layer thickness in EMR specimen (μm)	Sm layer thickness in surgical specimen (μm)	Sm invasion (Paris classification)	Sm invasion (pragmatic classification)	Tumor size (cm)	D	Vertical margin status	Subsequent management	Surgical pathology
1	EMR	560	760	3070	sm2-3	sm3	G1 0.7	No	Positive	Surgery	pT0N0M0R0
2	EMR	150	2000	950	sm1	sm1	G1 1.1	No	Negative	Surgery	pT0N0M0R0
3	EMR	50	790	1940	sm1	sm1	G3 0.8	No	Negative	Surgery	pT0N0M0R0
4	EMR	940	2070	4380	sm2-3	sm2	G1 1	No	Positive	Surgery	pT0N0M0R0
5	EMR	1180	2200	950	sm2-3	sm2	G2 0.7	No	Negative	Surgery	pT1aN0M0R0
6	EMR	30	2100	1400	sm1	sm1	G1 0.9	No	Negative	Surgery	pT1aN0M0R0
7	EMR	750	2320	900	sm2-3	sm1	G1 0.9	No	Negative	Surgery	pT0N0M0R0
8	EMR	1250	3580	1800	sm2-3	sm2	G2 0.9	No	Negative	Surgery	pT0N0M0R0
9	EMR	2910	3280	1700	sm2-3	sm3	G2 1.2	No	Positive	Surgery	pT1bN2M0R0
10	EMR	400	2250	1300	sm1	sm1	G3 0.6	No	Negative	Surgery	pT0N0M0R0
11	EMR	1000	1130	1350	sm2-3	sm3	G2 0.9	No	Negative	Surgery	pT0N0M0R0
12	EMR	1100	1820	1200	sm2-3	sm3	G2 1.2	No	Positive	Surgery	pT1bN0M0R0
13	EMR	60	400	690	sm1	sm1	G2 0.6	No	Negative	Surgery	pT1aN0M0R0
14	EMR	800	800	1400	sm2-3	sm3	G1 1.1	No	Positive	Surgery	pT0N0M0R0
15	EMR	600	600	1350	sm2-3	sm3	G2 1.6	No	Positive	Surgery	pT1aN0M0R0
16	EMR	300	1090	1150	sm1	sm1	G2 0.8	No	Positive	Surgery	pT1aN0M0R0
17	EMR	600	1570	1900	sm2-3	sm2	G2 0.5	No	Negative	Surgery	pT0N0M0R0

Paris classification: sm1 invasion, ≤ 500 μm; sm2-3 invasion, > 500 μm; D, differentiation; G1, good differentiation; G2, moderate differentiation; G3, poor differentiation; LVI, lymphovascular invasion.

was made, 5 of the 7 patients with sm2 tumors (71%) and 6 of the 16 patients with sm3 tumors (38%) had LNM. The median number of resected lymph nodes per patient was 11 (IQR 7–14).

Discussion

The high rates of morbidity and mortality in elderly patients,¹³ and the poor quality of life after esophagectomy,¹⁴ have prompted clinicians to search for expanded but safe indications for EMR, in particular in the case of sm1 adenocarcinomas. The present study demonstrates the efficacy of EMR for low risk sm1 adenocarcinomas and assesses the impact of various definitions of sm1 invasion (Paris and pragmatic classification) on subsequent clinical management and LNM involvement.

Manner et al. and Herrero et al. suggest that it is safe to rely on endoscopic resection in case of sm1 invasion in patients with low risk adenocarcinomas, which are defined as tumors with G1-2 differentiation and no LVI. Manner et al. showed that 87% of patients had a complete endoluminal resection with 84% long term remission, while Herrero et al. found no LNM even in sm2-3 adenocarcinomas, both in surgical specimens and during a follow up period of 26 months

after EMR.^{7,15} Likewise, we did not observe LNM in 10 patients with T1b sm1 adenocarcinomas that underwent EMR, while two of them are high risk patients having G3 adenocarcinomas. Median follow up after EMR for our patients with sm1 tumors was 27 months (IQR 14.5–42.5 months). Six patients had surgery after EMR with no LNM, three patients had supplementary endoscopic eradication therapy and one patient died of other causes after having undergone two follow-up endoscopies negative for dysplasia. The absence of LNM strongly suggests that EMR is a safe and effective treatment modality in low risk T1b sm1 adenocarcinomas.

