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CONTINUING EDUCATION – GASTROINTESTINAL ONCOLOGY

What Constitutes Optimal Management of T1N0 Esophageal Adenocarcinoma?

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ABSTRACT

Purpose and Design. Esophageal adenocarcinoma (EAC) develops as a consequence of gastroesophageal reflux disease and Barrett's esophagus (BE). While combination therapy with chemotherapy or concurrent chemoradiotherapy followed by esophagectomy improves survival in more advanced tumors, the optimal treatment strategy for early-stage EAC is undefined. Endoscopic eradication therapy, consisting of endoscopic resection and mucosal ablation, has revolutionized therapy for superficial (T1a) EAC in BE and allows for esophageal preservation in appropriate patients at low risk for lymph node metastasis (LNM). This review critically examines the literature regarding evaluation, treatment, and outcomes in patients with T1 EAC.

Methods. The literature was queried via the PubMed database to include articles published between 1990 and 2017. Search terms were generated from the key statements "Endoscopic eradication therapy results in equivalent overall survival when compared to esophagectomy for clinical T1aN0 EAC" and "Esophagectomy provides better overall survival than endoscopic eradication therapy for cT1b EAC". Abstracts were reviewed and included according to predefined selection and exclusion criteria, and were then assessed according to the GRADE system.

Results and Conclusions. In patients with T1aN0 EAC, overall survival with endoscopic eradication therapy is equal to esophagectomy. Given the substantial risk of LNM in patients with submucosal (T1b) EAC, esophagectomy remains the standard of care for surgical candidates. In the case of inoperability or low-risk lesions, endoscopic resection may be considered adequate therapy. Chemotherapy and radiation can be offered as primary therapy for non-surgical candidates with lesions not amenable to endoscopic therapy, but does not have a clear role in the adjuvant setting after either endoscopic or surgical resection.

Esophageal adenocarcinoma (EAC) develops as a consequence of gastroesophageal reflux disease (GERD) and Barrett's esophagus (BE). Patients are increasingly being identified with early-stage disease, either fortuitously related to more liberal use of upper endoscopy or as part of a BE surveillance program. While esophagectomy with or without concurrent chemoradiotherapy results in improved survival in locally and regionally advanced tumors,[1,2] the optimal treatment strategy for early-stage adenocarcinoma is still being defined. Superficial esophageal cancer is highly curable. The introduction of endoscopic resection and ablation techniques (endoscopic eradication therapy [ET]) has revolutionized the treatment of superficial esophageal cancer and allows for organ preservation rather

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than esophagectomy in appropriate patients.[3] A critically important concept guiding therapy is long-term quality of life and alimentary satisfaction.

From an oncologic standpoint, endoscopic ET, typically consisting of endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) followed by endoscopic ablation, can be safely applied only when complete resection is possible and patients are at low risk for lymph node metastasis (LNM).[4–15] Unfortunately, typical staging studies such as endoscopic ultrasound (EUS) and computed tomography with positron emission tomography (CT-PET) are of limited utility in patients with superficial tumors due to low staging accuracy[16–19]; therefore, the risk of LNMs must be evaluated on the basis of tumor characteristics, including size, depth of invasion, degree of differentiation, and presence of lymphovascular invasion (LVI). The decision for endoscopic therapy versus esophagectomy also depends on other factors, including the length of the BE segment, severity of GERD, presence of comorbid conditions, and patient compliance and willingness to undergo multiple endoscopic procedures.[3,4,6,20] This review critically examines the literature regarding evaluation, treatment, and outcomes in patients with T1 EAC.

METHODS

The English-language literature was queried via the PubMed database to include articles published between 1 January 1990 and 1 October 2017. Search terms were generated from the following key statements: “Endoscopic eradication therapy results in equivalent overall survival when compared to esophagectomy for clinical T1aN0 esophageal adenocarcinoma” and “Esophagectomy provides better overall survival than endoscopic eradication therapy for cT1b esophageal adenocarcinoma”. No randomized controlled trials comparing endoscopic ET with surgery for clinical T1N0 EAC or subgroups (T1a or T1b) were found with this strategy. Filters were then applied to include non-randomized trials, including retrospective case series and comparative studies. Abstracts were reviewed and included if they met the criteria of adenocarcinoma in all or most of the cohort, had > 30 patients, compared endoscopic ET with surgery, and described long-term outcomes after treatment. Exclusion criteria included case reports or reviews, studies with cohorts of either all or mostly squamous cell carcinoma, did not include patients with invasive adenocarcinoma, or report overall long-term survival or disease-related survival (Fig. 1). Complete review of each study was performed by at least two authors, and articles selected were assessed according to the GRADE system.[21]

The systematic search yielded 27 retrospective studies,[4,15,20,22–35] two prospective studies,[3,36] and one meta-analysis[37] addressing overall and cancer-specific survival in patients with early EAC treated with endoscopic ET or esophagectomy (Table 1).

