Today’s Mistakes and Tomorrow’s Wisdom… in the Management of T1b Barrett’s Adenocarcinoma

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Abstract
**Background:** Given the limitation that endoscopic resection only enables local intraluminal treatment without lymphadenectomy, the standard treatment of esophageal adenocarcinoma (EAC) with invasion of the submucosa (T1b) has long been surgical esophageal resection. However, in recent literature, the risk of lymph node metastases (LNM) associated with T1b EAC appears to be lower than previously assumed, and endoscopic management is increasingly being considered a valid and less invasive alternative to surgery. **Summary:** Surgical esophageal resection performed after radical endoscopic resection of T1b EAC often does not show any residual tumor or LNM in the resected specimen. Given the morbidity and mortality associated with surgical esophageal resection, endoscopic management with strict surveillance protocols has been more widely applied provided that the initial tumor was radically removed by endoscopic resection, reserving surgery for those cases where the additional risk of surgical esophageal resection is justified. These are the cases where intraluminal recurrent neoplasia is found that cannot be retreated endoscopically or cases with locoregional LNM detected during follow-up. In the future, selection of patients who can safely be managed endoscopically and those who may benefit from additional surgery after endoscopic resection of T1b EAC may become more tailored, using risk prediction calculators or sentinel node navigated surgery.

Key Messages: Management of patients with T1b EAC is shifting from surgical treatment to less invasive endoscopic treatment strategies, including watchful waiting approaches. The risk of LNM of T1b EAC appears to be lower than long assumed. In the future, management of T1b EAC may become more individualized based on tools to predict LNM risk per patient case.

Introduction

For early esophageal adenocarcinoma (T1 EAC), radical esophagectomy with regional lymphadenectomy has long been the standard management as it eliminates the tumor along with possible lymph node metastases (LNM) and any remaining Barrett’s epithelium [1]. However, given the significant operative mortality rates (up to 6%), morbidity rates (1.7–49.5%), and the substantial reduced quality of life for patients [2–5], endoscopic management has become the treatment of choice for early mucosal EAC (T1a EAC). For this indication, endoscopic treatment has been proven safe and effective, with excellent long-term outcomes [6, 7].

Accepted indications for endoscopic treatment are EAC limited to the mucosal layer (T1a) without poor histopathological tumor characteristics (i.e., poor differentiation and/or lymphovascular invasion (LVI)). For these tumors, the risk of LNM is <1% and a nonsurgical approach is considered the treatment of choice [6, 8–10]. If the tumor invades the submucosal layer (T1b), the risk of...
LNM – based on available data – varies from 0 to 46% depending on the extent of invasion and the presence of the aforementioned histopathological features [8, 11]. Given the limitation that endoscopic resection only enables local intraluminal treatment without lymphadenectomy, additional esophagectomy after an endoscopically radically removed T1b EAC is still widely advised. However, increasing data based on a series of endoscopically treated patients suggests that the LNM risk for T1b EAC is lower than previously assumed [8–10, 12, 13]. Optimal management of patients with T1b EAC is therefore being remodeled, looking at strict surveillance protocols, better patient stratification and sentinel node navigated surgery as alternatives to additional surgical esophagectomy in all patients. In this chapter, we will discuss the novel developments in management of patients with T1b EAC.

Today’s Mistakes

In patients with a visible lesion in a Barrett’s esophagus, endoscopic resection is the most important therapeutic step. Endoscopic resection is also considered to be the most important diagnostic step, since it results in a large tissue specimen, enabling accurate histological assessment of the resected tumor. In case of a mucosal EAC (T1a), without other histological risk factors, e.g., poor differentiation or LVI, further endoscopic management is the treatment of choice. However, if submucosal invasion is present, additional surgery is still advised to resect the esophagus and adjacent lymph nodes. The rationale for this approach is to remove any present LNM – the most important prognostic factor for survival [14]. There is, however, increasing data from more recent publications showing that the risk of LNM in T1b lesions is lower than we assumed (0–16%) and that the risk of LNM is not the same for all submucosal tumors [6, 8–10, 12, 13, 15]. We may thus be overtreating patients with invasive surgery, after radical endoscopic resection of a T1b EAC.