Definitions of the extent of the first submucosal layer vary in different studies which renders generalization of conclusions impossible. Most studies have used a pragmatic approach of subdividing the sm layer in three equal parts.^{7,8} This was decided because the exact measurement in microns of the depth of infiltration was considered to be highly variable and affected by the artifactual shrinkage due to fixation.⁸ Indeed, Ancona et al. reported that the base of an endoscopically resected sample shrinks both due to cauterization damage and due to the effect of the muscularis mucosae making the submucosa wrinkle.⁹ Artifactual shrinkage cannot be avoided and the extent of shrinkage cannot

Table 2. Histopathology and outcome of patients that underwent only EMR

No	sm layer thickness		sm invasion (Paris classification)	sm invasion (pragmatic classification)	D	tumor size (cm)	LVI	vertical margin status	FU and subsequent management	outcome	survival in months
	initial management	sm invasion (μm)	specimen (μm)								
1	EMR	50	1610	sm1	G2	1	No	Negative	EMR	CR	62
2	EMR	100	600	sm1	G1	1.4	No	Negative	EUS-RFA	No	18
3	EMR	690	2400	sm2-3	G3	1.3	No	Negative	Endoscopy	No dysplasia	Death of old age- 12
4	EMR	230	4180	sm1	G1	0.6	No	Negative	PDT		36
5	EMR	2300	2300	sm2-3	G3	1.5	Yes	Positive	Gastroscopy	No dysplasia	Death of old age-132
6	EMR	1600	1600	sm2-3	G2	1.2	No	Positive	Referred for surgery	Patient denied surgery	Death of unknown cause-14
7	EMR	70	1150	sm1	G1	0.6	No	Negative	Endoscopy	No dysplasia	Death of unrelated cause-4

Paris classification, sm1 invasion, ≤500 μm; sm2-3 invasion, >500 μm; D, differentiation, G1, good differentiation; G2, moderate differentiation; G3, poor differentiation; LVI, lymphovascular invasion, CR, complete resection; NO, no lymph nodes detected.

be predicted or measured. Importantly, the pragmatic classification is inadequate in its ability to define the exact depth of tumor infiltration because in most cases the complete submucosal layer is not included in the EMR specimen. In our opinion, it is logical to follow the widely accepted Paris classification, which if adopted more widely, offers a reliable comparison of results among different studies.

Peters et al. emphasized the inaccuracy of the pragmatic-practical classification considering the discrepancies they found between absolute measurements of tumor invasion in micrometers and practical measurements based on subdivision of the sm layer. In their series, cancers classified as sm2 had a small absolute submucosal penetration depth of only 120 and 200 micrometers.¹⁶ In our study, two patients with sm1 tumors according to pragmatic classification are staged as sm2-3 tumors according to the Paris classification. Importantly, different classifications of sm involvement amount to totally different management strategies, if endoscopic resection is to be regarded as the treatment of choice for low risk sm1 adenocarcinomas and surgical resection for lesions extending beyond sm1. The rate of the class divergence for the same patient amounts to 8% for EMR patients in the present study, but could be higher depending on the level of tumor invasion in relation to the resected part of the submucosa. Because even a few microns of tumor invasion may dramatically alter the assumed risk for lymph node metastases and hence the choice for endoscopic or surgical treatment, pathological assessment and reporting should be standardized.

In surgical series there is a great variability in the reported LNM rates in sm1-3 adenocarcinomas, as shown in Table 4. The main reason for this variability is probably the diversity in pathological characteristics of T1b tumors among these series. The prevalence of LNM in patients with submucosal esophageal adenocarcinoma ranges from 0% in sm1 invasion to 78% in sm3 cancers (Table 4).^{6,10,15,17-23} However, controversies arise over the prevalence of LNM in esophageal cancers with sm1 invasion. Leers et al. found that the prevalence of LNM is not significantly influenced by the absolute depth of submucosal invasion. They showed 21% LNM in patients with sm1 involvement and this observation would effectively exclude a safe maximal depth of sm invasion to justify EMR.²¹ Similar findings are reported by Barbour et al. and Sepesi et al. They demonstrated that stratification of the risk of lymph node invasion or survival could not be predicted by the depth of submucosal tumor invasion.^{23,24} In contrast, other studies describe low rates in sm1 stages.^{9,17,20} Westterterp et al. concluded that the combined group of mucosal (T1m1-m3) and superficial submucosal (T1sm1) adenocarcinomas carry only a 1%