RESULTS AND DISCUSSION

T1aN0 Esophageal Adenocarcinoma (EAC)

In recent years, ET has emerged as a viable treatment alternative to esophagectomy for early EAC confined to esophageal mucosa with low risk of LNM (i.e. T1aN0).[7] Initially mostly used for patients not felt able to withstand the high morbidity associated with esophagectomy, ET has increasingly been applied to patients who would otherwise be surgical candidates.[22,35] Prior studies investigating endoscopic techniques in EAC are limited by small cohorts treated with either EMR or ablative techniques alone.[27,36] It is now recognized that despite endoscopic resection of the primary tumor, up to one-third of patients may develop metachronous or recurrent neoplasia in residual Barrett’s epithelium.[38] Therefore, it is recommended that patients treated with endoscopic resection also undergo ablation of residual Barrett’s epithelium.[39] In a large, retrospective, single-center study, 1000 patients with T1a lesions undergoing endoscopic resection with or without ablation therapy (argon plasma coagulation [APC] or radiofrequency ablation [RFA]) were included.[3] In that study, patients had a mean follow-up of 56.6 months, from which 5- and 10-year overall survival rates of 91.5% and 75%, respectively, were reported. The results were not stratified based on the modality of treatment, but metachronous/recurrent high-grade dysplasia (HGD)/EAC was detected in 140 patients (14.5%), of whom 115 were successfully treated endoscopically.

Liquid nitrogen spray cryotherapy (LNSCT) has also been shown to be a safe and effective therapy for Barrett’s esophagus-associated T1a EAC.[40,41] A recent retrospective study examining long-term outcomes in patients with T1a EAC resected with EMR, and Barrett’s HGD treated with LNSCT, found that the incidence rate of HGD/EAC per person-year of follow-up after initial complete eradication was 1.4% per person-year.[40] While progression to adenocarcinoma was uncommon after treatment with LNSCT, 4% of patients progressed to adenocarcinoma despite treatment. Another study examining patients with EAC who did not respond to, or were not candidates for, conventional therapy and were treated with LNSCT, showed that in patients with T1a EAC, 76% of patients had complete response.[41] These data suggest that LNSCT can be an

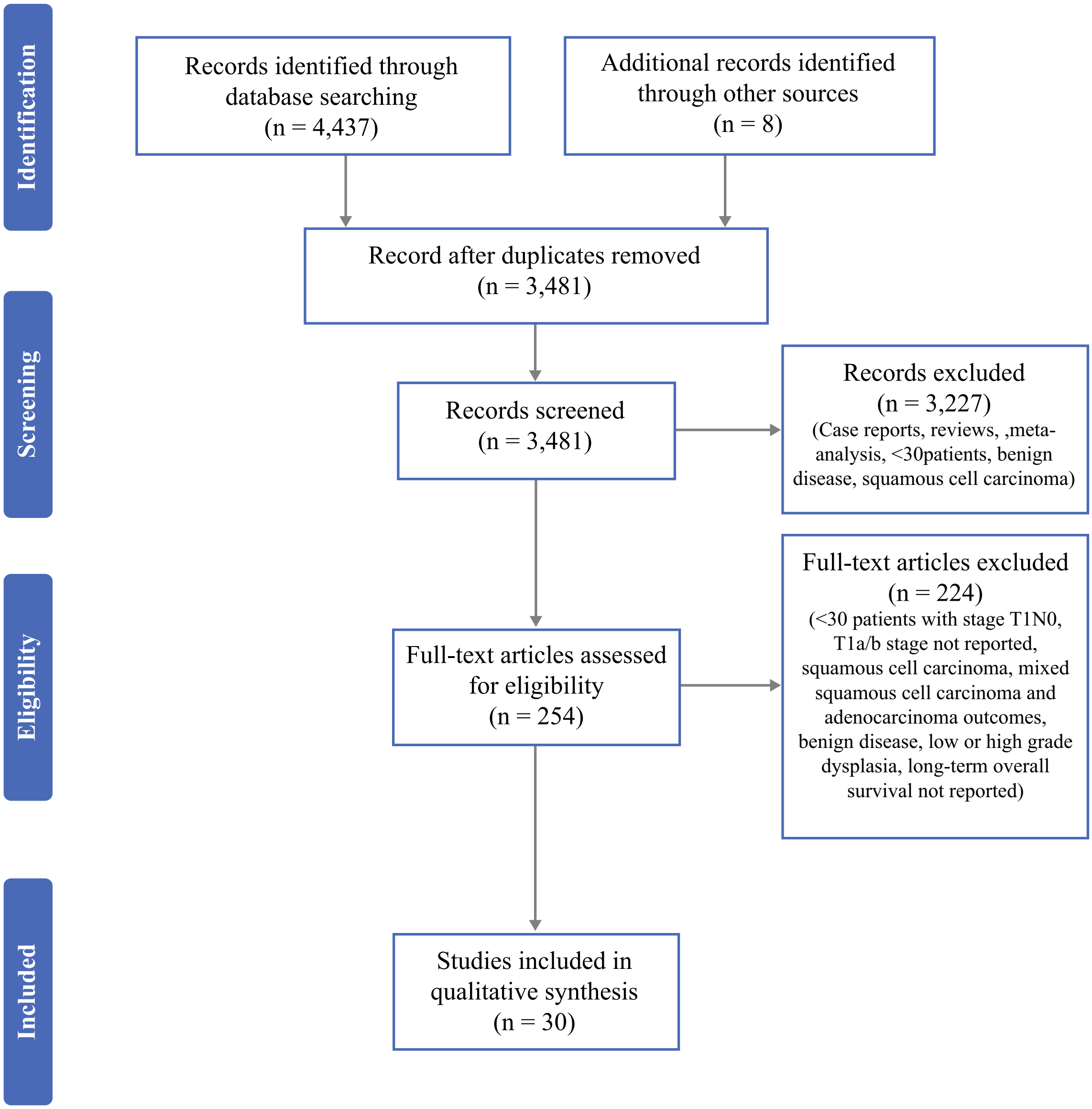

FIG. 1 T1N0 flow diagram

effective treatment option for early EAC, either as an adjunct to endoscopic resection or as primary therapy.