Traditionally, the risk of LNM in submucosal EACs has been based on dated, retrospective, surgical studies. In these series, exact histopathological staging of the tumor was not relevant, since the patients had already undergone surgery, and differentiating mucosal from submucosal invasion or assessing presence of certain poor histopathological characteristics did not change further management. In addition, there is a notable discrepancy between LNM rates reported by surgical and endoscopic series for T1b EAC. This discrepancy is possibly explained by a difference in preparing slides for histopathological assessment. Surgical resection specimens are cut at relatively wider intervals than endoscopic resection specimens. Potentially, these wider cuts may result in missing the deepest depth of tumor infiltration, thereby overestimating the risk of metastasis associated with a certain infiltration depth. In endoscopic resection specimens, additional cuts are made to identify the area with deepest tumor infiltration, resulting in more accurate tumor staging and thus better association with risk of LNM [8, 12].

Changing Perspectives

The risk of LNM in T1b EAC depends on several histopathological characteristics: exact tumor infiltration depth, tumor differentiation grade, and presence of LVI. These histopathological characteristics can be identified to stratify the risk of LNM of T1b EACs into two groups: low-risk (submucosal invasion of <500 μm, good to moderate differentiated cells (G1–G2), no LVI) and high-risk (submucosal invasion ≥500 μm, poor to undifferentiated cells (G3–G4) and/or LVI). Tumors with histopathological “high-risk” characteristics seem to be associated with a higher risk of LNM than tumors without these high-risk characteristics. By stratifying T1b EACs into a low-risk and a high-risk group, significant different LNM rates between these two groups have been demonstrated in recent literature. During the last years, various endoscopy-oriented studies reported on the frequency of LNM in cohorts with T1b EAC patients that were endoscopically managed after endoscopic resection [8, 9, 12, 13]. These studies report that after a median follow-up duration between 23 and 63 months, low-risk T1b patients have a LNM risk of 0–2% while high-risk T1b patients show a LNM risk varying between 0 and 16%.

These endoscopy-oriented studies have several strengths in common: all were conducted in tertiary referral centers for upper gastrointestinal neoplasia; cases with suspicion of LNM during staging examinations were excluded; for histopathological assessment, the endoscopic resection specimens were all cut in 2–3 mm strips and the paraffin blocks were cut into 4 μm slides minimizing the risk of understaging infiltration depth; and all specimens were examined or reviewed by an expert pathologist. However, a common limitation to address is that these studies consisted of retrospective cohorts, with heterogeneous follow-up schedules. Another limitation is that relatively small cohorts were studied, often with only a relatively short follow-up. Moreover, one may argue that including only patients who underwent endoscopic management after endoscopic resection, and thereby excluding those patients who underwent surgery may cause selection bias toward a relatively lower risk of LNM and better clinical outcome in the endoscopic group. On the other hand, the endoscopically managed groups probably included more patients who were poor surgical candidates due to comorbidity or old age.
Tomorrow’s Wisdom

Histopathological Assessment

Based on histopathological characteristics in the resected specimen, most centers stratify patients with T1b EAC into low-risk or high-risk. Low-risk T1b EAC is more widely accepted as an indication for endoscopic management [8]. There is however a note of caution in this stratification process. Van der Wel et al. [16] pointed out that a substantial interobserver variability exists in the histological assessment of tumor characteristics, even among expert Barrett pathologists. As adequate assessment of these risk factors is of the utmost importance in guiding further treatment, the authors propose that pathologists obtain multiple additional cuts of the deepest point of invasion for optimal evaluation of invasion depth. Furthermore, as assessment is often performed by a single pathologist, a review by at least one expert pathologist is strongly recommended when a histological feature potentially pushes the patient’s policy from endoscopic management to the need for additional esophagectomy.

Endoscopic Follow-Up Not Only for Inoperable Patients?

We initiated a prospective, international multicenter study (PREFER trial (NCT03222635)) with the rationale that endoscopic management may not only be a suitable option for inoperable patients, or for low-risk T1b patients, but for all patients with T1b EACs irrespective of histological characteristics. This ongoing multicenter study aims to prospectively include a total of 141 patients after radical endoscopic resection of a T1b EAC, without signs of lymph node or distant metastases at baseline. These patients will be surveyed with 3-monthly endoscopy and EUS during the first 2 years of follow-up, 6-monthly endoscopy and EUS during year 3 and 4, and then annually. A CT-scan will be performed after the first year of follow-up (Table 1). Using this strict follow-up regime, we aim to detect intraluminal recurrence or locoregional LNM in a still curable stage (as illustrated in a patient case in Fig. 1). To strengthen the validity of the study, first, patients undergo thorough baseline examinations after radical resection (i.e., CT chest plus abdomen or PET-CT and upper endoscopy with EUS) to exclude any suspicion of LNM or distant metastases. Second, the endoscopic resection specimens of the T1b cancer will be reviewed by a panel of expert pathologists to reach consensus diagnosis on histopathological tumor characteristics. Third, the quality of endoscopic follow-up is ensured by periodic central reviews of the standardized acquired endoscopic and EUS images.

