Treatment of Early Oesophageal Cancers: Current Consensus

[1]Sameh A. A. Mikhail, [2]Nader S. Zaki, [3]Tamer M. Nabil
Department of General Surgery [1]Cairo University,
[2]Fayoum University, [3]Beni Suef University

ABSTRACT

Barrett's oesophagus carries an annual risk of developing cancer. We reviewed the literature looking for best evidence papers addressing the management of early oesophageal cancer. A total of 510 papers were found using the reported searches. Oesophagectomy and lymph node dissection for early oesophageal cancer is the standard to which every other treatment modality is compared to. However, the associated mortality and morbidity rates highlight the need for alternative effective and less invasive procedures. Despite the fast growing interest in Minimally invasive oesophagectomy, there is no way to compare it to endoscopic treatment in terms of impact on patient. The evidence from the present review supports the following : Endoscopic resection (ER) and Radiofrequency Ablation (RFA) should be regarded as the first line treatment in T1a oesophageal cancer. The trade off for Endoscopic treatment is a higher recurrence rate which can be dealt with using a strict follow up and retreatment. The higher rates of lymph nodes involvement in T1b cancers preclude the use of endoscopic treatment in this setting except for patients unfit for surgery. G3, Vascular and lymphatic invasion are prognostic factors for lymph node involvement.

INTRODUCTION

Oesophageal adenocarcinoma incidence is rising exponentially in the west. Surveillance programs are already in place for people with Barrett's oesophagus. The advances in endoscopic techniques has led to new alternatives being offered in treating patients with early oesophageal adenocarcinoma. There is accumulating evidence that endoscopic treatment for early oesophageal cancer can be used as a first line treatment option as long as these patients are closely followed up and retreated if needed [(1,2)]. The aim of this review is to assess whether endoscopic treatment of early oesophageal cancers give equivalent oncological outcomes as compared with Surgery.

METHODOLOGY

Search using Medline from 1948 to January 2017 using the PubMed interface: "Endoscopic therapy" AND "Oesophagectomy" AND "Early oesophageal cancer". Reference lists of key articles were also searched for references. Only Articles written in English were searched.

Search outcome

A total of 510 papers were found using the above search. After reviewing the abstracts, 49 papers were selected to be appraised in view of relevance and methods used. Based on design, number of patients and origin (high volume/specialized centres and national registries) 24 papers were identified that provided the best evidence to answer the question. These are presented in Table 1.

Most of papers were retrospective cohort studies (Level 3 evidence). We found one metaanalysis [(3)] that looked at efficacy and durability of RFA in Barrett's Oesophagus.

Table 1: Best evidence papers

Authors	**Patient group**	**Outcomes**	**Key results**	**Conclusion/*Comment***
Chadwick et al. [1]	A population-based cohort study was undertaken of patients diagnosed with oesophageal using three linked national databases. Patients with early-stage disease (T1) were identified	Short-term outcomes after treatment and 5-year survival were evaluated.	Between 2007 and 2009, oesophagectomy remained the initial treatment of choice (73·2 per cent) among patients with early-stage oesophageal cancer treated with curative intent; one in five patients were managed endoscopically, and this treatment was more common in elderly patients. Although the groups had different patient characteristics, 5-year survival rates were similar. Repeat endoscopic therapy was needed in 56% of patients treated endoscopically. 30.3% of patients treated surgically had their disease upstaged after pathological staging.	*Understaging is a challenge that can affect outcomes*
Cummings et al. [18]	Retrospective cohort study identifying 2193 patients≥66 years with Tis or T1a tumours without nodal involvement diagnosed from 1994 to 2011	A composite endpoint, hospitalization and/or adverse events at 60 days.	41% underwent esophagectomy, and 12% underwent endoscopic treatment. Those treated endoscopically were older. A composite endpoint, hospitalization and/or adverse events at 60 days, was higher in surgical patients than in the endoscopic treatment group (30% vs 12%; P < .001). In a Cox model stratified by histology, adjusting for other factors, endoscopic treatment was associated with improved 2-year survival (hazard ratio 0.51; 95% CI, 0.36-0.73).	These results suggest that endoscopic treatment is a reasonable approach for early esophageal ca ncers in the elderly.
Gamboa et al. [19]	Data from the Surveillance, Epidemiology, and End Results database of the National Cancer Institute were abstracted from 2004 to 2010 for patients with early-stage OAC	The incidence of lymph node involvement for patients with Tis, T1a, and T1b tumours was examined and was stratified by predictors of spread.	715 patients with Tis, T1a, and T1b tumours were included. On multivariate analysis, tumor grade, T classification and tumor size were found to be independently associated with lymph node metastases. There was no lymph node spread noted with Tis tumours. For patients with low-grade (well or moderately differentiated) tumours measuring <2 cm in size, the risk of lymph node metastasis was 1.7% for T1a (P<.001) and 8.6% for T1b (P = 0.001) tumours. For highly selected patients with early OAC, endoscopic resection can be considered as an alternative to surgical management when followed by rigorous endoscopic and radiographic surveillance.	For patients with low-grade Tis or T1 tumours measuring ≤2 cm in size, the incidence of lymph node metastasis appears to be comparable to the mortality rate associated with esophagectomy.
Jin et al. [20]	Retrospective analysis of 99consecutive patients with pathologically confirmed early OAC between December 2007 and 2011.	Endoscopic resection (ER) was performed in 59 patients, whereas Minimally invasive Oesophagectomy (MIO) was performed in 40 patients. We compared the 2 groups according to R0 resection rates, treatment-related complications, mean hospital stay, local recurrence rates, and 3- and 4-year overall survival.	No significant differences were found in the R0 resection rates between ER and MIO (94.9% vs. 97.5%, P>0.05). The occurrence rate of minor complications in the ER group was significantly lower than that in the thoracoscopic esophagectomy group (11.8% vs. 32.5%, P>0.05). The mean operative time in the ER group was 74±23 minutes, which was significantly shorter than that in the MIE group (298±46 min). The average length of hospital stay in the ER group was significantly shorter than that in the MIO group (P<0.001). No significant differences were observed in the local recurrence rates between the 2 groups (P>0.05). Similarly, no differences were found in the 3-year survival rate (ER: 96.6%, vs. MIE: 97.5%, P>0.05) and 4-year survival rate (ER: 91.5% vs. MIE: 90%, P>0.05) between the 2 groups	ER achieves the same positive results as MIE in the treatment of early esophageal can cer and is associated with a lower complication rate, a shorter recovery time, and a similar survival rate. However, multiple ER procedures were required for several patients in this study.
Le Page et al. [21]	A prospectively collected database of consecutive patients staged with high-grade dysplasia (HGD) or T1 oesophageal adenocarcinoma (OAC)treated	Outcomes included treatment variables, recurrence and complications.	83 patients treated; 50 with endoscopic therapy and 38 by surgery (33 straight to surgery and 5 following EMR). High Grade Dysplasia was more common in the endoscopic group. Significant complications were more common	Due to additional morbidity of surgery, endoscopic treatment is appropriate first-line treatment.

