

Retrospective Study

Outcomes of submucosal (T1b) esophageal adenocarcinomas removed by endoscopic mucosal resection

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Abstract**AIM**

To investigate the outcomes and recurrences of pT1b esophageal adenocarcinoma (EAC) following endoscopic mucosal resection (EMR) and associated treatments.

METHODS

Patients undergoing EMR with pathologically confirmed T1b EAC at two academic referral centers were retrospectively identified. Patients were divided into 4 groups based on treatment following EMR: Endoscopic therapy alone (group A), endoscopic therapy with either chemotherapy, radiation or both (group B), surgical

resection (group C) or no further treatment/lost to follow-up (< 12 mo) (group D). Pathology specimens were reviewed by a central pathologist. Follow-up data was obtained from the academic centers, primary care physicians and/or referring physicians. Univariate analysis was performed to identify factors predicting recurrence of EAC.

RESULTS

Fifty-three patients with T1b EAC underwent EMR, of which 32 (60%) had adequate follow-up \geq 12 mo (median 34 mo, range 12-103). There were 16 patients in group A, 9 in group B, 7 in group C and 21 in group D. Median follow-up in groups A to C was 34 mo (range 12-103). Recurrent EAC developed overall in 9 patients (28%) including 6 (38%) in group A (median: 21 mo, range: 6-73), 1 (11%) in group B (median: 30 mo, range: 30-30) and 2 (29%) in group C (median 21 mo, range: 7-35). Six of 9 recurrences were local; of the 6 recurrences, 5 were treated with endoscopy alone. No predictors of recurrence of EAC were identified.

CONCLUSION

Endoscopic therapy of T1b EAC may be a reasonable strategy for a subset of patients including those either refusing or medically unfit for esophagectomy.

Key words: Esophageal cancer; Submucosal; T1b; Endoscopic mucosal resection; Chemotherapy; Esophagectomy

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Core tip: Endoscopic eradication therapy (EET) is reported as safe and effective for low risk T1b esophageal adenocarcinomas (EAC), but overall data is lacking. We retrospectively evaluated patients with T1b EAC treated with EET, EET with chemotherapy and/or radiation therapy and surgical resection. The overall recurrence rate was 28% at median 21 mo (range: 6-73) following EMR. In those treated with endoscopic mucosal resection alone, recurrence rate was 38% at median 21 mo (range: 6-73). Six of the 9 recurrences were local; 5 were treated with endoscopy alone. EET of T1b EAC may be a reasonable treatment strategy for a subset of these patients.

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INTRODUCTION

Due to the inherent morbidity and rare mortality associated with esophagectomy and lymph node

dissection, endoscopic eradication therapy [including endoscopic mucosal resection (EMR) and ablative techniques] has been increasingly used as a safe, effective and potentially curative organ-sparing procedure to treat high grade dysplasia (Tis lesions) and intramucosal esophageal cancer (T1a lesions)^[1-5]. When complete resection or eradication of T1a cancers is confirmed, disease is generally considered cured due to the low rate of reported lymph node metastasis (< 2%) in these patients^[6]. Tumors that penetrate the submucosa of the esophagus (T1b cancers), however metastasize to regional lymph nodes in up to 30% of cases and the likelihood for metastases increases the further the tumor penetrates from the first third (sm1) into the lower two thirds (sm2 and sm3) of the submucosal layer^[7-11]. Therefore, endoscopic eradication therapies (EET) have generally not been employed in patients with T1b cancers.