We anticipate that the results of this study will demonstrate that strict endoscopic follow-up after endoscopic resection of T1b EAC is a safe and minimally invasive alternative to surgery. Furthermore, by collecting quality of life questionnaires, the study will also help us understand what the impact of endoscopic follow-up is on patients’ well-being.

Table 1. Follow-up protocol after radical endoscopic resection for T1b EAC patients (PREFER trial)

| Procedure | Description | Interval |
|-----------|-------------|---------|
| HR-WLE with virtual chromoendoscopy | Survey the residual BE segment and evaluate for local recurrence | Year 1 and 2: 3-monthly  Year 3 and 4: 6-monthly  Year 5 and on: yearly |
| EUS | Assess lymph nodes in mediastinal and truncal regions; FNA should be performed in case of suspicious lymph nodes | Year 1 and 2: 3-monthly  Year 3 and 4: 6-monthly  Year 5 and on: yearly |
| CT chest and abdomen or PET-CT | Evaluate for distant metastasis | After 1 year (and on indication) |

HR-WLE, high-resolution white light endoscopy; BE, Barrett’s esophagus; EUS, endoscopic ultrasound; FNA, fine needle aspiration.
follow-up (Table 1). However, whether 3-monthly follow-up intervals are too intense, or if the lengthened 6-monthly follow-up intervals during year 3 and 4 are too lenient, still has to be evaluated based on prospectively collected data.

Another question that arises is whether EUS is an adequate tool to detect LNM. Pech et al. [19] demonstrated in a cohort of 179 patients who underwent endoscopic resection for EAC and squamous cell cancer that EUS offers a diagnostic accuracy for positive lymph nodes of 73% (95% CI: 65–79). Earlier, Buskens et al. [20] demonstrated an accuracy of 93% in predicting the absence of LNM based on the histopathology of esophagectomy specimens from a cohort with 61 HGD and EAC patients. Besides the possibility to perform real-time EUS-fine needle aspiration and potentially improve accuracy to confirm metastatic disease, EUS is yet the best available modality for the detection of locoregional LNM and is superior to other imaging modalities (CT or PET-CT) [12]. In a strict post-resection follow-up regimen with frequent endoscopic surveillance including repeated EUS assessments, conducted in tertiary referral centers with a low threshold for performing fine needle aspiration, it is likely that LNM is detected at an early stage.

**Prediction Tools**

More robust data confirming a clear advantage of endoscopic management over esophagectomy for patients with high-risk T1b EACs is still required. As discussed, available data do suggest that endoscopic resection and strict follow-up may be a valid management option. Therefore, after endoscopic resection of T1b EAC, the decision to opt for strict endoscopic surveillance or to perform additional esophagectomy should be discussed with the patient and within a multidisciplinary team meeting. In this decision, patients’ wish, comorbidity, surgical risk, and LNM risk should be considered.

To better predict risk of LNM on a patient case, several attempts have been made to base the prediction on certain tumor characteristics [21–23]. Most recently, Gotink et al. [23] created a prediction model that incorporates individual histopathological tumor characteristics to estimate the risk of LNM in patients with T1b EAC. Based on their internally validated model using a retrospectively constructed cohort with 248 T1b EAC patients, the estimated risk of developing metastases within 5 years after initial treatment ranged between 5.9 and 70.1%, depending on the combination of histopathological parameters (LVI and submucosal invasion depth) and tumor
size (per increase of 10 mm). Concerning the latter, there is increasing evidence suggesting this to be an additional important histopathological factor associated with LNM [21, 24, 25]. Limitations of this calculator were the fact that it was based on retrospective, mostly surgical data, and that it was not externally validated. In the future, prediction tools based on robust data that have been externally validated may be of help to enable tailored decision-making.

**Sentinel Node Navigation Surgery as a New Treatment Algorithm**

Next to strict surveillance, another esophagus preserving treatment algorithm for T1b patients after radical endoscopic tumor resection might be sentinel node navigation surgery (SNNS): selective lymphadenectomy without concomitant esophagectomy [26, 27]. In two pilot studies with a total of 10 high-risk T1b patients scheduled for esophagectomy, the feasibility and safety of SNNS combined with an endoscopically injected radioactive tracer around the esophagectomy scar were studied. All sentinel nodes could be visualized and resected prior to the esophagectomy, without acute adverse events. The same study group now continues the evaluation of this SNNS approach in an ongoing trial (NL8100) which includes patients after radical endoscopic resection of a high-risk T1b EAC to similarly undergo a SNNS procedure with selective lymphadenectomy. In this trial, however, the esophagus is only resected in case of proven tumor positive sentinel node(s). In case of tumor negative sentinel nodes, patients will be subjected to a strict endoscopic surveillance regime according to the follow-up protocol of the PREFER trial (Table 1). Regarding its potential as a valid treatment in future perspectives, this procedure should remain to be considered with reservation until more convincing results are achieved based on a larger sample size.