The use of ESD has been increasing in Western centers and may expand the applicability of ET to larger tumors or those with superficial submucosal invasion.[42–49] In a meta-analysis including all gastrointestinal tumors, higher rates of en bloc and complete resection were reported with ESD when compared with EMR, but with longer procedure times and higher rates of adverse events.[50] A randomized prospective trial comparing ESD with EMR for EAC identified complete resection (R0) of both EAC and HGD as the primary outcome measure. While the R0 rates were higher with ESD (58.8% vs. 11%, p = 0.01), on follow-up endoscopy after 30 days there was no difference in complete remission rates between ESD and EMR (93.75% vs. 94.12%, p = 1.0). Whether the higher rates of curative resection with ESD after initial endoscopic treatment translate into superior long-term survival is as yet unanswered[42–49] given the short follow-up periods (up to 24 months) and variable outcome measures in contemporary series.

Studies on esophagectomy for the treatment of early-stage cancer have generally been small and heterogeneous with respect to depth of invasion, histopathology, and surgical technique. Most include a combination of HGD, T1b tumors, and/or squamous cell carcinomas, with few reporting outcomes separately for those with T1a adenocarcinomas.[4,5,13,15,28,30,31] One of the larger series described the outcomes of 78 patients who underwent either transhiatal, vagal-sparing, en bloc or transthoracic

TABLE 1 Results from observational studies of T1N0 esophageal adenocarcinoma

Author, year (study years)	No. of patients	Study type	Procedure	Outcomes	Results	Conclusions
Ancona et al. 2008[4]	Total: 98	Retrospective	Ivor Lewis or McKeown	5-year OS (%)	T1: 56.7	Independent predictive factors for lymph node metastasis were angiolymphatic invasion, depth of invasion, low-grade lymphocytic invasion and neural invasion
(1980–2006)	T1a: 27				T1a: 77.7	
	T1b: 71				T1b: 53.3	
	SM1: 36				SM1: 67.3	
	SM2: 7				SM2/3: 44.2	
	SM3:28				SCC: 43.3	
	SCC: 67				AC: 100	
	AC: 31			10-year OS (%)	SCC: 37.3	
					AC: 90.9	
Badreddine et al. 2010[51]	Total: 80	Retrospective	Ivor Lewis: 56	Mean follow-up (months)	40.5 ± 4	Overall and cancer-free survival were not different between superficial submucosal (SM1) and deeper submucosal (SM2/3) invasion
(1997–2007)	T1b: 80		THE: 24	OS (months)	T1b: 46.5	
	SM1: 21				SM1: 52	
	SM2/3: 49				SM2/3: 38	
				DFS (months)	T1b: 30	
					SM1: 35.3	
					SM2/3: 27.8	
Barbour et al. 2010[23]	Total: 85	Retrospective	Ivor Lewis: 6	Median follow-up (months)	59	Where HGD or T1a is confirmed, local resection techniques may be a suitable alternative to esophagectomy. Esophagectomy should remain the standard of care for submucosal tumors
(1991–2008)	T1a: 35		MIE: 73	5-year OS (%)	T1a: 97	
	T1b: 49		Total gastrectomy: 5		T1b: 65	
	Unknown: 1		Proximal gastrectomy: 1		SM1: 70 (NS)	
	AC: 100%				SM2: 60	
					SM3: 71	
				DFS (%)	T1a: 100	
					T1b: 70	
					SM1: 82 (NS)	
					SM2: 60	
					SM3: 82	

TABLE 1 continued

Author, year (study years)	No. of patients	Study type	Procedure	Outcomes	Results	Conclusions
Bogoevski et al. 2011[5] (1992–2007)	Total: 113 HGD: 16 T1a: 41 T1b: 56	Retrospective	THE (LR): 51 LR of the esophagogastric junction: 21 Thoracoabdominal (ER): 41	Median follow-up (months) OS, all (months) 5-year OS, all (%) OS, T1b (months) 5-year OS, T1b (%)	39 LR: 203 ER: 88 LR: 67.7 ER: 57.8 LR: 63 months ER: 85 months LR: 51.5 ER: 53.3	Patients with T1b submucosal invasion have a high (27%) rate of lymph node metastasis, making them unsuitable for ET. LR is a valuable alternative to ER for T1b tumors with no difference in overall survival
Bolton et al. 2009[6] (1979–2007)	Total: 133 T1a: 64 T1b: 69	Retrospective	Ivor Lewis: 57 THE: 63 Three-field: 7 MIE: 6	Median follow-up (months) 3-year OS (%) 5-year OS (%)	42 T1a: 100 T1b: 90 T1a: 90 T1b: 69	In combination with submucosal invasion, tumor length > 3 cm identifies a group of patients with T1 esophageal adenocarcinoma at high risk for lymph node involvement and decreased survival
Cummings et al. 2016[34] (1994–2011)	Total: 2193 Tis: 284 T1a: 1909 AC: 1311 SCC: 882	Retrospective, SEER database	No surgery or ET 1045 Esophagectomy 893 ET 255	Mean follow-up (years) 2-year OS, AC (%) Adjusted 2-year mortality risk, ET Propensity matched 2-year mortality risk, ET	3.5 Esophagectomy 71 ET 84 HR 0.61, 95% CI 0.45–0.85 HR 0.59, 95% CI 0.41–0.86	Esophagectomy was associated with worse short- and long-term outcomes in this elderly population
Estrella et al. 2011[8] (1997–2010)	Tot: 99 T1a: 69 T1b: 30	Retrospective	THE: 43 Ivor Lewis: 41 MIE: 10 Three-field: 5	Mean RFS (months)	T1a: 124.5 T1b: 141	Patients with submucosal invasion were significantly more likely to have lymph node metastasis and shorter recurrence-free survival
Kaneshiro et al. 2011[24] (1983–2008)	Total: 185 T1a: 150 T1b (SM1): 35	Retrospective	Esophagectomy	Mean follow-up (years) 5-year OS (%) 10-year OS (%)	T1a: 7.7 ± 4.6 T1b: 7.1 ± 4 T1a: 76–90 SM1: 63 (NS) T1a: 63–83 SM1: 56 (NS)	No survival difference according to depth of invasion within histologic sublayers