The use of EET for primary treatment of T1b tumors was initially reported in patients with "low risk" submucosal esophageal cancers (macroscopically polypoid or flat, invasion limited to the upper 1/3 of the submucosa, no invasion of the vessels or lymphatic system, well to moderate tumor differentiation); this has more recently been updated in a larger series ($n = 66$) from the same group with similar characteristics showing recurrent or metachronous carcinomas developed in 19% of patients with an estimated 5 year survival rate of 84%^[12,13]. A study from two referral centers in the Netherlands examined EET of deep T1a and T1b EAC ($n = 75$) with an overall recurrence rate of 9%^[14]. A study from a tertiary center in the United States reported a group of patients ($n = 29$) with T1b EAC with sm1 (46%) and sm2-3 (54%) invasion that underwent either EET, chemo/radiation or a combination of both and showed mean survival of 34.8 mo with a 38% mortality rate^[15].

To our knowledge, there are no studies examining the outcomes and predictors of disease recurrence in patients with pathologically staged T1b esophageal cancer treated with EET alone, surgery, or adjuvant therapy following endoscopic resection. Identification of predictive factors for recurrence and outcomes following endoscopic therapy in this population would help to identify and tailor appropriate treatment. For this reason, we aimed to (1) retrospectively evaluate the clinical outcomes of pT1b esophageal cancers following EMR; (2) to compare the recurrence rates of cancer when patients are treated with EET alone, EET in association with chemotherapy, radiation therapy or both and surgical resection; and (3) to evaluate the predictors of recurrence of T1b esophageal cancer following EMR.

MATERIALS AND METHODS

Study population and design

All patients age \geq 18 years of age who underwent EMR of the esophagus from 2001 to 2013 at India-

na University Medical Center and the University of Michigan were retrospectively identified from institutional endoscopic databases. Patient charts were then reviewed to identify the subset of patients with pathologically (p) staged T1b esophageal cancer that comprised the study population. Patients with treatment by endoscopic submucosal dissection or ≤ 12 mo of follow-up after resection were excluded. Approval for this study was obtained by the institutional review boards at both participating institutions prior to any study activities.

Pre-procedure imaging with CT and/or PET scans was initially obtained in all patients to exclude distant metastasis. Endoscopic ultrasound (EUS) was also used in selected patients to assess the depth of any visualized mass or detect and sample any suspicious lymph nodes. Prior to EMR, all patients underwent EGD with a detailed exam of the mucosa of the esophagus and gastric cardia. The use of advanced imaging techniques such as narrow band imaging and chromoendoscopy was at the discretion of the endoscopist. After identification of the site(s) for resection, either cap-assisted (Olympus America Inc., Center Valley, PA) or band ligation-assisted EMR (Cook Medical Inc., Winston Salem, NC) was performed. The specimens retrieved were placed into formalin and sent to pathology for evaluation for examination by an experienced gastrointestinal pathologist.

Treatment groups

Treatment after identification of a pT1b esophageal cancer at each institution was at the discretion of the endoscopist as well as referring physicians based on the pathology findings, patient comorbidities and patient wishes. For study purposes, treatment after EMR was classified as utilizing endoscopy alone (group A), endoscopy with either chemotherapy, radiation or both (group B), surgical resection alone (group C), or no further treatment or lost to follow-up (group D). Patients in group A underwent additional EMR with or without ablation, surveillance endoscopies and cross-sectional imaging as determined by the treating physicians.

Pathology assessment

Endoscopic resection specimens from both institutions were initially reviewed by local pathologists. For the current study, slides from both institutions were re-reviewed by a single gastrointestinal pathologist at Indiana University for the following characteristics: Depth of tumor invasion (sm1 vs sm2/3), tumor differentiation (well, moderate and poor), presence or absence of lymphatic or perineural invasion (LPI) and the status of deep and lateral margins following resection. A T1b esophageal cancer was defined as tumor extending beyond the muscularis mucosa and into tissue which contains submucosal glands or tumor adjacent to large caliber arteries which would not be present in the mucosa. Tumors classified as sm1 had invasion of tumor into the upper 1/3 of the submucosa and sm2/3 depth

of invasion was defined as invasion into the lower 2/3 of the submucosa. Tumor differentiation was determined based on standard histologic features such as growth pattern, gland formation and degree of atypia. LPI was defined as the presence of malignant tumor cells within a lymphatic channel or neural bundle.