Authors	**Patient group**	**Outcomes**	**Key results**	**Conclusion/*Comment***
	with curative intent between 2005 and 2013 was undertaken.		following surgery. Recurrence of HGD/invasive cancer was diagnosed in 5.6%, of endoscopic therapy patients.	
Phoa et al. *(Euro II study)*[10]	13 European centres, patients with BO≤12 cm with HGD and/or OAC on 2 separate endoscopies were eligible for inclusion. Visible lesions (<2 cm length; <50% circumference) were removed with ER, followed by serial RFA every 3 months (max 5 sessions). eradication of neoplasia (CE-neo) and intestinal metaplasia (CE-IM); durability of CE-neo and CE-IM (once achieved) during follow-up.	long-term outcomes of combined Endoscopic resection and RFA for Barrett's Oesophagus (BO) (HGD and/or OAC) from a single-arm multicentre interventional study	Per-protocol analysis, CE-neo and CE-IM were achieved in 98% and 93%, respectively. After a median of 27 months following the first negative post-treatment endoscopic control, neoplasia and IM recurred in 4% and 8%, respectively. Mild-to-moderate adverse events occurred in 25 patients (19%); all managed conservatively or endoscopically.	In patients with early Barrett's neoplasia, intensive multimodality endotherapy consisting of ER combined with RFA is safe and highly effective, and the treatment effect appears to be durable during mid-term follow-up.
Pech et al.[22]	1000 consecutive patients with mucosal OAC (481 with short-segment and 519 with long-segment Barrett's esophagus) who presented at a tertiary care center from October 1996 to September 2010.	Long term outcomes	+ After a mean follow-up period of 56.6 ± 33.4 months, 96.3% had achieved a complete response; surgery was necessary in 12 patients (3.7%) after endoscopic therapy failed. + Metachronous lesions or recurrence of cancer developed during the follow-up period in 140 patients (14.5%) but endoscopic re-treatment was successful in 115, resulting in a long-term complete remission rate of 93.8%; + The calculated 10-year survival rate of patients who underwent endoscopic resection was 75%. + Major complications developed in 1.5% but could be managed conservatively. + Endoscopic therapy is highly effective and safe for patients with mucosal OAC, with excellent long-term results.	Endoscopic therapy should become the standard of care for patients with mucosal OAC.
Park et al.[16]	cT1N0M0 Oesophageal Cancer patients at Asan Medical Center between 2003 and 2012 were retrospectively reviewed. 264 Surgically treated patients & 20 patients treated Non surgically. Performance status and Charlson comorbidity index score were poorer in the Non Surgical group.	The baseline characteristics, treatment outcomes and complications, and survival were compared (median follow-up of 49.0 months)	Recurrence rate was around 15% in both groups. The median time-to-recurrence could not be calculated in either group. The estimated median overall survival was 64.4 months (in the Non Surgical group and could not be calculated in the Surgical group (P = 0.056).	*The main histologic finding was squamous cell carcinoma in both groups (97% and 100%)*
Lorenz et al.[15]	the results of 168 patients who had an esophageal resection because of an early OAC. On the basis of specimen histologies and clinical follow-up (median, 64 months),	Influence of lymph node metastases (N+), tumor infiltration depth, tumor differentiation (G1-3), and lymphatic or venous infiltration (L+ or V+) on overall and tumor-specific survival and recurrence rates.	The 5-year survival rate was 79%. Lymph node infiltration was the only prognostic factor for the overall survival, tumor-specific survival, and tumor recurrence that was consistently present in all multivariate analyses. 47% of the patients who had an N+ status developed tumor recurrences compared with 5.2% of those who had no lymph node involvement We found a significant correlation between N+ status and increasing depth of tumor infiltration (P = 0.004), lymphatic vessel infiltration (P = 0.002), tumor differentiation (G1 + G2 vs G3; P = 0.014) and vascular infiltration (P = 0.01). Lymph node status is the only independent risk factor for survival and recurrence rates. Tumor infiltration depth correlates with the rate of the lymph node metastases, but a clear watershed between deep mucosal and submucosal infiltration does not exist.	Careful staging procedures, including diagnostic ER, are mandatory to determine which patients are better treated with Oesophagectomy.
Wani et al.. [17]	Patients with early Oesophageal Cancer (OC) (stages T0 and T1)	Compare overall survival & OC-related	A total of 430 (21%) and 1586 (79%) patients underwent Endoscopic treatment	comparable mid- and long-term OC-related