TABLE 1 continued

Author, year (study years)	No. of patients	Study type	Procedure	Outcomes	Results	Conclusions
Kappui et al. 2013[25] (1984–2001)	Total: 85 T1a: 35 T1b: 44 Unknown: 6	Retrospective	En bloc transthoracic: 36 THE: 39 Vagal-sparing esophagectomy: 5 EMR: 5	Median follow-up (years)	5	Recurrence of superficial AC was the most important determinant of 5-year survival. Risk of recurrence of intramucosal tumors may be higher than reported
				5-year OS (%)	T1a: 73 T1b: 62	
				10-year OS (%)	T1a: 58 T1b: 40	
				5-year DSS (%)	T1a: 92 T1b: 72	
				10-year DSS (%)	T1a: 86 T1b: 68	
				5-year RFS (%)	T1a: 89 T1b: 70	
				10-year RFS (%)	T1a: 89 T1b: 70	
Leers et al. 2011[9] (1985–2008)	Total: 126 T1a: 75 T1b: 51	Retrospective	En bloc esophagectomy: 64 THE: 56 Vagal-sparing esophagectomy: 6	Median follow-up (months)	50	No significant survival difference in overall survival between T1a and T1b tumors
				5-year OS (%)	T1: 78 T1a: 82 T1b:71 (p = 0.25)	
				5-year DSS (%)	T1a: 98 T1b: 78 (p = 0.001) N0: 92 N1: 70 (p = 0.001)	

TABLE 1 continued

Author, year (study years)	No. of patients	Study type	Procedure	Outcomes	Results	Conclusions
Lorenz et al. 2014[10] (2000–2012)	Total: 168 T1a: 42 M1-2: 10 M3-4: 32 T1b: 126 SM1: 37 SM2: 33 SM3: 56 AC: 168	Retrospective	En bloc esophagectomy: 130 Limited esophagectomy: 30 THE: 2 MIE: 6	Median follow-up (months)	64	The presence of lymph node metastasis was a significant factor for 5-year survival: 87.1 versus 56% ($p < 0.001$). Lymph node infiltration was the only prognostic factor for OS, tumor-specific survival and tumor recurrence in multivariate analysis
				5-year OS (%)	All: 79 M1-2: 100 M3-4: 89.2 SM1: 83.5 SM2: 67.8 SM3: 70.4 (NS)	
				Tumor-specific survival (%)	All: 79 M1-2: 100 M3-4: 96.4 SM1: 92.3 SM2: 89.2 SM3: 81 (NS)	
Manner et al. 2013[53] (1996–2010)	Total: 66 T1b SM1: 66 AC: 66	Retrospective	ER + APC: 66	Mean follow-up (months)	47 ± 29.1	Risk of developing lymph node metastases after EMR is lower than the risk of surgery. No tumor-associated deaths were observed
				Complete endoluminal remission	Overall: 53/61 (86.9%) Lesions < 2 cm: 30/31 (97%) Lesions ≥ 2 cm: 23/30 (77%)	
				Long-term remission	Overall: 51/61 (83.6%) Lesions < 2 cm: 28/31 (90%) Lesions ≥ 2 cm: 23/30 (77%)	
				Metachronous neoplasia	10/53 (18.9%)	
				5-year OS (%)	84	

TABLE 1 continued

Author, year (study years)	No. of patients	Study type	Procedure	Outcomes	Results	Conclusions
Manner et al. 2017[33] (1996–2010)	Total: 62 T1b SM2: 23 T1b SM3: 39 AC: 62	Retrospective	*T1b SM2-hisLR:* ET: 3 Esophageal resection: 9 hisHR: ET: 1 Esophageal resection: 10 T1b SM3-hisLR: ET: 0 Esophageal resection: 7 hisHR; ET: 0 Esophageal resection: 7 Note: 58 patients underwent esophageal resection where pT1b SM2 versus SM3 status was not defined	Mean follow-up with EUS after ET (months) Lymph node metastasis (%) Lymph node metastasis per histologic risk (%)	41–43 T1b SM2: 21.7 T1b SM3: 35.9 *T1b SM2:* hisLR: 8.3 hisHR: 36.3 combLR: 0 combHR: 27.8 *T1b SM3* hisLR: 28.6 hisHR: 37.5 combLR: 25 combHR: 37.1	In ADC with pT1b SM2/3 invasion, the rate of lymph node metastasis appears to be higher than the mortality risk of surgery. Whether a highly selected group of pT1b SM2 patients with a favorable risk pattern may be candidates for endoscopic therapy cannot be determined until the results of larger case volumes are available