Follow-up

Follow-up cross-sectional imaging and endoscopy were performed at the discretion of the endoscopist and consulting physicians at each institution. These data on the study population were obtained both from the treating institution as well as referring physicians and primary care physicians and consisted of endoscopic procedures, imaging studies and clinic visits. The end point of follow-up for study patients included: Death, surgery for esophageal cancer, or loss of patient contact. Patient death was identified by reviewing medical records or by searching the Social Security Death Index. Tumor recurrence was diagnosed when biopsies from the previous or adjacent esophageal EMR site or from either regional or metastatic sites demonstrated pathology consistent with the primary cancer. A univariate analysis was performed in order to identify factors predicting recurrence of cancer after EMR and associated treatment. Variables analyzed in the analysis included: method of EMR (cap vs band), pathology depth (sm1 vs sm2/3), initial tumor location (proximal 2/3 vs distal 1/3 of the esophagus), lymphovascular and/or perineural invasion, degree of tumor differentiation, positive vs negative deep and lateral EMR margins, and primary treatment modality (endoscopic \pm chemotherapy and/or radiation therapy vs surgery).

Statistical analysis

The data were analyzed descriptively using means, medians, ranges and standard deviations. The variables between groups were compared using Fisher's exact tests (GraphPad). $P < 0.05$ was considered statistically significant.

RESULTS

Sixty patients who underwent EMR were found to have pT1b esophageal cancer, including 53 (88%) with adenocarcinoma and 7 (12%) with squamous cell carcinoma. Of the 53 patients with adenocarcinomas, 32 patients (60%) had adequate follow-up after EMR of ≥ 12 mo (median 34 mo, range 12-103). There were 16 patients in group A, 9 patients in group B, 7 patients in group C and 21 patients in group D (8 with no further treatment and 13 without required 12 mo follow-up). Demographics, EMR method (cap vs band), pathology findings and follow-up are summarized in Table 1. Pathology in patients who underwent esophagectomy (group C) showed no residual dysplasia or malignancy in 2, adenocarcinoma with negative nodes in 1, dysplasia in 3 and 1 with unknown findings.

No recurrence of carcinoma developed in 23 patients

Table 1 Characteristics of T1b esophageal adenocarcinoma by treatment modality following endoscopic mucosal resection

	Group A (n = 16)	Group B (n = 9)	Group C (n = 7)	Group D (n = 21)	Overall (n = 53)
Average age, yr	75 ± 78	70 ± 14	62 ± 5	72 ± 13	71 ± 12
Median follow-up after EMR, mo (range)	34 (12-102)	27 (12-56)	49 (13-103)	N/A	34 (12-103) (for groups A-C, n = 32)
EMR method, n (%)					
Cap	6 (38)	0 (0)	2 (29)	4 (19)	12 (23)
Band	10 (62)	9 (100)	5 (71)	17 (81)	41 (77)
Pathology depth, n (%)					
sm1	6 (38)	4 (44)	1 (14)	2 (10)	13 (25)
sm2/3	10 (62)	5 (56)	6 (86)	19 (90)	40 (75)
Tumor location, n (%)					
Proximal two-thirds	2 (13)	1 (11)	1 (14)	5 (24)	9 (17)
Distal one-third	14 (88)	8 (89)	6 (86)	16 (76)	44 (83)
LPI, n (%)					
Yes	1 (6)	1 (11)	0 (0)	3 (14)	5 (9)
No	15 (94)	8 (89)	7 (100)	18 (86)	48 (91)
Differentiation, n (%)					
Well-moderate	14 (88)	6 (67)	7 (100)	15 (71)	42 (79)
Poor	2 (13)	3 (33)	0 (0)	6 (29)	11 (21)
EMR margins for cancer, n (%)					
Deep -/lateral -	6 (38)	2 (22)	1 (14)	2 (10)	11 (21)
Deep -/lateral +	5 (31)	1 (11)	1 (14)	4 (19)	11 (21)
Deep +/lateral +	4 (25)	6 (66)	5 (71)	13 (62)	28 (53)
Deep +/lateral -	1 (6)	0 (0)	0 (0)	2 (10)	3 (6)
Recurrences, n (%)					
Yes	6 (38)	1 (11)	2 (29)	N/A	9 (28)
No	10 (63)	8 (88)	5 (71)		23 (72)
Median time to recurrence (mo, range)	21 (6-73)	30 (30-30)	21 (7-35)		21 (6-73) (for groups A-C, n = 32)
Location of recurrence					
Local	5	0	1	N/A	6
Metastatic	1	1	1		3