Authors	**Patient group**	**Outcomes**	**Key results**	**Conclusion/*Comment***
	were identified from the Surveillance, Epidemiology, and End Results database (1998-2009). Demographics, tumor specific data, and survival were compared. Cox proportional hazards regression models were used to evaluate the association between treatment and Oesophageal cancer specific mortality	mortality in patients with early OC treated Endoscopically and by oesophagectomy. Mid- (2 years) and long- (5 years) term overall survival and OC-specific mortality, outcomes based on histology and stage, treatment patterns, and predictors of cancer-specific mortality.	and oesophagectomy, respectively. There was no difference in the 2-year OC-related mortality rates between the 2 groups. Endoscopically treated patients had higher mortality rates attributed to non-OC causes (5 years: 46.6% vs 20.6%, P < .001). .	mortality in patients with early O C undergoing Endoscopic treatment and surgical resection. *Squamous cancer patients included.*
Lada et al. [23]	Data were obtained retrospectively for all patients who underwent endoscopic therapies or oesophagectomy for a diagnosis of BE with HGD or IMC between January 2004, and December 2012. Complete remission (CR) of BO or HGD or mucosal cancer (IMR) was defined as 2 negative consecutive biopsy sessions and no subsequent recurrence.	Determine the efficacy of RFA with or without EMR in the management of BO with HGD or IMR Discern factors predictive of endoscopic treatment failure, and to assess the effect of endoscopic therapies on oesophagectomy volume.	+ 57 patients underwent 181 RFA sessions with a median follow-up duration of 35.4 months. + Only 2 minor complications including 1 symptomatic stricture requiring dilation. + Use of oesophagectomy as primary therapy for BO with HGD or IMC has diminished since we began using endoscopic therapies in 2007. + Although recurrence of BE or dysplasia/IMC was not uncommon, RFA with or without EMR ultimately resulted in CR of IMC in all patients, No patient treated endoscopically subsequently required oesophagectomy. + Multifocal HGD or IMC was present in 43% of patients. + Factors associated with failure to achieve CR of BE included increasing length of BE (6.0 ± 0.6 vs 4.0 ± 0.6cm, P = 0.03) and shorter duration of follow-up (28.5 ± 3.8 months vs 49.0 ± 5.8 months, P = 0.004with the latter being the only significant factor.	The use of endoscopic therapies appears justified as the new standard of care in most cases of BE with early esophageal neoplasia.
Phoa et al. [24].	54 patients with BO (2-12 cm) were followed up. They underwent EMR followed by serial RFA every 3 months. Patients underwent high-resolution endoscopy with narrow-band imaging at 6 and 12 months after treatment and then annually for 5 years. After 5 years, EUS and endoscopic resection of neosquamous epithelium were performed.	Outcomes included sustained complete remission of neoplasia or intestinal metaplasia (IM), IM in gastric cardia, or buried glands in neosquamous epithelium.	+ After 5 years, Kaplan-Meier analysis showed sustained complete remission of neoplasia and intestinal metaplasia in 90% of patients. + Neoplasia recurred in 3 patients and was managed endoscopically. + Focal IM in the cardia was found in 35% of patients. + The incidence of IM of the cardia did not increase over time. + Buried glands were detected in 3 of 3543 neosquamous epithelium biopsies (0.08%, from 3 patients). + No endoscopic resection samples had buried glands.	This treatment approach is therefore an effective and durable alternative to oesophagectomy.
Manner et al. [8]	66 patients with sm1 low-risk lesions (macroscopically polypoid or flat, with a histologic pattern of sm1 invasion, good-to-moderate differentiation [G1/2], and no lymphovascular invasion treated by endoscopic therapy from 1996 through 2010.	Efficacy of endoscopic therapy on the basis of rates of complete endoluminal remission (CER), metachronous neoplasia, lymph node events, and long-term remission (LTR). Safety was assessed on the basis of rate of complications.	+87%achieved CER. 97%Of patients with small focal neoplasias ≤2 cm achieved CER. For those with tumours ≥2 cm, 77%. Metachronous neoplasias were observed in 19% of patients +One patient developed a lymph node metastasis (1.9%). 84%of patients achieved LTR. 90% of those with focal lesions ≤2 cm achieved LTR after a mean follow-up period of 47 ± 29.1 months. +No tumor-associated deaths were observed, and the estimated 5-year survival rate was 84%. +The rate of major complications from endoscopic resection was 1.5%, and no patients died.	+Endoscopic therapy is good alternative to oesophagectomy for patients with *pT1b sm1 OAC*, on the basis of macroscopic and histologic analyses. +The risk of developing lymph node metastases after endoscopic resection for sm1 EAC is lower than the risk of surgery.
Berry et al. [25]	T1N0M0 squamous cell or adenocarcinoma of the mid or distal esophagus treated with	Five-year cancer-specific and overall survival (OS)	Of 1458 patients with T1N0 esophageal cancer, 1204 (83%) had surgery and 254 (17%) had local therapy only. The use of local therapy increased	The use of local therapy for T1N0 esophageal cancers