Table 3. Histological outcome of surgical resection specimens in the patients who underwent only surgery

No	Sm invasion (μm)	Sm layer thickness (μm)	Sm invasion (Paris classification)	Sm invasion (pragmatic classification)	Differentiation	Tumor size (cm)	LVI	Surgical pathology
1	6060	6060	sm2-3	sm3	G3	3	No	pT1bN2M0R0
2	3750	4120	sm2-3	sm3	G2	2.5	No	pT1bN0M0R0
3	690	2400	sm2-3	sm1	G3	3.5	No	pT1bN2M0R0
4	1410	1490	sm2-3	sm3	G1	3	No	pT1bN0M0R0
5	3300	3600	sm2-3	sm3	G2	2.1	No	pT1bN0M0R0
6	1730	2070	sm2-3	sm3	G3	4.5	Yes	pT1bN2M0R0
7	100	1950	sm1	sm1	G2	2.2	No	pT1bN0M0R0
8	1710	3980	sm2-3	sm2	G3	3	Yes	pT1bN2M0R0
9	2130	3350	sm2-3	sm2	G2	3	Yes	pT1bN1M0R0
10	310	3100	sm1	sm1	G2	3	No	pT1bN0M0R0
11	2960	3620	sm2-3	sm3	G2	2.5	No	pT1bN1M0R0
12	1900	2200	sm2-3	sm3	G3	3	Yes	pT1bN0M0R0
13	2650	6300	sm2-3	sm2	G2	9	No	pT1bN0M0R0
14	2720	3900	sm2-3	sm3	G3	3	No	pT1bN0M0R0
15	4580	5230	sm2-3	sm3	G3	2.5	No	pT1bN1M0R0
16	1400	3960	sm2-3	sm2	G1	2.4	No	pT1bN0M0R0
17	2220	2950	sm2-3	sm3	G2	5	No	pT1bN2M0R0
18	550	1030	sm2-3	sm2	G3	1.2	No	pT1bN1M0R0
19	4520	4980	sm2-3	sm3	G3	5.3	Yes	pT1bN0M0R0
20	5300	6300	sm2-3	sm3	G1	1.7	No	pT1bN0M0R0
21	4370	4800	sm2-3	sm3	G3	4	No	pT1bN0M0R0
22	1820	2890	sm2-3	sm2	G2	2.5	No	pT1N1M1R1
23	1520	1680	sm2-3	sm3	G3	2	No	pT1bN0M0R0
24	700	7400	sm2-3	sm1	G2	2	No	pT1bN1M0R0
25	350	1100	sm1	sm1	G2	2.5	Yes	pT1bN0M0R0
26	1320	1500	sm2-3	sm3	G2	1.5	No	pT1bN1M0R0
27	40	1550	sm1	sm1	G1	1	No	pT1bN0M0R0
28	1000	3650	sm2-3	sm1	G2	3	No	pT1bN0M0R0
29	1550	2200	sm2-3	sm3	G2	1.7	No	pT1bN0M0R0
30	900	1840	sm2-3	sm2	G3	1.5	No	pT1bN1M0R0

Paris classification, sm1 invasion, ≤ 500 μm; sm2-3 invasion, > 500 μm; G1, good differentiation; G2, moderate differentiation; G3, poor differentiation; LVI, lymphovascular invasion.

risk of lymphatic dissemination in combination with a 5-year recurrence free period of 97%.¹⁷ Their results suggest that patients with sm1 invasion are suitable candidates for curative endoscopic therapy. In the present study, review of the pathologic examinations for 30 patients that underwent only surgical resection showed seven sm1 tumors according to the pragmatic classification. Two patients (29%) with sm1 tumors showed LNM, one of them having a low risk adenocarcinoma. This rate is higher than a LNM rate of 11% reported in the literature to date. LNM rates for sm2 and sm3 adenocarcinomas were 71% and 38% respectively, not showing a consistent increase of lymph node involvement with progressive sm infiltration depth.