EMR: Endoscopic mucosal resection; LPI: Lymphatic/perineural invasion.

Table 2 Recurrence rates of esophageal adenocarcinoma investigated risk factors of esophageal adenocarcinoma (n = 30) (%)

Variable	Recurrence rates	P value
EMR method		
Cap	4/8 (50)	0.18
Band	5/24 (21)	
Pathology depth		0.11
sm1	3/11 (27)	
sm2/3	6/21 (29)	
Tumor location		0.56
Proximal 2/3 esophagus	2/4 (50)	
Distal 1/3 esophagus	7/28 (25)	
LPI		1.00
Yes	0/2 (0)	
No	9/30 (30)	
Differentiation		1.00
Well-moderate	8/27 (30)	
Poor	1/5 (20)	
Deep EMR margins		1.00
Positive	4/16 (25)	
Negative	5/16 (31)	
Lateral EMR margins		1.00
Positive	6/22 (27)	
Negative	3/10 (30)	
Primary treatment		1.00
Endoscopic +/- CRT	7/25 (28)	
Surgical	2/7 (29)	

EMR: Endoscopic mucosal resection; LPI: Lymphatic/perineural invasion; CRT: Chemoradiation.

Table 3 Endoscopic ultrasound staging/path accuracy for T1b esophageal adenocarcinoma

EUS staging (n = 51)	Pathologic staging		
	pT1sm1 (n = 12)	pT1sm2/3 (n = 39)	Overall (all pT1b) (n = 51)
uT0 Nx	0	1	1
uT1 Nx	11	36	47
uT2 Nx	1	2	3
T staging accuracy	91.7%	92.3%	92.2%

(72%) during a median follow-up of 31 mo (range 12-103). Recurrent adenocarcinoma developed in 9 (28%) patients among all 3 groups. There was no statistically significant differences between recurrences in group A (n = 6; 38%), group B (n = 1; 11%) and group C (n = 2; 29%). Median time to recurrence was 21 mo (range 6-73) in group A, 30 mo in group B, and 9 mo (range 8-10) in group C. Of the recurrences in group A, 5 were local and 1 was metastatic. These local recurrences in group A were treated with further EET alone in two, EET and radiation in one, EET with chemotherapy with radiation in one and radiation in one. The single metastatic recurrence in group A was treated with chemotherapy and radiation. The single recurrence in group B was metastatic and had no further treatment. The two recurrences in group C were

Table 4 Studies evaluating endoscopic management of T1b esophageal adenocarcinoma

Ref.	# Patients	Depth of invasion	Histology	Margins	Remission	Recurrence	Survival
Manner <i>et al</i> ^[12]	21	sm1	Well to moderately differentiated, no lymphovascular invasion	Lateral margins negative in 12	95% at mean 5.3 mo	28% at mean 62 mo (range 45-89)	67% estimated 5-yr survival
Alvarez Herrero <i>et al</i> ^[14]	18	sm1 and sm2/3	Well, moderately and poorly differentiated, some with lymphovascular invasion	Not reported	Not reported	17%	Not reported
Tian <i>et al</i> ^[15]	29	sm1 and sm2-3	Not reported	Not reported	Not reported	Not reported	62% with median duration 34.8 mo
Manner <i>et al</i> ^[13]	66	sm1	Well to moderately differentiated, no lymphovascular invasion	Not reported	84% at mean 4.5 mo	21% at mean 22 mo (range 6-60)	84% estimated 5-yr survival

local in one and metastatic in one. The local recurrence in group C was treated with chemotherapy and the metastatic recurrence in group C was treated with local resection of a hepatic metastasis. No predictors of recurrence of adenocarcinoma were identified on univariate analysis (Table 2).