Authors	**Patient group**	**Outcomes**	**Key results**	**Conclusion/*Comment***
	either surgery or local therapy, with ablative and/or excision techniques, in the Surveillance Epidemiology and End Results cancer registry from 1998 to 2008, were compared using the Kaplan-Meier approach, and multivariable and propensity-score adjusted Cox proportional hazard, and competing risk models.		significantly from 8.1% in 1998 to 24.1% in 2008 ($p < 0.001$). The 5-year OS after local excisional therapy and surgery was not significantly different (55.5% versus 64.1% respectively, $p = 0.07$), and 5-year cancer-specific survival (CSS) also did not differ (81.7% versus 75.8%, $p = 0.10$). However, after propensity-score adjustment, CSS was better for patients who underwent local therapy compared with those who underwent surgery (hazard ratio: 0.46, 95% confidence interval: 0.27-0.77, $p = 0.003$), whereas OS remained similar.	increased significantly from 1998 to 2008. Compared with those treated with oesophagectomy, patients treated with local therapy had similar OS but improved CSS, indicating a higher chance of dying from other causes.
Griffin et al.[5]	One hundred nineteen consecutive patients underwent radical esophagectomy alone for treatment of superficial esophageal adenocarcinoma or high-grade dysplasia. The resection specimens were analyzed by an expert gastrointestinal pathologist and the presence of LNM and the depth of tumor invasion were recorded. Depth of invasion was classified as either confined to the mucosa, the first third of the submucosa, the middle third of the submucosa, or the final third of the submucosa.	To accurately document the incidence of lymph node metastases (LNM) in early esophageal adenocarcinoma with regard to the depth of invasion of the mucosa or submucosa.	Fifty-four patients had high-grade dysplasia or tumours confined to the mucosa with no evidence of LNM (0/54, 0%), 65 patients had tumor invading the submucosa with 8 patients having LNM (8/65, 12%). Subclassification of submucosal invasion showed that 5 of 22 "first third of the submucosa" tumours had LNM (23%), 1 of 24 "middle third of the submucosa" tumours had LNM (4%), and 2 of 19 "final third of the submucosa" tumours had LNM (11%).	Invasion of the submucosa is associated with significant risk of LNM. Patients with submucosal invasion are not suitable for endoscopic treatment and surgical resection remains the gold standard treatment for patients with submucosal adenocarcinoma who are fit to undergo the procedure.
Hölscher et.al.[6]	One hundred seventy-one patients had transthoracic en bloc (n = 161) or transhiatal esophagectomy (n = 10) for pT1 esophageal cancer adenocarcinomas (AC), 50 squamous cell carcinomas (SCC)]. The histologic analysis of the specimen comprised depth of wall penetration of the carcinoma in thirds of pT1a = mucosa (m1, m2, m3) or pT1b = submucosa (sm1, sm2, sm3) and number and infiltration of the resected lymph nodes.	To identify differences in survival of patients with pT1 esophageal cancer relating to depth of wall infiltration	The rate of LNM was 0% for 70 mucosal carcinomas and 34% for 101 submucosal carcinomas ($P = 0.001$). For sm1, this rate was 13%, for sm2 19% and for sm3 56%. The 5-year survival rate (5Y-SR) was 82% for pN0 and 45% for pN+ patients ($P < 0.001$). There was no significant prognostic difference between AC and SCC (5Y-SR: 74% vs 71%). The 5Y-SR of the pT1a group was 87% compared with 66% for pT1b ($P = 0.046$). The 5-year survival rate for sm1 and sm2 were similar; sm1 + sm2 were together significantly better (80%) than sm3 (46%) ($P = 0.008$). In multivariate analysis, only sm3 was an independent prognostic factor ($P = 0.01$).	After esophagectomy, the prognosis of patients with sm1/sm2 infiltration is as good as for patients with mucosal carcinoma. Sm3 infiltration is the worst prognostic factor in pT1 esophageal cancer.
Pech et al.[9]	A total of 114 patients with mucosal BC who were treated either surgically or endoscopically between 1996 and 2009 in two high-volume centers. Thirty-eight patients received transthoracic esophageal resection with 2-field lymphadenectomy (median 29 lymph nodes removed; all pN0). Seventy-six patients treated with EMR followed by argon-plasma-coagulation of the remaining non-dysplastic Barrett's oesophagus. Patients were matched according to age, gender, infiltration depth (pT1m1-3), differentiation grade	Complete remission (CR) Major complications Ninety day mortality Overall recurrence rate Disease free follow-up (5 years) Overall survival (5 years) Tumor related mortality (EMR vs	98.7% (1 patient died of other causes before achieving CR) vs 100% 0% vs. 32% ($p<0.001$) 0% vs. 2.6% ($p=0.333$) 6.6% (1 local, 4 metachronous with successful repeat endoscopic treatment in all patients) vs. 0% ($p=0.17$) 91% vs 100% ($p=0.19$) 89% vs 93% ($p=0.91$) 0% in both groups (EMR vs Oesophagectomy)	No LNM noted in both groups. For patients with mucosal BC, both surgery and EMR are effective treatment modalities. Surgery is associated with a higher morbidity rate and shows a risk for procedure-related mortality. The recurrence rate is higher in patients treated with EMR, hence thorough follow-up is mandatory

Authors	**Patient group**	**Outcomes**	**Key results**	**Conclusion/*Comment***
	(G1/2 vs. 3) and follow-up period. The median follow-up periods were 4.1 years in the ER group and 3.7 years in the surgical group	Oesophagectomy)		
Prasad et al. [26]	Retrospective analysis of 178 patients treated for mucosal (T1a) oesophageal adenocarcinoma between 1998 and 2007. Patients were divided into an endoscopically treated group (n=132, 111 male, mean age 71.2 years) and a surgically treated group (n=46, 43 male, mean age 67.7 years). The mean follow-up period was 64 months (standard error of the mean 4.8 months) in the oesophagectomy group and 43 months (standard error of the mean 2.8 months) in the EMR group. Median age-adjusted Charlson Comorbidity Index, (IQR) was 4 (0–5) in the EMR and 0 (0–4) in the surgery arm (p<0.001)	Complication rate Cumulative mortality Cancer free survival (5 years) Overall survival (5 years) Recurrence	13% vs 34% 17% vs. 20% (p=0.75) 80% vs 97% (p=0.33) 83% vs 95% (p<0.001) 16/132 (all successfully retreated without an impact on survival) vs 1/46	outcome is comparable between EMR and esophagectomy. Limitations: Retrospective analysis. Smaller number of patients with longer Barrett's oesophagus segment in the surgery arm. Older patients with more comorbidities in the EMR arm.
Cen et al. [27]	Ninety nine patients with T1,N0 or T1,N1 adenocarcinoma of the oesophagus or the GOJ who underwent primary oesophagectomy at the University of Texas M. D. Anderson Cancer Center between November 1988 and November 2005. Preoperative assessment comprised upper GI endoscopy with biopsies, EUS, CT and in 32 patients (32.3%) also a PET scan. All 99 patients underwent resection with lymph node dissection for curative intent. No patient received adjuvant chemotherapy or chemoradiation after surgery The following data were obtained: size, depth, location of the cancer, LVI status, degree of differentiation, presence of Barrett's mucosa, margin status, and the presence or absence of LNM The time to relapse and location of relapse (local and distant), the date of death, and the cause of death were ascertained. Mean follow up 60 months.	LNM Overall survival (OS) and survival prognosis Recurrence-free survival (5 years)	T1a vs. T1b 4% vs 23% 88% (all non-cancer related deaths) vs 62% 5 year OS (p=0.001) [T1a vs T1b without LVI is 90% vs 77%, p=0.078. T1b without LVI vs T1b with LVI is 77% vs 27% p=0.006] The multivariate analysis demonstrated that LNM (P=0.03) and age >65 years (P =0.04) were independent factors that were predictive of a poor OS. The presence of LVI was of borderline significant as an independent factor that was predictive of poor OS (P=0.05) 100% vs 74% (T1b without LVI, p=0.006), 35% (T1b with LVI, p<0.0001). Distant metastasis in 96% of patients with recurrence	Low risk for LNM in T1a as compared to T1b cancers. This endorses the concept of less invasive procedures such as EMR being used as first line treatment in T1a cancers.