TABLE 1 continued

Author, year (study years)	No. of patients	Study type	Procedure	Outcomes	Results	Conclusions
Ngamruengphong et al. 2013[26] (1998–2009)	Total: 1618 *ET:* Tis: 55 T1a: 174 T1b: 39 T1, NOS: 38 *Surgery:* Tis: 110 T1a: 561 T1b: 523 T1, NOS: 118	Retrospective, SEER	Surgery: 1312 (81%) ET: 306 (19%)	Median follow-up (months)	36	Older age and radiation therapy were associated with worse OS and DSS. Submucosal invasion was significantly associated with worse OS and DSS. Outcomes were not different for surgery compared with ET when stratified by depth of invasion
				5-year OS, Tis/T1 (%)	ET: 58 Surgery: 70 ($p = 0.003$)	
				5-year OS, Tis/T1a (%)	ET: 60 Surgery: 76 ($p = 0.002$)	
				5-year OS, T1b (%)	Surgery: 66 ET: 64 ($p = 0.26$)	
				5-year DSS, Tis/T1 (%)	Surgery: 81 ET: 77 ($p = 0.26$)	
				5-year DSS, Tis/T1a (%)	Surgery: 83 ET: 84 ($p = 0.64$)	
				5-year DSS, T1b (%)	Surgery: 89 ET: 71 ($p = 0.31$)	
Nurkin et al. 2014[27] (2001–2012)	Total: 81 Tis: 37 T1a: 10 At least T1a: 13 T1b: 6 At least T1b: 15	Retrospective	EMR: 77 ESD: 4 Esophagectomy: 14	5-year OS (%)	T1a: 83	EMR can result in a cure for T1s/T1a disease. Patients with T1b esophageal cancer, low-risk features and negative deep margins can be observed
				5-year DFS (%)	T1a: 100 T1b: 100	
Oh et al. 2006[28] (1987–2006)	Total: 78 T1a: 78	Retrospective	En bloc esophagectomy: 23 THE: 31 Vagal-sparing esophagectomy: 20 Transthoracic esophagectomy: 4	Median follow-up (months)	En bloc: 68 THE: 21 Vagal-sparing: 22 Transthoracic: 34	The vagal-sparing technique had less morbidity than other forms of resection, and no mortality. Survival after all types of resection was similar
				Lymph node metastasis (in patients undergoing en bloc resection)	1/23 (4%)	
				5-year OS (%)	88	

TABLE 1 continued

Author, year (study years)	No. of patients	Study type	Procedure	Outcomes	Results	Conclusions
Pech et al. 2005[36] (1996–2002)	Total: 66 HGD: 35 T1a: 31	Prospective	PDT-ALA	Median follow-up (months)	HGD: 37 T1a: 36	Local recurrence in 10 patients in the T1a group
				5-year OS (%)	HGD: 97 T1a: 80	
				5-year DSS (%)	HGD: 89 T1a: 68	
Pech et al. 2011[29] (1996–2009)	Total: 114 T1a: 114	Retrospective	Transthoracic esophagectomy: 38 EMR + APC: 76	Median follow-up (years)	Esophagectomy: 3.7 EMR + APC: 4.1	
				Long-term remission rates allowing for repeat endoscopic therapy (%)	Transthoracic esophagectomy: 100 EMR + APC: 98.7	Esophagectomy was associated with a higher morbidity rate and a mortality rate of 2.6% versus 0% in the EMR cohort (NS). Recurrence rate was higher in the EMR cohort (NS)
				Disease-free survival rate (%)	Esophagectomy: 100 EMR + APC: 98.7	
Pech et al. 2014[3] (1996–2010)	Total: 1000 T1a: 1000	Prospective	EMR	Mean follow-up (months)	56.6	Repeat endoscopic treatment was successful in 82.1%. Surgery was necessary in 3.7% after failure of endoscopic therapy
				Long-term complete remission rate (%)	93.8	
				Recurrence of neoplasia (%)	14.5	
				5-year OS (%)	91.5	
				10-year OS (%)	75	
				5-year DSS (%)	87.1	

TABLE 1 continued

Author, year (study years)	No. of patients	Study type	Procedure	Outcomes	Results	Conclusions
Peyre et al. 2007[30] (1992–2006)	Total: 109 HGD: 36 T1a: 73	Retrospective	Vagal-sparing esophagectomy: 49 THE: 39 En bloc esophagectomy: 21	30-day mortality (%)	Vagal-sparing esophagectomy: 2 THE: 5 En bloc esophagectomy: 0	Length of hospital stay and the incidence of major complications was significantly reduced with vagal-sparing esophagectomy compared with transhiatal or en bloc resection. Recurrent cancer developed in only one patient
				Duration of follow-up (months)	Vagal-sparing esophagectomy: 39 THE: 25 En bloc esophagectomy: 60	
Prasad et al. 2009[20] (1998–2007)	Total: 178 T1a: 178	Retrospective	Endoscopic: 132 EMR alone: 75 (57%) EMR + PDT: 57 (43%) *Surgery: 46* THE: 20 (43%) TTE: 26 (57%)	5-year OS (%)	Endoscopic: 83 Surgery: 95	
				5-year DSS (%)	Endoscopic: 80 Surgery: 97	
Rice et al. 2001[11] (1985–1999)	Total: 122 HGD: 38 T1a: 53 T1b: 31	Retrospective	THE: 75 TTE/TA: 46 Laparotomy: 1	Mean follow-up (months)	Mean: 47 ± 41 Median: 38	Depth of invasion predicted survival on univariate analysis but not on multivariate analysis, LNM was most predictive of poor long-term survival
				OS, all (%)	5-year: 77 10-year: 68	
				OS, T1a (est %)	5-year: 77 10-year: 65	
				OS, T1b (est %)	5-year: 61 10-year: 40 ($p = 0.009$)	