Of the 32 patients in groups A, B and C, 7 died within 3 years of EMR giving an overall 3 year mortality for all causes of 22%. Specifically within each group, 3 year mortality rates were 13% in group A (2/16), 44% in group B (4/9), and 14% in group C (1/7).

EUS was performed prior to EMR in 51 (96%) of the 53 patients with T1b EAC. T staging accuracy (for T1 malignancy) on EUS for pT1b tumors overall was 92%; specifically for pT1sm1 tumors was 92% and for pT1sm2/3 tumors was 92% (Table 3).

DISCUSSION

Endoscopic therapy is an alternative to esophagectomy for mucosal EAC in select populations^[1] and has been included in national guidelines as a curative form of treatment^[16]. More recently, "low risk" T1b EAC have been treated with EET as primary therapy in Germany with recurrence rates ranging from 19% to 28% and estimated five-year survival rates up to 84%^[12,13]. Two small studies from the United States ($n = 15$) and the Netherlands ($n = 18$) showed a recurrence rate of 21% and 17% respectively, with all recurrences in the latter study having initial sm2/3 depth of invasion^[14,15].

In our study, we aimed to retrospectively evaluate and compare outcomes of various treatments for T1b EAC after EMR and to evaluate predictors of recurrence after those treatments. We found an overall recurrence rate of 28%, which was not statistically different between those treated with endotherapy alone (38%), chemotherapy, radiation or both (11%) or those undergoing esophagectomy (29%). The overall observed rate of recurrence in our study for those undergoing EET alone is higher than previously reported in patients undergoing EET as primary therapy (Table 4). These differences likely reflect differences in population between most other series (which included primarily

low risk T1b sm1 EAC) and our study which evaluated outcomes for all T1b patients. The rate of recurrence in our study does compare favorably to that previously reported for a small cohort of patients with sm2/3 invasion of 33%^[14].

We found that most recurrences following EMR in those treated at least partly endoscopically (groups A and B) were localized. Of the patients who underwent EET alone, there were 6 recurrences (38%), five of which were localized to the esophagus with only 1 having metastatic disease 21 mo following EMR. Of the patients who underwent EET + chemotherapy and/or radiation, 1 (11%) had metastatic recurrence 30 mo after resection. Therefore, EET with or without chemotherapy or radiation, may be a reasonable initial treatment strategy for a subset of patients with T1b EAC, especially those that refuse or are unfit for surgical intervention due to medical comorbidities or home support since most recurrences appear to be localized.

In those that underwent esophagectomy, we identified 2 recurrences out of 7 patients (29%). Our recurrence rate is similar to a recent retrospective study including 26 patients with T1b EAC undergoing surgical resection which showed a 23% recurrence rate^[17]. Recurrence or metastatic disease discovered after resection may be related to micrometastatic disease that was unable to be identified prior to esophagectomy.

Overall, we found a 3-year survival rate of 78% when evaluating the patients in our study; more specifically a rate of 87% in those treated with EET only and 56% in those treated with EET + chemotherapy and/or radiation. When combining those treated at least partly endoscopically, the survival rate at 3 years was 76%. Manner *et al*^[13] previously have shown an estimated 5-year survival rate of 84% in those treated with EET with "low risk" T1b. Our lower survival rate is likely reflected in our patient population, as we evaluated all patients with T1b EAC and not only those with "low risk" disease. Tian *et al*^[15] reported on a group of patients ($n = 29$) more similar to our cohort including "low risk" and higher risk T1b EAC patients [sm1 (46%) and sm2-3 (54%) invasion] that underwent either EET, chemo/radiation or a combination of both and showed a

survival rate of 72% at mean 34.8 mo.