Authors	**Patient group**	**Outcomes**	**Key results**	**Conclusion/*Comment***
Das et al. [28]	A total of 742 patients registered between 1998 and 2003 in the Surveillance Epidemiology and End Results database (SEER) of the National Cancer Institute, with the diagnosis of Tis (high grade dysplasia) or T1N0M0 nonsquamous and squamous cell-type esophageal cancer Ninety nine (13.3%) patients underwent endoscopic treatment (group A) and the remainder was managed by surgical resection (group B). Endocopic treatment comprised EMR (65.7%), EMR plus ablative therapy (14.1%) and ablative therapy alone (16.2%). Data on demographic features, tumour characteristics, types of treatment received (endoscopic vs surgical resection), and cancer-specific mortality were analyzed.	Cancer specific mortality Median cancer-free survival Predictors of survival	Endoscopic therapy vs. Oesophagectomy Cox proportional hazards model demonstrates a relative hazard [RH] of 0.89 (95% confidence interval [CI] 0.51-1.56, P= 0.68) 56 vs 59 months, p=0.41. Significant predictors of survival were age at diagnosis (RH 1.06, 95% CI 1.03-1.08, P < 0.001) and absence of exposure to radiation therapy (RH 0.32, 95% CI 0.21-0.48, P < 0.001).	Equivalent long term survival between endoscopic therapy and surgery in early oesophageal cancer. Cumulative experience from multiple institutions, not only highly-specialised, high-volume centres. First population-based data supporting the effectiveness of endoscopic therapy for managing these patients. Radiation therapy detrimental to overall survival. Limitations: Small percentage of endoscopically treated patients, with inhomogeneous treatment modalities
Schembre et al. [29]	A retrospective study of 94 patients with Barrett's oesophagus and dysplasia or intramucosal cancer who received either endoscopic or surgical therapy between 1998 and 2005 was performed. Sixty-two patients with a median age of 70 years underwent endoscopic therapy (2 APC alone, 18 EMR + APC, 20 PDT + APC, and 22 EMR + PDT + APC). Seventy three percent were male. Thirty two patients underwent oesophagectomy (93% male with a median age of 64 years). Average ASA level was 2.6 in the endotherapy and 2.5 in the surgery group. Median follow-up of 20 months for endotherapy and 48 months for surgery.	Oesophageal cancer-related mortality Thirty day mortality Cancer recurrence rate Major/ Minor complications Median cost	Endoscopic therapy vs. Oesophagectomy 0% in both groups 1 (2%) vs 0% (p=0.49) 6% vs 0% (p<0.05) 8% / 31% vs 13% / 63% (p=0.5 / p<0.001) $40,079 vs $66,060 (p<0.001)	Modalities equally effective. Higher morbidity and cost for surgery. Higher risk of recurrence with endoscopic therapy mandating careful follow up. Limitations: Retrospective analysis. Small numbers. Relatively short follow up with higher patient age and inhomogeneous treatment modalities in the endoscopic therapy group.
Pacifico et al. [30]	Retrospective study (1996-2001) of 88 patients with early stage BC undergoing either EMR plus an ablative procedure (PDT, n=24, 21 men, mean age 68 years) or oesophagectomy (n=64, 58 male, mean age 67 years). Follow-up of 12 +/-2 and 19+/-3 months respectively. Pulmonary comorbidities were significantly higher in the EMR/PDT group (42% vs 19%, p=0.03).	Procedure -related complications Procedure-related deaths Failure to respond to therapy Cancer free at the end of follow-up	EMR/PDT vs Oesophagectomy 31 vs 4 (p<0.01) 0 vs 1 4 (2 underwent alternative therapies and rendered free of disease, 2 died of unrelated causes) vs 0 83% (20/24) vs 100%	Endoscopic therapy appears to constitute a viable option for the treatment of early Barrett's adenocarcinoma. Limitations: Small number of patients in the endoscopic therapy group. Retrospective study. Short follow-up. Higher pulmonary comorbidities in the