**Conclusion**

Management of patients with T1b EAC is complex and requires multidisciplinary effort and agreement to optimize patient outcomes. In recent years, the management of T1b EAC is shifting from surgical treatment to less invasive endoscopic treatment strategies, due to a lower risk of LNM than previously assumed. Feasibility of a watchful waiting strategy after radical endoscopic resection of T1b EAC, with strict endoscopic follow-up, is currently prospectively studied. In the future, management of T1b EAC may become more individualized due to better knowledge of histological characteristics that influence the risk of LNM, tools to predict risk of LNM per patient case, and possible sentinel node navigation surgery for patients with increased risk of LNM.

**Conflict of Interest Statement**

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**Author Contributions**

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**References**

1. Pohl H, Sirovich B, Welch HG. Esophageal adenocarcinoma incidence: are we reaching the peak? *Cancer Epidemiol Biomarkers Prev.* 2010;19(6):1468–70.
2. Bailey SH, Bull DA, Harpole DH, Rentz J, Neumayer LA, Pappas TN, et al. Outcomes after esophagectomy: a ten-year prospective cohort. *Ann Thorac Surg.* 2003;75(1):217–22; discussion 222.
3. Markar SR, Karchikesalingam A, Thrumurthy S, Low DE. Volume-outcome relationship in surgery for esophageal malignancy: systematic review and meta-analysis 2000–2011. *J Gastrointest Surg.* 2012;16(5):1053–63.
4. Raymond DP, Seder CW, Wright GD, Magee MJ, Kosinski AS, Cassivi SD, et al. Predictors of major morbidity or mortality after resection for esophageal cancer: a society of thoracic surgeons general thoracic surgery database risk adjustment model. *Ann Thorac Surg.* 2016;102(1):207–14.
5. Varghese TK Jr, Wood DE, Farjah F, Oelschlager BK, Symons RG, MacLeod KE, et al. Variation in esophagectomy outcomes in hospitals meeting Leapfrog volume outcome standards. *Ann Thorac Surg.* 2011;91(4):1003–9; discussion 1009–10.
6. Pech O, May A, Manner H, Behrens A, Pohl J, Wefering M, et al. Long-term efficacy and safety of endoscopic resection for patients with mucosal adenocarcinoma of the esophagus. *Gastroenterology.* 2014;146(3):652–60 e1.
7. van Munster S, Nieuwenhuis E, Weusten BLAM, Alvarez Herrero L, Bogte A, Alkhalf A, et al. Long-term outcomes after endoscopic treatment for Barrett’s neoplasia with radiofrequency ablation +/- endoscopic resection: results from the national Dutch database in a 10-year period. *Gut.* 2021;71(2):265–76.
8. Scholvinck D, Künzli H, Meijer S, Seldensrijk K, van Berge Henegouwen M, Bergman J, et al. Management of patients with T1b esophageal adenocarcinoma: a Retrospective Cohort Study on patient management and risk of metastatic disease. *Surg Endosc.* 2016;30(9):4102–13.
9. Alvarez Herrero L, Pouw RE, van Vilsteren FG, ten Kate FJ, Visser M, van Berge Henegouwen M, et al. Risk of lymph node metastasis associated with deeper invasion by early adenocarcinoma of the esophagus and cardia: Study Based on Endoscopic Resection Specimens. *Endoscopy.* 2010;42(12):1030–6.
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10 Manner H, May A, Pech O, Gossner L, Rabenstein T, Günter E, et al. Early Barrett’s carcinoma with “low-risk” submucosal invasion: long-term results of endoscopic resection with a curative intent. Am J Gastroenterol. 2008;103(10):2589–97.

11 Bollschweiler E, Baldus SE, Schröder W, Prenzel K, Gutschow C, Schneider PM, et al. High rate of lymph-node metastasis in submucosal esophageal squamous-cell carcinomas and adenocarcinomas. Endoscopy. 2006;38(2):149–56.