TABLE 1 continued

Author, year (study years)	No. of patients	Study type	Procedure	Outcomes	Results	Conclusions
Saha et al. 2009[31] (2000–2009)	T1: 44 T1b: 11	Retrospective	Esophagectomy Ivor Lewis: 24 THE: 20	Median follow-up (months) 1-year DFS (%) 3-year survival (%)	44 95 93	Differentiation seems to be a marker of poor prognosis
Schmidt et al. 2016[35] (2000–2012)	Total: 85 T1a: 85	Retrospective	Esophagectomy: 49 ET: 36	Mean follow-up (months)	Esophagectomy: 70 ET: 42.6	Comparable outcomes are noted between patients treated with surgery or ET. More frequent recurrences after ET mandate close follow-up
				Age-adjusted OS (%)	Esophagectomy: 80 ET: 78 ($p = 0.13$)	
				3-year survival (%)	Esophagectomy: 93 ET: 80 ($p = 0.25$)	
				5-year survival (%)	Esophagectomy: 86 ET: 69 ($p = 0.19$)	
				Recurrence (%)	Esophagectomy: 1 ET: ($p = 0.08$)	
Sepesi et al. 2010[12] (2000–2008)	Total: 54 T1a: 25 T1b: 29 SM1: 14 SM2: 11 SM3: 6	Retrospective	En bloc esophagectomy: 10 THE: 39 Ivor Lewis: 2 Vagal-sparing esophagectomy: 2 McKeown: 1	Median follow-up (months) 5-year OS (%) Died with recurrence	42 T1a: 85 T1b: 60 ($p = 0.08$) 5/15 (33%)	Nodal metastasis was significantly different between intramucosal and submucosal tumors, but not different according to the depth of submucosal invasion. Nodal metastasis in submucosal tumors was high
Sgourakis et al. 2013[37] (1997–2011)	Total: 4241 Endoscopic: 2092 LGD: 4% HGD/CIS: 33.6% T1a: 54% T1b: 16% Surgery: 2149, included AC and SCC	Systematic review	*Endoscopic therapy:* EMR and/or ESD (42 studies) APC (3 studies) PDT (2 studies) RFA (2 studies) *Surgery:* Various (38 studies)	Mean follow-up (months) Endoscopic local recurrence (30 studies) Development of metachronous lesions after endoscopic management (10 studies)	ET: 12–62 0–17% AC: 0.8% SCC: 1% 2–14% ADC: 6% SCC: 1%	In endoscopically managed patients, local tumor recurrence was predicted by poor differentiation and piecemeal resection; lymph node positivity by LVI. In surgically resected patients for ADC, the best predictor for lymph node positivity was LVI

TABLE 1 continued

Author, year (study years)	No. of patients	Study type	Procedure	Outcomes	Results	Conclusions
Stein et al. 2000[14] (1987–1999)	Total: 94 T1a: 38 T1b: 56	Retrospective	Esophagectomy-subtotal: 71 Limited resection/jejunal interposition: 24	Median follow-up (months)	15	There was no survival difference between node-negative T1a and T1b. Lymph node metastasis had a significant effect on survival
				30- and 90-day mortality (%)	Limited: 0 Subtotal: 4.2	
				LNM	T1a: 0 T1b: 10/56 (17.8%)	
				5-year OS (%)	T1a: 85 T1b: 78	
Stein et al. 2005[13] (1990–2004)	Total: 290 HGD: 14 *T1a:* AC: 57 SCC: 25; *T1b:* AC: 87 SCC: 107	Retrospective	Esophagectomy-abdominothoracic: 146 Radical THE: 144	Median follow-up (months)	66 months	Presence of lymph node metastasis and histologic tumor type were the only significant factors affecting survival favoring node-negative disease and adenocarcinoma
				LNM AC	T1a: 0 T1b: 20.7%	
				5-year OS (%)	AC: 83.4 SCC: 62.9	
Tian et al. 2011[54] (1995–2010)	Total: 68 T1b: 68	Retrospective	EMR: 68 Esophagectomy: 39	Median survival (months)	All: 39.5 (IQR 23.9–70.3) EMR: 34.8 Surgery: 48.9 (p = 0.09)	Patients who underwent esophagectomy after EMR lived longer, but not significantly so. Most of the EMR-only mortality was in patients deemed not fit for esophagectomy
				Overall mortality (%)	EMR: 37.9 Surgery: 25.6 (p = 0.28)	
				5-year survival (%)	All: 69.5%	
				Risk factors for overall survival, univariate (HR, 95% CI)	Surgery: 0.4, 0.2–1.1 (p = 0.09) Lymph node metastasis 6.8, 1.4–33.8 (p = 0.02)	

TABLE 1 continued

Author, year (study years)	No. of patients	Study type	Procedure	Outcomes	Results	Conclusions
Westerterp et al. 2005[15] (1980–2002)	Total: 120 HGD: 13 T1: 107	Retrospective	THE	Median follow-up (months)	44	N stage was the only independent predictor of recurrence at 5 years, but, when excluded, depth of invasion was significant
				5-year recurrence-free rate (%)	T1a/T1b-SM1: 96 T1b-SM2/SM3: 57 ($p < 0.0001$)	
				5-year RFS (%)	T1a/T1b-SM1: 80 T1b-SM2/SM3: 42 (significant)	
				Recurrence-free period risk for T1N0	T1b-SM2/SM3: HR 7.5 (95% CI 2.0–2.7 versus T1a/T1b-SM1)	
				5-year DFS (%)	68	