Authors	**Patient group**	**Outcomes**	**Key results**	**Conclusion/*Comment***
	Patient demographics, tumor staging, procedure-related morbidity and mortality, persistence or recurrence of cancer, and cancer-related deaths after therapy were studied.			EMR/PDT group. Lack of discrimination between T1a and
Fujita et al.[13]	A total of 150 patients diagnosed with T1a (n=72) or T1b (n=78) oesophageal cancer from 1981 to 1997 were evaluated (17 women and 133 men, mean age of 63 years). Mortality and morbidity rates, survival rate, and recurrence rate were retrospectively compared for (1) 35 patients who underwent EMR and 37 patients who underwent oesophagectomy for a mucosal oesophageal cancer and (2) 45 patients who underwent extended radical oesophagectomy and 33 patients who underwent less radical oesophagectomy for a submucosal oesophageal cancer. Follow-up of 32 months in average (4-68) for the EMR and 62 months (1-153) for the oesophagectomy group.	 LNM Survival (5-year) Hospital Mortality Morbidity Recurrence	T1a vs T1b 1% vs 38% EMR vs Oesophagectomy (T1a) 61% vs 71% (p=NS) No difference in disease specific survival 0% vs 14% (p=0.017) 7% vs 69% (p<0.001) 0% vs 0%	No difference in survival and recurrence rates in T1a oesophageal cancers treated with either EMR or oesophagectomy. Significantly lower morbidity and mortality with EMR. Authors conclude that EMR should be a mainstay treatment for T1a cancers. Substantially lower LNM rate in the T1a group. Limitations: retrospective analysis.
Ell et al.[31]	64 patients who had early OAC or HGD in BO. 35 patients met the criteria for low risk: macroscopic types I, IIa, IIb, and IIc; lesion diameter up to 20 mm; mucosal lesion; and histological grades G1 and G2 and/or high-grade dysplasia (group A). The remaining 29 patients were included in group B (high risk).	Short and long term outcomes	+ The mean number of treatment sessions per patient was 1.3 ± 0.6 in group A and 2.8 ± 2.0 in group B (P < 0.0005). +Only one major complication occurred, a case of spurting bleeding, which was managed endoscopically. + Complete local remission was achieved significantly earlier (P = 0.008) in group A than in group B. + Complete remission had been achieved in 97% of the patients in group A and in 59% of those in group B. +During a mean follow-up of 12 ± 8 months, recurrent or metachronous carcinomas were found in 14%.	*Tumours classified into High and low risk. Prospective study*

APC=Argon-Plasma-coagulation; **BC=**Barrett's Cancer (adenocarcinoma); **CI =** confidence interval; **EMR**= Endoscopic Mucosal Resection; ER= Endoscopic resection; **GI =** Gastrointestinal; **GOJ =** Gastrooesophageal junction; **OAC=** Oesophageal adenocarcinoma**; PET =** positron emission tomography; **PDT**=photodynamic therapy; **LNM =** lymph node metastasis; **LVI=** lymphovascular invasion**.**

DISCUSSION

Incidence of oesophageal carcinoma is increasing exponentially in the west. Early detection and treatment is associated with better outcomes. Early detection maybe prohibited by late onset of alarming symptoms that would prompt the primary physician to refer to a specialist. However, more early cancers are being diagnosed recently due to Barrett's surveillance protocols. The question now arises on how these patients should be treated that they should have the best outcomes.

Despite the improved outcomes of Surgery and the growing interest in minimally invasive oesophagectomies, it remains a challenging surgery with a big impact on patients.

However, the advantages of early detection should be met with a modality of treatment, that

doesn't compromise oncologically, in order to ensure cure.

The first challenge for these patients is to stage them adequately as understaging may influence the treatment modality these patients will receive. Up to 30% of patients with early cancer treated surgically have their disease upstaged at pathology [(1)]. Lutz et al.[(4)] stated that pretherapeutic staging is highly unreliable.

Once staged, a decision needs to be made on whether to treat them endoscopically or surgically. There is an agreement that T1b cancers should be treated surgically except for the unfit patients. This offers a better oncological clearance especially that the chance of Lymph node involvement for submucosal cancers is up to 34% [(5,6,7)].

Submucosal cancers have been further subdivided into 3 groups (sm1,2,3) according to the depth of invasion and it has been suggested that T1b sm3 cancer patients are the ones who need surgery [(8)]. However many surgical centres would argue and recommend surgery for any submucosal cancer [(1,5)]

There are many studies including a metaanalysis [(3)] that confirmed safety of Endoscopic resection. Most of the complications reported were minor and dealt with endoscopically (Table 1).

In terms of oncological outcomes, there is also an agreement that endoscopic resection especially when combined with RFA can eventually achieve satisfactory disease eradication. However, this necessitates strict follow up for treated patients as recurrence/metachronous lesions appear in 14% of patients [(9)]. This often dictates many treatment sessions in up to 56% of patients [(1)] till achievement of complete eradication. Once this is achieved, data from studies that looked into long term outcomes of endoscopic therapy, confirm the satisfactory oncologic results [(10)]

Endoscopic resection and ablation have become the preferred therapy for most patients with high-grade dysplasia or superficial esophageal cancer. Endoscopic therapy offers esophageal preservation with similar oncologic outcomes and significantly fewer complications compared with the alternative of oesopahgectomy. The goal of endotherapy is eradication of all the premalignant intestinal metaplasia to minimize the risk for metachronous cancer development. Once accomplished, careful follow-up is necessary to address recurrent intestinal metaplasia or dysplasia and prevent long-term failure of an endoscopic approach in these patients.[(11)]

Based on EMR's high neoplasia eradication rate and its fewer and more manageable complications, EMR, especially when combined with RFA, appears to be a viable alternative to surgery in early submucosal cancers, that is, sm1.[(12)]

Adding RFA aims to ablate Barrett's mucosa as this represents a change of field. This is currently the most effective therapy [(13)]. Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) allow for removal of visible lesions and histopathologic review of resected tissue, which help in diagnostic staging of the disease. EMR is limited with respect to resection size, and large lesions must be resected in several fragments. Piecemeal resection of lesions is associated with high local recurrence rates, probably because of minor remnants of neoplastic tissue being left in situ. ESD provides larger specimens than does EMR in patients with early Barrett's neoplasia. This in turn allows for more precise histological analysis and higher en bloc and curative resection rates, potentially reducing the incidence of recurrence [(14)]

There is an agreement that endoscopic therapy should only be offered to patients with a negligible risk of lymph node metastases or when the risk of lymph node metastases is equal to the risk of surgery. Decision of not having surgery should as well be revised after pathological assessment of endoscopic resection specimens. Patients with their disease understaged prior to endoscopic therapy should be offered surgery.