12 Kunzli HT, Belghazi K, Pouv RE, Meijer SL, Seldenrijk CA, Weusten B, et al. Endoscopic management and follow-up of patients with a submucosal esophageal adenocarcinoma. United European Gastroenterol J. 2018;6(5):669–77.

13 Manner H, Pech O, Heldmann Y, May A, Pauthner M, Lorenz D, et al. The frequency of lymph node metastasis in early-stage adenocarcinoma of the esophagus with incipient submucosal invasion (pT1b sm1) depending on histological risk patterns. Surg Endosc. 2015;29(7):1888–96.

14 van der Schaaf M, Johar A, Wijnhoven B, Lagarde SM, Bergman JJ, ten Kate FJ, et al. Prediction of appropriateness of local endoscopic treatment for high-grade dysplasia and early adenocarcinoma by EUS and histopathologic features. Gastrointest Endosc. 2004;60(5):703–10.

15 Semenkovich TR, Hudson JL, Subramanian M, Mullady BF, Puri V, et al. Trends in treatment of T1N0 esophageal cancer. J Natl Cancer Inst. 2010;101(4):356–63.

16 van der Wel MJ, Klaver E, Pouv RE, Brosens LAA, Biermann K, Doukas M, et al. Significant variation in histopathological assessment of endoscopic resections for Barrett’s neoplasia suggests need for consensus reporting: propositions for improvement. Dis Esophagus. 2021;34(12):doab034.

17 Westerterp M, Koppert LB, Buskens CJ, Tilanus HW, ten Kate FJ, Bergman JJ, et al. Outcome of surgical treatment for early adenocarcinoma of the esophagus or gastro-esophageal junction. Virchows Arch. 2005;446(5):497–504.

18 Dresner SM, Griffin SM. Pattern of recurrence following radical oesophagectomy with two-field lymphadenectomy. Br J Surg. 2000;87(10):1426–33.

19 Pech O, Günter E, Dusemund F, Origer J, Lorenz D, Ell C. Accuracy of endoscopic ultrasound in preoperative staging of esophageal cancer: results from a referral center for early esophageal cancer. Endoscopy. 2010;42(6):456–61.

20 Buskens CJ, Westerterp M, Lagarde SM, Bergman JJ, ten Kate FJ, van Lanschot JJ. Prediction of appropriateness of local endoscopic treatment for high-grade dysplasia and early adenocarcinoma by EUS and histopathologic features. Gastrointest Endosc. 2004;60(5):703–10.

21 Gockel I, Domeyer M, Sgourakis GG, Schimanski CC, Moehler M, Kirkpatrick CJ, et al. Prediction model of lymph node metastasis in superficial esophageal adenocarcinoma and squamous cell cancer including D2-40 immunostaining. J Surg Oncol. 2009;100(3):191–8.

22 Ancona E, Rampado S, Cassaro M, Battaglia G, Ruol A, Castoro C, et al. Prediction of lymph node status in superficial esophageal carcinoma. Ann Surg Oncol. 2008;15(11):3278–88.

23 Gotink AW, van de Ven SEM, Ten Kate FJC, Nieboer D, Suzuki L, Weusten BLAM, et al. Individual risk calculator to predict lymph node metastases in patients with submucosal (T1b) esophageal adenocarcinoma: a Multi-center Cohort Study. Endoscopy. 2021;54(2):109–17.

24 Lee L, Ronellenfitsch U, Hofstetter WL, Darling G, Gaiser T, Lippert C, et al. Predicting lymph node metastases in early esophageal adenocarcinoma using a simple scoring system. J Am Coll Surg. 2013;217(2):191–9.

25 Leers JM, DeMeester SR, Oezcelik A, Klipfel N, Ayazi S, Abate E, et al. The prevalence of lymph node metastases in patients with T1 esophageal adenocarcinoma: a retrospective review of esophagectomy specimens. Ann Surg. 2011;253(2):271–8.

26 Kunzli HT, van Berge Henegouwen MI, Gisbertz SS, van Esser S, Meijer SL, Bennink RJ, et al. Pilot-study on the feasibility of sentinel lymph node navigation surgery in combination with thoracolaparoscopic lymphadenectomy without esophagectomy in early esophageal adenocarcinoma patients. Dis Esophagus. 2017;30(11):1–8.

27 Overwater A, Weusten BLAM, Ruurda JP, van Hillegersberg R, Bennink RJ, de Keizer B, et al. Feasibility of sentinel node navigated surgery in high-risk T1b esophageal adenocarcinoma patients using a hybrid tracer of technetium-99 m and indocyanine green. Surg Endosc. 2021;36(4):2671–9.