In our surgical series the rate of patients with low risk sm1 tumors having LNM was 20%, which is in contrast to 0% in patients with low risk sm1 tumors in the EMR series. As already mentioned, sm1 tumors that had LNM would classify as sm2-3 tumors according to the Paris classification. Consequently, the absolute depth of tumor invasion should be taken into account when defining a “safe” depth in μm for the application of endoscopic therapy in esophageal adenocarcinomas. Three of the seven surgically treated patients (43%) having sm1 adenocarcinoma according to the pragmatic classification were classified into the sm2-3 group according to the Paris classification. Two of these (66%) presented with LNM, implicating that

Table 4. Lymph node positivity in sm1–3 depth of infiltration in surgical specimens: results in the literature

References	ACC	n	sm1		n	sm2		n	sm3	
			N1	%		N1	%		N1	%
Westerterp et al. ¹⁷	66	25	0	0	23	6	26	18	12	67
Manner et al. ⁶	19	2	1	50	7	2	29	10	3	30
Badreddine et al. ^{18 a}		31	4	13						
Gockel et al. ¹⁰	15	8	1	13	2	1	50	5	1	20
Bollschweiler et al. ¹⁹	22	9	2	22	4	0	0	9	7	78
Buskens et al. ²⁰	52	16	0	0	13	3	23	13	9	69
Leers et al. ²¹	51	19	4	21	9	1	11	23	6	26
Scheil-Bertram et al. ²²	21	7	1	14	2	0	0	12	4	33
Barbour et al. ²³	49	12	2	17	17	2	15	20	4	20
Herrero et al. ^{15 a}	7	3	0	0						
Total	302	132	15	11	77	15	19	110	46	42
Present study	30	7	2	29	7	5	71	16	6	38

ACC, adenocarcinomas.

^aNo subdivision of the respective numbers of sm2 and sm3 adenocarcinomas was provided in these studies.**Table 5.** Rate of LNM for surgically treated patients with sm1 EAC according to Paris and pragmatic classification and risk of histological parameters

Patients treated with surgery ^a				
Tumor invasion depth/ histological risk	Low risk sm1 EAC (Paris classification)	Low risk sm1 EAC (Pragmatic classification)	Sm1 EAC (Paris classification)	Sm1 EAC (Pragmatic classification)
LNM rate	(0/7) 0%	(1/10) 10%	(0/10) 0%	(2/14) 14%

LNM; lymph node metastases, sm; submucosal invasion, EAC; esophageal adenocarcinoma.

^aIncluding patients that underwent EMR before surgery.

patients should probably have sm1 tumors staged according to the Paris classification in order to safely undergo EMR. The LNM rates for the different groups of surgically treated T1b patients, including patients that initially underwent EMR, are illustrated in Table 5.

Due to the retrospective nature of our analysis, it was not possible to control for specimen slicing and preparation of histologic slides, which limited the assessment of the deepest tumor margin. While surgical resection specimens are routinely cut in 5-mm slices, endoscopic resection specimens are routinely cut in 2-mm slices, making it possible defining more precisely the areas with the deepest infiltration. This fact renders any correlation between LNM risks in EMR and surgical patients difficult, a problem already highlighted by Herrero et al.¹⁵ Another limitation of this study is the inability to completely exclude the presence of LNM in patients who did not undergo esophagectomy after EMR. The limited median follow up period of 18 months and the relative inaccuracy of EUS for the diagnosis of LNM, do not allow to conclude with absolute certainty that LNM are truly absent.

There is little doubt that early recognition of early esophageal cancer will lead to an increase in the detection and treatment of sm1 adenocarcinomas. The decision for endoscopic or surgical treatment of sm1 adenocarcinomas should be based on reliable classification of the tumor invasion depth. The pragmatic approach of subdividing the sm layer in three equal parts is unreliable due to the fact that the submucosal layer often is not fully included in EMR resection specimens. However, patients with low risk tumors (G1/G2 tumors with no LVI) and less than 500 µm tumor invasion depth into the submucosa appear to be suitable candidates for endoscopic therapy with excellent clinical outcome. Therefore, the key requirement for proper patient selection and management is uniform and standardized assessment and reporting of histopathological examinations of EMR specimens.

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Conflict of interest

The authors declare that there is no conflict of interest.

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