Prognostic factors affecting lymph node involvement and hence favoring surgical treatment are: Tumour size (≤2cm), Lymphovascular invasion, Grade of differentiation (Worse in G3) and depth of invasion (Submucosal involvent) with Tumor size and lymphovascular invasion being the strongest predictors [(7)]. Lymph node status is the only independent risk factor for survival and recurrence rates [(15)]

Early squamous cancers were treated in a similar way to early Adenocarcinoma. Reported results in mid and lower oesophageal tumours found no difference in results and both types can be treated similarly in early stages [(16,17)]

There is a need for a study that provides stronger evidence for the results published in literature. Evidence available is mostly either from retrospective cohort studies or expert opinions.

Clinical Bottom line:

1. Endoscopic therapy (Resection + RFA) is currently the first line used in management of Early oesephageal cancer as it allows organ preservation and satisfactory oncological results.
2. More than one endoscopic session is needed to achieve initial eradication in a substantial proportion of patients.
3. Recurrence rates / Metachronous lesions are common after endoscopic treatment necessitates high quality endoscopic surveillance.
4. Lymphovascular invasion, Tumor size (≥2cm), involvement of submucosa and poorly differentiated tumours are bad prognostic indices for lymph node involvement and recurrence.
5. Surgery is the recommended treatment for T1b cancers in the fit patients.

Disclosure:

One of the authors co-authored an article looking at the best evidence in this topic in 2012. We believe the current article encompasses the latest evidence and is much more comprehensive.

REFERENCES

1. Chadwick, G., Riley, S., Hardwick, R. H., Crosby, T., Hoare, J., Hanna, G., … Groene, O. (2016). Population-based cohort study of the management and survival of patients with early-stage oesophageal adenocarcinoma in England. *British Journal of Surgery*, *103*(5), 544–552.
2. Fovos, A., Jarral, O., Panagiotopoulos, N., Podas, T., Mikhail, S., & Zacharakis, E. (2012). Does endoscopic treatment for early oesophageal cancers give equivalent oncological outcomes as compared with oesophagectomy? Best evidence topic (BET). *International Journal of Surgery*, *10*(9), 415–420.
3. Orman, E. S., Li, N., & Shaheen, N. J. (2013). Efficacy and durability of radiofrequency ablation for barrett's esophagus: Systematic review and meta-analysis. *Clinical Gastroenterology and Hepatology*.
4. Lutz, M. P., Zalcberg, J. R., Ducreux, M., Ajani, J. A., Allum, W., Aust, D., … First St Gallen EORTC Gastrointestinal Cancer Conference 2012 Expert Panel. (2012). Highlights of the EORTC St. Gallen International Expert Consensus on the primary therapy of gastric, gastroesophageal and oesophageal cancer – Differential treatment strategies for subtypes of early gastroesophageal cancer. *European Journal of Cancer*, *48*(16), 2941–2953.
5. Griffin, S. M., Burt, A. D., & Jennings, N. A. (2011). Lymph Node Metastasis in Early Esophageal Adenocarcinoma. *Annals of Surgery*, *254*(5), 731–737.
6. Hölscher, A. H., Bollschweiler, E., Schröder, W., Metzger, R., Gutschow, C., & Drebber, U. (2011). Prognostic Impact of Upper, Middle, and Lower Third Mucosal or Submucosal Infiltration in Early Esophageal Cancer. *Annals of Surgery*, *254*(5), 802–808.
7. Lee, L., Ronellenfitsch, U., Hofstetter, W. L., Darling, G., Gaiser, T., Lippert, C., … Ferri, L. E. (2013). Predicting Lymph Node Metastases in Early Esophageal Adenocarcinoma Using a Simple Scoring System. *Journal of the American College of Surgeons*, *217*(2), 191–199.
8. Manner, H., Pech, O., Heldmann, Y., May, A., Pohl, J., Behrens, A., … Ell, C. (2013). Efficacy, Safety, and Long-term Results of Endoscopic Treatment for Early Stage Adenocarcinoma of the Esophagus With Low-risk sm1 Invasion. *Clinical Gastroenterology and Hepatology*, *11*(6), 630–635.
9. Pech, O., Bollschweiler, E., Manner, H., Leers, J., Ell, C., & Hölscher, A. H. (2011). Comparison between endoscopic and surgical resection of mucosal esophageal adenocarcinoma in Barrett's esophagus at two high-volume centers. *Annals of Surgery*, *254*(1), 67–72.
10. Phoa, K. N., Pouw, R. E., Bisschops, R., Pech, O., Ragunath, K., Weusten, B. L. a M., … Bergman, J. J. G. H. M. (2015). Multimodality endoscopic eradication for neoplastic Barrett oesophagus: results of an European multicentre study (EURO-II). *Gut*,

1–8.