SM submucosal, *OS* overall survival, *HGD* high-grade dysplasia, *LGD* low-grade dysplasia, *CIS* carcinoma in situ, *NS* not significant, *THE* transhiatal esophagectomy, *MIE* minimally invasive esophagectomy, *LR* limited resection, *ER* extended resection, *ET* endoscopic therapy, *EMR* endoscopic mucosal resection, *ESD* endoscopic submucosal dissection, *APC* argon plasma coagulation, *PDT* photodynamic therapy, *RFA* radiofrequency ablation, *DFS* disease-free survival, *DSS* disease-specific survival, *RFS* recurrence-free survival, *AC* adenocarcinoma, *SCC* squamous cell carcinoma, *hisLR* histologically low risk, *hisHR* histologically high risk, *combLR* combined low risk, *combHR* combined high risk, *EUS* endoscopic ultrasound, *ALA* 5-aminolevulinic acid, *LNM* lymph node metastasis, *SEER* Surveillance, Epidemiology, and End Results, *NOS* not otherwise specified, *HR* hazard ratio, *CI* confidence interval, *LVI* lymphovascular invasion, *IQR* interquartile range

esophagectomy, and reported an overall 5-year survival of 88% after a median follow-up of 68 months.[28] In another series, 75 patients with T1a adenocarcinomas undergoing esophagectomy (majority en bloc or transhiatal esophagectomy) were included. During a median follow-up period of 50 months, a comparable 5-year survival rate of 82% was reported.[9] These findings are supported by those of smaller series of esophagectomy, demonstrating overall 5-year survival rates ranging from 73% to 100%.[10–12,14,23,25]

Of the few studies that directly compare ET with surgery, all are retrospective, with most spanning a decade or longer.[20,29,35] Outcomes are similar between the two modalities, except in the series by Prasad and colleagues, where an older ET population, with more comorbidities, showed a trend toward lower 5-year overall survival.[20] In that study, 132 patients undergoing ET, and 46 patients treated with esophagectomy, were followed for a mean of 43 and 64 months, respectively. While 5-year overall survival was not significantly different (83% ET, 95% esophagectomy, $p = 0.15$), 5-year cancer-free survival was higher in the surgery group (80% ET, 97% esophagectomy, $p = 0.01$). Pech et al. matched the baseline characteristics of 76 patients undergoing exclusively EMR and APC with 38 transthoracic esophagectomy patients, although the ET cohort had a significantly shorter mean BE segment length (3 vs. 6 cm, $p = 0.02$).[29] After a median follow-up of 4.1 and 3.7 years for the ET and esophagectomy patients, 5-year overall survival was similar in both groups (89% ET, 93% esophagectomy, $p = 0.91$). Disease-free survival at 5 years was also not significantly different (91% ET, 100% esophagectomy, $p = 0.19$). Seeking to overcome the confounding effects of age and debility, Schmidt and colleagues compared outcomes between ET (36 patients) and esophagectomy (49 patients) in a cohort of surgery-eligible patients.[35] Overall age-adjusted survival was again similar (78% ET, 80% esophagectomy, $p = 0.13$) after a mean follow-up of 42.6 and 70 months, respectively.

Results from population-based investigations show inconsistent survival outcomes and do not differentiate between Tis and T1a tumors. One analysis of 1618 patients from the Surveillance, Epidemiology, and End Results (SEER) tumor registry revealed that ET was associated with equivalent 5-year overall survival (hazard ratio 1.29, 95% confidence interval 0.93–1.81, $p = 0.13$) compared with esophagectomy.[26] Another SEER analysis looking at a combined Tis/T1a population of 2193 older patients ($\geq$ age 66 years) found that ET was associated with improved unadjusted survival after 2 years, in the adenocarcinoma cohort (84% ET, 71% esophagectomy, $p < 0.01$).[34]

The trend toward higher local recurrence rates after ET (1.3–12%) when compared with surgery (0–2%) has been largely offset by the ability to re-treat most of T1a EACs successfully with ET, and has not resulted in a significant decrease in either overall or disease-specific survival relative to esophagectomy. Features that contribute to elevated recurrence risk include the presence of residual BE after EMR with ablation, and longer BE segments.[20] Regardless of the lesion characteristics, close surveillance with endoscopy and biopsy is mandatory after ET in order to achieve optimal long-term results.

cT1b EAC

Esophagectomy for the treatment of EAC with submucosal invasion is well-established and is typically performed by combined transabdominal and transthoracic approaches or by the transhiatal approach, with increasing use of minimally invasive techniques.[37] Studies have shown that patients with T1b lesions have a substantial rate of LN involvement and have subsequently advised against endoscopic treatment for those who are surgical candidates.[23,51]