We failed to identify any individual predictors of cancer recurrence in this population. A previous retrospective study with 39 patients with T1b EAC treated with EET alone showed decreased survival in patients with older age and lymphovascular invasion, although it did not specifically assess for predictors of cancer recurrence^[18]. In our study, we were unable to identify lymphatic and perineural invasion as predictors of recurrence.

A recent prospective study from Germany evaluated the risk of lymph node metastases when comparing "low risk" (sm1 invasion) to "high risk" (sm2/3 invasion) T1b EAC in patients treated both surgically and with EET, and found a 2% risk of lymph node metastasis in pT1bsm1 tumors and 9% in pT1bsm2/3 tumors, which is lower than has generally been reported in prior studies^[19]. In our study which includes both sm1 and sm2/3 invasion, we similarly found 6% of patients with metastatic lymph nodes either on initial staging or on surveillance (one each with sm1 and sm2/3 tumors).

Previous studies have shown excellent accuracy for staging both T1a and T1b esophageal cancers. Specifically, a previous meta-analysis showed good accuracy with area under the curve > 0.93 for both T1a and T1b esophageal cancers^[20]. We also demonstrated overall diagnostic accuracy of 91% for pT1 lesions in our cohort.

Our study has several strengths including data from all T1b cancers removed by EMR from two tertiary care referral centers, re-review of all pathology by a single pathologist, and evaluation of outcomes of medical and surgical therapy for these patients. However, our study is limited by the number of patients who refused further therapy or were lost to follow-up which may limit the ability to compare outcomes from various treatments after resection.

In conclusion, our study shows that endoscopic therapy alone following EMR of a T1b cancer is associated with a recurrence rate of 38%. Therefore, treatment with adjuvant therapy appears reasonable in this population when possible. No particular variable is predictive of recurrence following EMR of T1b adenocarcinomas. Therefore, future research into the management and risk stratification of these patients after EMR is warranted.

COMMENTS

Background

Endoscopic eradication therapy (EET) (including endoscopic mucosal resection and ablative techniques) have become standard of care for high grade dysplasia and T1a esophageal cancer. The use of EET for T1b cancers is more controversial due to the higher risk of lymph node involvement and data is lacking.

Research frontiers

Recent studies have shown that "low risk" T1b esophageal cancer can be treated safely and effectively with EET. Many of these studies include relatively small numbers of patients, and do not address higher risk T1b esophageal

cancers or the use of EET in conjunction with other treatment modalities such as chemotherapy or radiation.

Innovations and breakthroughs

In the current study, the authors attempted to evaluate the clinical outcomes and recurrence rates of T1b esophageal cancers treated with EET alone, as well as those treated with EET in conjunction with chemotherapy and/or radiation as well as those undergoing surgical resection. In addition, the authors attempted to identify factors that may predict recurrence.

Applications

For patients with T1b esophageal cancer and treated with EET alone, the recurrence rate was 38%; therefore treatment with adjuvant therapy in conjunction with EET seems reasonable in patients that are either unable to or refuse to undergo esophagectomy. No particular variables were identified that predict recurrence of cancer in this population following EMR. Further research in these areas regarding management and risk stratification will be required.

Terminology

T1b esophageal adenocarcinoma - cancer which invades into but not through the submucosal layer; Endoscopic eradication therapy - Endoscopic treatment including endoscopic mucosal resection and ablative techniques such as radiofrequency ablation and cryotherapy.

Peer-review

A retrospective study is reported to investigate outcomes and recurrences of T1b esophageal adenocarcinomas following EMR. The topic is relevant, and the data collection done by the authors are very useful.

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