11. Worrell, S., & DeMeester, S. R. (2016). Endoscopic Resection and Ablation for Early-Stage Esophageal Cancer. *Thoracic Surgery Clinics*, *26*(2), 173–176.
12. Smith, I., & Kahaleh, M. (2015). Endoscopic versus surgical therapy for Barrett's esophagus neoplasia. *Expert Review of Gastroenterology & Hepatology*, *9*(1), 31–35.
13. Bennett, C., Vakil, N., Bergman, J., Harrison, R., Odze, R., Vieth, M., … Jankowski, J. A. Z. (2012). Consensus Statements for Management of Barrett's Dysplasia and Early-Stage Esophageal Adenocarcinoma, Based on a Delphi Process. *Gastroenterology*, *143*(2), 336–346.
14. Ishihara, R., Yamamoto, S., Hanaoka, N., Takeuchi, Y., Higashino, K., Uedo, N., & Iishi, H. (2014). Endoscopic submucosal dissection for superficial Barrett's esophageal cancer in the Japanese state and perspective. *Annals of Translational Medicine*, *2*(3), 24.
15. Lorenz, D., Origer, J., Pauthner, M., Graupe, F., Fisseler-Eckhoff, A., Stolte, M., … Ell, C. (2014). Prognostic Risk Factors of Early Esophageal Adenocarcinomas. *Annals of Surgery*, *259*(3), 469–476.
16. Park, I., Kim, Y.-H., Yoon, D. H., Park, S. R., Kim, H. R., Kim, J. H., … Kim, S.-B. (2014). Non-surgical treatment versus radical esophagectomy for clinical T1N0M0 esophageal carcinoma: a single-center experience. *Cancer Chemotherapy and Pharmacology*, *74*(5), 995–1003.
17. Wani, S., Drahos, J., Cook, M. B., Rastogi, A., Bansal, A., Yen, R., … Das, A. (2014). Comparison of endoscopic therapies and surgical resection in patients with early esophageal cancer: a population-based study. *Gastrointestinal Endoscopy*, *79*(2), 224–232.e1.
18. Cummings, L. C., Kou, T. D., Schluchter, M. D., Chak, A., & Cooper, G. S. (2016). Outcomes after endoscopic versus surgical therapy for early esophageal cancers in an older population. *Gastrointestinal Endoscopy*, *84*(2), 232–240.e1.
19. Gamboa, A. M., Kim, S., Force, S. D., Staley, C. A., Woods, K. E., Kooby, D. A., … Willingham, F. F. (2016). Treatment allocation in patients with early-stage esophageal adenocarcinoma: Prevalence and predictors of lymph node involvement. *Cancer*, *122*(14), 2150–2157.
20. Jin, X.-F., Gai, W., Chai, T.-H., Li, L., & Guo, J.-Q. (2016). Comparison of Endoscopic Resection and Minimally Invasive Esophagectomy in Patients With Early Esophageal Cancer. *Journal of Clinical Gastroenterology*, 1.
21. Le, P. A., Velu, P. P., Penman, I. D., Couper, G. W., Paterson-brown, S., & Lamb, P. J. (2015). ScienceDirect The Surgeon , Journal of the Royal Colleges of Surgeons of Edinburgh and Ireland Surgical and endoscopic management of high grade dysplasia and early oesophageal adenocarcinoma. *The Surgeon*, 1–7.
22. Pech, O., May, A., Manner, H., Behrens, A., Pohl, J., Weferling, M., … Ell, C. (2014). Long-term efficacy and safety of endoscopic resection for patients with mucosal adenocarcinoma of the esophagus. *Gastroenterology*, *146*(3), 652–660e1.
23. Lada, M. J., Watson, T. J., Shakoor, A., Nieman, D. R., Han, M., Tschoner, A., … Peters, J. H. (2014). Eliminating a Need for Esophagectomy: Endoscopic Treatment of Barrett Esophagus With Early Esophageal Neoplasia. *Seminars in Thoracic and Cardiovascular Surgery*, *26*(4), 274–284. https://doi.org/10.1053/j.semtcvs.2014.12.004
24. Phoa, K. N., Pouw, R. E., Van Vilsteren, F. G. I., Sondermeijer, C. M. T., Ten Kate, F. J. W., Visser, M., … Bergman, J. J. G. H. M. (2013). Remission of Barrett's esophagus with early neoplasia 5 years after radiofrequency ablation with endoscopic resection: A Netherlands cohort study. *Gastroenterology*, *145*(1), 96–104.
25. Berry, M. F., Zeyer-Brunner, J., Castleberry, A. W., Martin, J. T., Gloor, B., Pietrobon, R., … Worni, M. (2013). Treatment Modalities for T1N0 Esophageal Cancers: A Comparative Analysis of Local Therapy Versus Surgical Resection. *Journal of Thoracic Oncology*, *8*(6), 796–802.
26. Prasad, G. A., Wu, T. T., Wigle, D. A., Buttar, N. S., Wongkeesong, L. M., Dunagan, K. T., … Wang, K. K. (2009). Endoscopic and Surgical Treatment of Mucosal (T1a) Esophageal Adenocarcinoma in Barrett's

Esophagus. *Gastroenterology*, *137*(3), 815–823.

27. Cen, P., Hofstetter, W. L., Correa, A. M., Wu, T. T., Lee, J. H., Ross, W. A., … Ajani, J. A. (2008). Lymphovascular invasion as a tool to further subclassify T1b esophageal adenocarcinoma. *Cancer*, *112*(5), 1020–1027.
28. Das, A., Singh, V., Fleischer, D. E., & Sharma, V. K. (2008). A comparison of endoscopic treatment and surgery in early esophageal cancer: an analysis of surveillance epidemiology and end results data. *The American Journal of Gastroenterology*, *103*(6), 1340–5.
29. Schembre, D. B., Huang, J. L., Lin, O. S., Cantone, N., & Low, D. E. (2008). Treatment of Barrett's esophagus with early neoplasia: a comparison of endoscopic therapy and esophagectomy. *Gastrointestinal Endoscopy*, *67*(4), 595–601.
30. Pacifico, R. J., Wang, K. K., Wongkeesong, L. M., Buttar, N. S., & Lutzke, L. S. (2003). Combined endoscopic mucosal resection and photodynamic therapy versus esophagectomy for management of early adenocarcinoma in Barrett's esophagus. *Clinical Gastroenterology and Hepatology*, *1*(4), 252–257.
31. Ell, C., May, A., Gossner, L., Pech, O., Günter, E., Mayer, G., … Stolte, M. (2000). Endoscopic mucosal resection of early cancer and high-grade dysplasia in Barrett's esophagus. *Gastroenterology*, *118*(4), 670–677.