One study of patients with T1b EAC undergoing esophagectomy found that 18% of patients had LNM and 34% had LVI.[51] Patients with tumors showing poor differentiation, LVI, or LNMs may represent a group in whom even surgery alone is inadequate and can be considered for neoadjuvant or adjuvant therapy. Another study evaluating the rate of LNM in T1b cancer with mid to deep submucosal invasion (T1b SM2-3) in patients undergoing EMR versus surgery found that the rate of LNM ranged from 0 to 28% and 25 to 38% in the T1b SM2 and SM3 groups, respectively, based on histological and macroscopic risk patterns.[33] Thirty-day mortality after esophagectomy was 1.7% and there was no treatment-related mortality with EMR. Although the 30-day mortality after esophagectomy is low, perioperative morbidity remains high, with no significant difference between the open and minimally invasive approaches.[52] This contrasts with the lower rate of procedure-related complications after endoscopic procedures.[3] Small studies have examined outcomes following endoscopic therapy for T1b EAC. Therapy was predominantly EMR in select patients with low-risk T1b lesions. Low risk was defined as macroscopically polypoid or flat lesions with a histologic pattern of invasion into the most superficial third of the submucosa (SM1), well-to-moderate differentiation, and no LVI.[53] Since EMR typically does not resect the entire submucosa, SM1 (superficial) disease after EMR is defined as tumor involvement of $\leq$ 500 microns below the muscularis mucosae, with involvement past 500 microns categorized as SM2-3 lesions.[54,55] One study of patients with low-risk lesions treated with endoscopic therapy (EMR followed by ablation) found that 87% achieved complete endoluminal remission (CER) of neoplasia.[53] Estimated 5-year survival was 84%. Metachronous cancers were observed in 19% of patients with prior CER, while LNM was seen in one patient (2%). The authors concluded that EMR is a reasonable alternative to esophagectomy in select patients, with the risk of developing LNMs lower than the risks of surgery. Another retrospective study of 68 patients with T1b EAC diagnosed by EMR investigated treatment outcomes with and without esophagectomy.[54] In patients undergoing esophagectomy, 33% had LNM, a risk factor for increased mortality on univariate, but not multivariate, analysis. Cumulative mortality and overall survival differences did not reach statistical significance between groups in this small study. Despite the substantial rates of LNM in T1b tumors overall, lesions with superficial submucosal invasion demonstrated variability in rates of LNM (8–21%), suggesting that further segregation according to the presence or absence of risk factors other than tumor depth for LNM could identify a low-risk subset for which endoscopic therapy may be appropriate. Pathologic factors post-esophagectomy, including LVI, multifocality, length, differentiation, and age, have been incorporated into several scoring nomograms to predict LNM, with good model discriminating abilities (c-statistics 0.71–0.82).[56–58]

A study evaluating 1618 patients from the SEER database with Tis (HGD) or T1N0M0 EAC undergoing endoscopic ET versus surgery found that endoscopic therapy demonstrated equivalent overall and esophageal cancer-specific survival compared with the surgery group, after adjusting for clinical factors including age and depth of tumor invasion.[26] In subgroup analysis by tumor stage, overall and esophageal cancer-specific survival rates did not differ significantly between patients with Tis/T1a and T1b EAC. Long-term outcomes in T1b EAC were not significantly different between the endoscopic therapy and surgery groups, and the authors suggest that these findings should be interpreted with caution given the relatively small number of patients with T1b cancer undergoing endoscopic therapy.

In summary, given the substantial risk of LNMs in patients with submucosal EAC, esophagectomy remains the standard of care for patients with T1b tumors who are surgical candidates. In the case of selected low-risk lesions with superficial submucosal invasion or inoperability, endoscopic therapy with endoscopic resection can be considered adequate therapy. Adjuvant systemic therapy (chemotherapy or radiation therapy) may be considered for high-risk lesions after EMR, but there are insufficient data to define a clear benefit in this setting.[59]

T1N0 Unspecified Disease

Some surgical studies of T1 disease do not differentiate between T1a and T1b tumors.[5,13,31] Although limited, these studies support the understanding that T1b tumors confer a high risk of LNM precluding curative intent with endoscopic therapy.

Limitations

This review has several limitations. First, there are no published randomized controlled trials that compare endoscopic therapy with esophagectomy, leaving the potential for selection bias in the available observational studies. Current treatment trends suggest that such a randomized trial is unlikely to be performed as there is a growing lack of equipoise regarding the issue. Furthermore, although most of the trials reviewed demonstrate good results with endoscopic therapy for superficial EAC, many of them involve small sample sizes and/or combine different tumor types and ablation techniques. Differentiation of survival according to the specific T stage varies among the studies, where patients with superficial adenocarcinoma are often reported together with HGD patients, or are combined with patients who have submucosal invasion, making it difficult to draw clear conclusions.

Our literature search included articles published between 1 January 1990 and 1 October 2017. In earlier years, older patients with more comorbidities were more likely to have been treated with endoscopic therapy. It should also be noted that during this 17-year period, endoscopic therapy and available ablative therapies evolved dramatically, with decreased procedure-related morbidity as experience with endoscopic treatments grew. Therefore, over time, a greater proportion of patients have been treated endoscopically, leading to a decrease in both age and Charlson scores in this treatment group. In addition, the accuracy of pathologic differentiation may have also varied over time. The effect of this variability on survival outcomes cannot be definitively quantified but must be taken into account.

Lastly, the outcomes of these studies may not be reproducible outside of the specialized high-volume centers in which they were performed. Review by experienced gastrointestinal pathologists is needed to accurately characterize tumor depth and determine appropriate treatment. As complications have been shown to decrease with more experience in endoscopic therapy, centers that do not have high enough volumes may not show similar outcomes.

CONCLUSION

In patients with T1aN0 EAC, overall survival and cancer-specific survival with endoscopic ET are equivalent to esophagectomy. Although patients treated with endoscopic therapy have an increased chance of cancer recurrence, most can be re-treated endoscopically without impacting overall survival. Patients must therefore undergo close follow-up and surveillance for metachronous or recurrent lesions with EGD every 3 months for the first year followed by every 6 months for the following year.[45] Given the substantial risk of LNM in patients with submucosal EAC, esophagectomy remains the standard of care for patients with T1b tumors who are surgical candidates. In the case of inoperability, endoscopic therapy with endoscopic resection can be considered adequate therapy. Adjuvant systemic therapy (chemotherapy or radiation) should be offered for high-risk lesions following endoscopic resection.

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